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	Clinical Protocol, Amendment 3
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TITLE PAGE

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 Number: OP0201-C-006

Amendment Number: 3

Product: OP0201 metered dose inhaler

Study Phase: 2a

Sponsor Name: Novus Therapeutics, Inc.

Legal Registered Address: Novus Therapeutics, Inc., 19900 MacArthur, Suite 550, Irvine, California, US, 92612

Regulatory Agency Identifying Number(s): US FDA IND 106778

Date of Amendment 3: 21 August 2019

Date of Protocol: 15 January 2019

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

[redacted] **Date**

Medical Monitor name and contact information can be found in Appendix 2.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document History

Document	Date	Substantial	Region
Amendment 3	21 August 2019	Yes	US
Amendment 2	05 June 2019	Yes	US
Amendment 1	8 March 2019	No	US
Original Protocol	15 January 2019	-	-

Amendment 3 (21 August 2019)

Overall Rationale for the Amendment:

This Phase 2a, double-blind, placebo-controlled exploratory study represents the first evaluation of OP0201 in treating acute otitis media (AOM) and in reducing the likelihood of middle ear effusion (MEE) following AOM in children. Enrollment is ongoing and the treatment code remains blinded. This amendment does not change the overall study design (ie, no change to sample size, inclusion/exclusion criteria, study Participant assessments or the study visit schedule, treatment dose or duration).

The following changes are intended to address a request by the Food and Drug Administration (FDA) and to further inform the design of future clinical studies.

1. An additional secondary efficacy endpoint has been added to address FDA's request to include an evaluation of AOM cure rate. This new secondary efficacy endpoint is specifically defined as "complete or near complete resolution of symptoms (AOM cure), defined as an Acute Otitis Media Severity of Symptoms (AOM-SOS) score ≤2,[(1)] assessed at the Day 4 Visit, Day 12 Visit and Day 28 Visit by in-clinic AOM-SOS score assessments".

2. To reposition the key secondary efficacy endpoint ("no MEE [OME] assessed at the Day 12 Visit by pneumatic otoscopy") as an additional primary efficacy endpoint. Persistent MEE would most likely lead to recurrence of AOM. This endpoint is proposed to evaluate likelihood of MEE at completion of therapy. Both treating an AOM event ("no bulging of the tympanic membrane (TM) assessed at Day 4 Visit by pneumatic otoscopy") and/or reducing the proportion of children with OME ("no MEE [OME] assessed at the Day 12 Visit by pneumatic otoscopy") are clinically important endpoints. It is unknown which efficacy endpoint will be most sensitive to establishing a clinically meaningful OP0201 treatment effect. Accordingly, it is important that we study both endpoints by testing them as a family of primary endpoints; ie, a statistically significant

result for either endpoint will be considered criterion for success. Appropriate control for multiplicity – the step-up Hochberg procedure – is also included.

Table 2 Description of Changes in Amendment 3

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Rationale Section 2.1 Study Rationale	Updated to state that AOM resolution for primary efficacy endpoints will be determined by evidence of no bulging of the TM early in the course of the treatment and no MEE (OME) at the conclusion of the treatment.	To reposition the key secondary efficacy endpoint as a primary efficacy endpoint as both treating an AOM event and reducing likelihood of MEE (OME) represent clinically important endpoints (see amendment rationale above).
Section 1.1 Statistical Methods Section 9.1 Statistical Hypotheses Section 9.2 Power Calculation Section 9.3 Populations for Analyses Section 9.4 Statistical Analyses	Updated power calculations and efficacy analysis for the additional primary endpoint. Updated statistical sections to include new secondary endpoint for the evaluation of AOM cure.	To restate the overall power for the study based on study design assumptions to detect a treatment effect in at least 1 of the 2 endpoints (based on a 40% of placebo responder rate at Day 4 and 30% of placebo responder rate at Day 12). To address FDA's request to include an evaluation of AOM cure (see amendment rationale above).
Section 1.1 Objectives and Endpoints Section 3.0 Objectives and Endpoints	Moved "No MEE (OME) assessed at the Day 12 Visit by pneumatic otoscopy" from secondary to primary endpoint. Added secondary endpoint for "complete or near complete resolution of symptoms (AOM cure)".	To update to align with proposed amendment of primary and secondary endpoints (see amendment rationale above).

Section # and Name	Description of Change	Brief Rationale
	Removed secondary endpoint "Probability of MEE on Days 4, 12, and 28 determined from tympanograms using a derived algorithm".	The derived algorithm is not a well-recognized interpretation of tympanogram results.
	Revised tympanogram secondary endpoint wording to "Normal tympanogram (Type A) assessed at the Day 4 Visit, the Day 12 Visit, and the Day 28 Visit by tympanometry".	To clarify secondary endpoint wording to analyze "improvement" since it is assumed tympanogram will be abnormal at baseline.
	Updated clinical success definition for AOM relapse and AOM recurrence endpoints as (1) no moderate to severe bulging of the TM (Key Action Statement 1A), and (2) no mild bulging of TM and no recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B), and (3) no mild bulging of the TM and no intense erythema of the TM (Key Action Statement 1B).	To clarify definition wording to analyze clinical success based on resolution of all AOM diagnostic signs and symptoms.
Section 8.2 Safety Assessments	Tympanometry removed as a safety assessment.	Tympanometry was incorrectly listed as a safety assessment and has been removed to align with Study Objectives and Endpoints as described in Section 1.0 and Section 3.0.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.1 Efficacy Analysis	Descriptive statistics updated to include gender and race as primary efficacy endpoint sub-groups.	To ensure comprehensive sensitivity analyses of the primary efficacy endpoint.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

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

Rationale:

Novus Therapeutics, Inc. is developing OP0201 metered dose inhaler ("OP0201"), a drug-device combination product comprised of a 20:1 fixed combination of dipalmitoylphosphatidylcholine (DPPC; a phospholipid surfactant) and cholesteryl palmitate (CP; a neutral phospholipid spreading agent) suspended in a propellant (hydrofluoroalkane-134a [HFA-134a]). There are no other ingredients (ie, no excipients, no fillers) in the formulation other than the active ingredients and the propellant. None of these ingredients contain any animal or human derivatives.

Both DPPC and CP are highly endogenous surfactants in the human respiratory tract, Eustachian tube (ET) and nasopharynx. The product is administered via an intranasal pressurized metered dose inhaler (pMDI). Together these 2 active ingredients effectively absorb the mucosal air-liquid interface and reduce the interfacial surface tension and passive opening pressure of the ET to promote "de-sticking" and restoration of the physiologic activity of the ET. In the setting of inflammation in the nasopharynx, the ET fails to open as it should and therefore the middle ear is not ventilated. It is well established that Eustachian tube dysfunction (ETD) is an important underlying cause of otitis media. To date, there is no drug product that has been approved to treat or prevent otitis media.

The study treatment will be delivered as a local treatment through each nostril using a pMDI device. This device holds the canister that contains the drug product. The device has an angled tip to deliver the drug towards the lateral wall of the nasal cavity so that the usual nasal mucociliary clearance pathway can facilitate delivery of the drug to the ET.

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 acute otitis media (AOM) in infants and children, and to assist in the design of future clinical studies. The study will assess whether 20 mg per day intranasal OP0201 (10 mg administered twice daily [BID] for a total of 20 doses [over approximately 10 days]) as an adjunct treatment to 20 doses of oral antibiotics is at least 25 percentage points more effective than placebo in AOM resolution as evidenced by no bulging of the tympanic membrane(s) (TM[s]) at the Day 4 Visit or is at least 25 percentage points more effective than placebo in reducing the likelihood of MEE (OME) assessed at the Day 12 Visit. OP0201 has an acceptable safety and tolerability profile when given to healthy adult volunteers and adults with otitis media or ETD. To date only 1 child has been exposed via the intranasal route to the active ingredients in OP0201 (Investigator's Brochure [IB]). This study will provide further data on the safety and tolerability of intranasal OP0201 in infants and children.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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 middle ear effusion (MEE) in infants and children when given as an adjunct treatment to oral antibiotics as assessed using pneumatic otoscopy.	• Incidence, seriousness, severity, and relatedness to study treatment of adverse events (AEs) and shifts from baseline (normal, abnormal) in vital signs, physical examination (including visual examination of the nasopharynx and oropharynx), and examination of TM (via otoscopy and endoscopy).

Objectives	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.
Secondary	
• 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, AOM recurrence, and AOM relapse rates).	The following secondary endpoints will be evaluated at the stated visits: • No MEE assessed at the Day 4 Visit and the Day 28 Visit by pneumatic otoscopy. • No bulging of the TM assessed at the Day 12 Visit and the Day 28 Visit by pneumatic otoscopy. • Normal tympanogram (Type A) assessed at the Day 4 Visit, the Day 12 Visit, and the Day 28 Visit 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 by in-clinic AOM-SOS score assessments. • Change from baseline in AOM-SOS score over the planned 10-day treatment period by parent/caregiver diary data. • At least a 50% reduction from baseline in the AOM-SOS score assessed at the Day 4 Visit, the Day 12 Visit, and the Day 28 Visit by in-clinic AOM-SOS score assessments. • AOM treatment failure (clinical failure)* at the Day 12 Visit. • AOM relapse defined as those with clinical success# at the Day 12 Visit and return for an interim/sick visit before Day 17 and have AOM. • AOM recurrence defined as those with clinical success# at the Day 12 Visit and return for an interim/sick visit from Day 17 through Day 28 and have AOM. *Treatment failure (clinical failure) is defined as (1) moderate to severe bulging of the TM (Key Action Statement 1A), or (2) mild bulging of TM and recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B), or (3) mild bulging of the TM and intense erythema of the TM (Key Action Statement 1B). #Clinical success for AOM relapse and AOM recurrence endpoints is defined as (1) no moderate to severe bulging of the TM (Key Action Statement 1A), and (2) no mild bulging of TM and no recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B), and (3) no mild bulging of the TM and

Objectives	Endpoints
	no intense erythema of the TM (Key Action Statement 1B).
Other	
• Another objective of this study is to obtain feedback from parents/caregivers on the pMDI device to optimize design of the device for pivotal studies.	• Parent/caregiver's input on device experience at the Day 12 Visit.

Overall 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 BID 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). Participants will be followed for up to 20 days after study treatment is discontinued. The total duration of study participation for each Participant is up to 30 days, which includes 4 clinic visits: Visit 1: (Day 1) Screening/Enrollment and initiation of the study treatment and oral antibiotics administration; Visit 2: (Day 4 [+2]); Visit 3: (Day 12 [+2]); and Visit 4: (Day 28 [±2]) Study Exit. On Day 1 potential Participants' parents/legal guardians in attendance at the study center will be told about the study and those Participants whose parents/legal guardian provide written informed consent will be evaluated for study eligibility. Those who meet all inclusion and no exclusion criteria will be enrolled and randomized (1:1 ratio) to receive a total of 20 intranasal doses (over approximately 10 days) with 20 mg per day OP0201 (10 mg BID) or placebo as an adjunct treatment to standard oral antibiotics (amoxicillin-clavulanate given BID for 20 doses).

Parents/caregivers of the Participants will complete an electronic daily diary on all days when study treatment is given (approximately 10 days) to record BID administration of the oral antibiotic and study treatment, and to record daily AOM-SOS scores.

At each study visit, assessments include a physical examination (including visual examination of the nasopharynx and oropharynx) and measurement of vital signs, pneumatic otoscopy to assess TM of each ear, endoscopic examination with image capture of each ear when possible, and tympanogram of each ear (to be performed when possible). Adverse events (AEs) and concomitant medication use will be recorded. At the Day 12 Visit, parents/caregivers will complete the Device Experience Questionnaire.

Parents/caregivers will be instructed to contact the Investigators if concerned about the Participant's status. An interim evaluation will be scheduled if a parent/caregiver notifies the Investigators that the Participant shows no improvement, has significantly worsened, or has recurrence of signs and symptoms of AOM or develops symptoms that may be related to the study treatment. If a child failed treatment, based on clinical judgment, after receiving antibiotics and study treatment for at least 48 to 72 hours, and additional antimicrobial therapy is deemed advisable, the child will receive guideline-concordant therapy.

Number of Investigators and Study Centers:

One Principal Investigator at 1 study center along with up to 4 satellite sites in the US are expected to participate in this study.

Number of Participants:

Approximately 140 Participants with AOM in at least 1 ear will be randomly assigned to study treatment such that approximately 70 evaluable Participants per treatment group complete the study.

Treatment Groups and Duration:

Twice daily treatment with 10 mg intranasal OP0201 or 0 mg intranasal placebo for a total of 20 doses, as well as standard oral antibiotic treatment for a total of 20 doses, will be initiated on Day 1. The first dose of the intranasal study treatment will be administered in the study center under supervision of the study staff.

Statistical Methods:

Power Calculation

The power calculation is based on a 2-sided Pearson chi square test of each of the 2 endpoints in the primary efficacy endpoint family and control for Type 1 error using the step-up Hochberg procedure. The minimally important difference in proportions for both endpoints is approximately 0.25. With 70 Participants randomized per treatment group, and assuming a 12% dropout rate with dropouts counted as failures, this Phase 2a study will have 87% power to detect a treatment effect in at least 1 of the 2 endpoints assuming 40% of placebo-treated Participants will have no bulging TM at Day 4 and 30% of placebo-treated Participants will have no MEE at Day 12.

Populations for Analyses

Four populations will be considered.

Screened population is defined as all Participants whose parent/legal guardian signs the informed consent form.

Safety population is defined as all Participants who received at least 1 intranasal spray of study treatment and will be used to assess the safety and secondary efficacy endpoints.

Intent-to-treat (ITT) population is defined as all randomized Participants and will be used to assess the primary efficacy endpoint family.

Per-Protocol (PP) population is defined as the subset of the ITT population who have no protocol violations affecting the primary efficacy endpoint family and will be used to confirm results from the primary efficacy endpoint family.

Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the Participant population sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

Safety Analyses

Safety will be evaluated using the safety population.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after administration of study treatment and no later than 2 calendar days after the last dose of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, numbers of TEAEs and incidence rates will be tabulated by primary system organ class (SOC) and by preferred term within each primary SOC.

Treatment-emergent AEs, TEAEs related to study treatment, serious adverse events (SAE), and TEAEs leading to discontinuation of study treatment will be summarized.

Vital sign measurements and changes from baseline will be summarized.

Test results from otoscopy, AOM-SOS, physical examination, nasopharynx, and oropharynx will be summarized.

Efficacy Analyses

The primary efficacy endpoint family consists of 2 endpoints: (1) no bulging of the TM at the Day 4 Visit assessed by pneumatic otoscopy and (2) no MEE (OME) at the Day 12 Visit assessed by pneumatic otoscopy. The step-up Hochberg procedure will be used to adjust for multiplicity. Specifically, the endpoint with the highest p-value will be tested first at 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 1 of the 2 endpoints is significant.

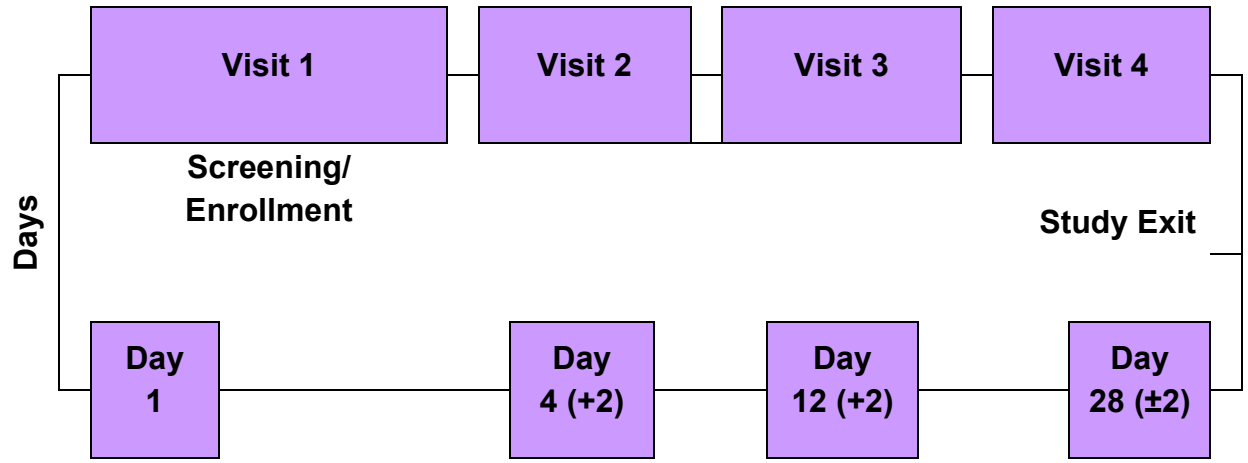
In general, categorical variables (including binary outcomes) will be summarized as frequencies and percentages and will be analyzed using logistic regression to control for covariates, including the randomization stratifiers. Continuous variables will be summarized by numbers of observations, means, measures of variances, percentiles, and ranges and will be analyzed using general linear models to control for covariates.

Safety Monitoring Committee: Yes

The Safety Monitoring Committee (SMC) will review blinded safety data for all Participants when approximately 25% of enrolled Participants have completed the Day 12 Visit. 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 separate charter document.

1.2 Schema

Figure 1 Study Schema



1.3 Schedule of Activities

Table 3 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	

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)**
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.

2.0 INTRODUCTION

2.1 Study Rationale

Novus Therapeutics, Inc. is developing OP0201, a drug-device combination product comprised of a 20:1 fixed combination of dipalmitoylphosphatidylcholine (DPPC; a phospholipid surfactant) and cholesteryl palmitate (CP; a neutral phospholipid spreading agent) suspended in a propellant (hydrofluoroalkane-134a [HFA-134a]). There are no other ingredients (ie, no excipients, no fillers) in the formulation other than the active ingredients and the propellant. None of these ingredients contain any animal or human derivatives.

Both DPPC and CP are highly endogenous surfactants in the human respiratory tract, Eustachian tube (ET) and nasopharynx. The product is administered via an intranasal pressurized metered dose inhaler (pMDI). Together these 2 active ingredients effectively absorb the mucosal air-liquid interface and reduce the interfacial surface tension and passive opening pressure of the ET to promote “de-sticking” and restoration of the physiologic activity of the ET. In the setting of inflammation in the nasopharynx, the ET fails to open as it should and therefore the middle ear is not ventilated. It is well established that Eustachian tube dysfunction (ETD) is an important underlying cause of otitis media. To date, there is no drug product that has been approved to treat or prevent otitis media.

OP0201 is a focal, intranasal treatment and is not anticipated to have either focal or systemic toxic effects since both active ingredients, DPPC and CP, are ubiquitous in nearly every cell of the human body, including those of the nasopharynx and respiratory system. Safety data from 3 nonclinical pharmacology studies did not identify adverse effects of repeated once or twice daily (BID) intranasal dosing over multiple days in gerbils, mice, or chinchillas (Investigator’s Brochure [IB]). Single and cumulative total doses on a mg/kg basis used in Phase 1 studies in adults were less than single or cumulative total dose exposure from products currently approved and marketed. Concentrations of surfactants, including DPPC, in the ET and respiratory system of persons with otitis media are reduced compared to ontologically healthy persons (IB). The intranasal administration of OP0201 is not anticipated to attain levels in the nasopharynx and respiratory system that are supraphysiologic.

The study treatment will be delivered as a local treatment through each nostril using a pMDI device. This device holds the canister that contains the drug product. The device has an angled tip to deliver the drug towards the lateral wall of the nasal cavity so that the usual nasal mucociliary clearance pathway can facilitate delivery of the drug to the ET.

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 acute otitis media (AOM) in infants and children, and to assist in the design of future clinical studies. The study will assess whether 20 mg per day intranasal OP0201 (10 mg administered BID for a total of

20 doses [over approximately 10 days]) as an adjunct treatment to 20 doses of oral antibiotics is at least 25 percentage points more effective than placebo in AOM resolution as evidenced by no bulging of the tympanic membrane(s) (TM[s]) at the Day 4 Visit and/or more effective than placebo in reducing the likelihood of MEE (OME) as evidenced by no MEE at the Day 12 Visit. For both endpoints, the minimal clinically meaningful difference in proportions for indication of efficacy of OP0201 is approximately 0.25. OP0201 has an acceptable safety and tolerability profile when given to healthy adult volunteers and adults with otitis media or ETD. To date only 1 child has been exposed via the intranasal route to the active ingredients in OP0201 (IB). This study will provide further data on the safety and tolerability of intranasal OP0201 in infants and children.

2.2 Background

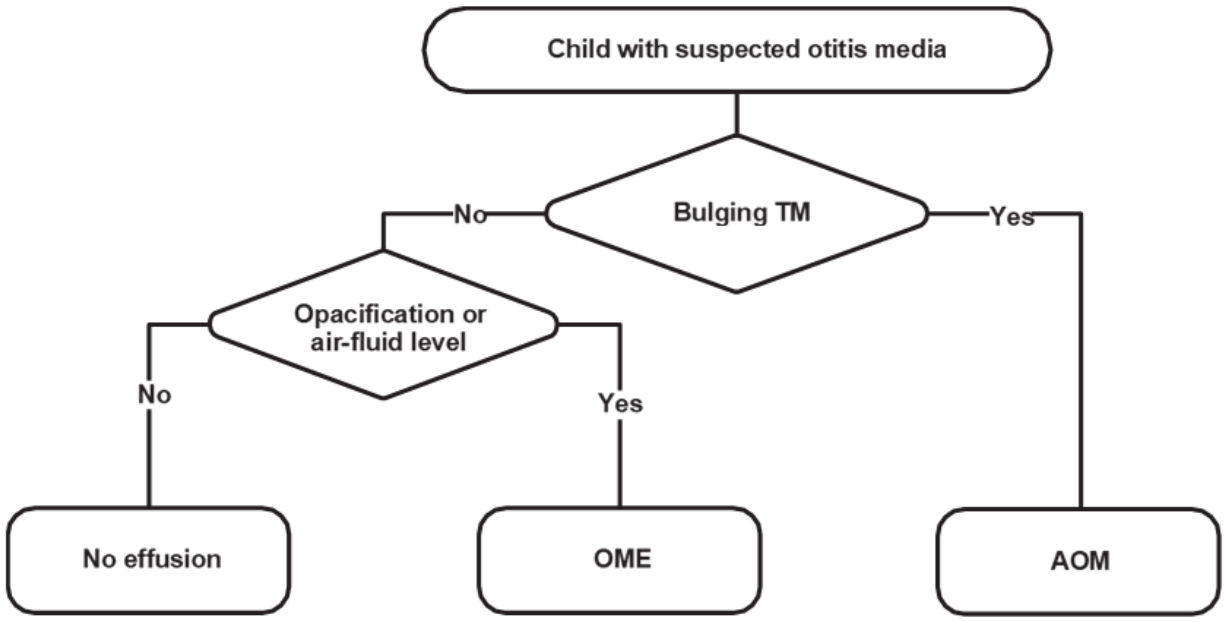
It has been established that many (approximately 70%) of young children with AOM will have persistent middle ear effusion (MEE, or otitis media with effusion [OME]) 2 to 3 weeks after a diagnosis of AOM, despite treatment with oral antibiotics.[(2)] It has been reported that negative effects of OME include ear discomfort/fullness, conductive hearing loss, and vestibular problems, as well as affecting quality-of-life and school performance.[(3,4,5,6)]

An algorithm that used bulging and opacification of the TM has been previously shown to correctly classify 99% of ears regarding a confirmed diagnosis of AOM (Figure 2).[(7)] Bulging of the TM was the main finding that otoscopists used to discriminate AOM from OME. Information regarding the presence or absence of other signs and symptoms added little to the diagnostic process. Overall, 92% of children with AOM had a bulging TM compared with 0% of children with OME. Opacification and/or an air fluid level was the main finding that otoscopists used to discriminate OME from no effusion. In total, 97% of children diagnosed with OME had an opaque TM compared with 5% of children diagnosed with no effusion.

On Day 7 of a 10-day antibiotic (amoxicillin/clavulanate) treatment course, 44% of children with AOM still had bulging TM (with or without symptoms).[(8)] If an otoscopic assessment was made earlier in the 10-day antibiotic treatment course, ie, Day 4 to Day 6, an estimated additional 10% to 15% of children would have bulging TM still present (with or without symptoms) (based on personal communication with Alejandro Hoberman, MD, Principal Investigator, 2018).

Antibiotics are prescribed to treat a presumed bacterial infection of the middle ear associated with AOM, but there are no drug products available to treat the underlying cause of otitis media (ie, ETD) and facilitate draining the MEE.

Figure 2 Algorithm for the Diagnosis of Otitis Media



AOM = acute otitis media; TM = tympanic membrane; OME = otitis media with effusion

2.3 Benefit/Risk Assessment

The active components of OP0201, DPPC and CP, are endogenous surfactant compounds in several products that have been approved by health authorities, including the Food and Drug Administration (FDA). HFA-134a, utilized as the propellant in OP0201, is also utilized as a propellant in other approved intranasal and orally inhaled products for adults and children.

The clinical safety and tolerability of OP0201 (20:1 weight/weight [w/w]) for human use is guided by data from animal studies of DPPC:CP (200:1 weight/weight [w/w]), data from 9 human cases exposed to 1 or more doses of DPPC:CP in HFA-134a (200:1 w/w or 16:1 w/w) (see IB), and from 15 adult healthy volunteers exposed to intranasal OP0201 30 mg per day (n = 12) or placebo (n = 3) as 2 sprays to each nostril 3 times a day × 14 days with no severe or serious adverse events (SAEs) reported and there was no consistent or unexpected pattern of AEs (Novus Study OP0201-C-002).

Based on a diminished beneficial effect of DPPC:CP (200:1 w/w) when combined with phenylephrine in animal model studies, it may be prudent to avoid co-administration of phenylephrine containing products during the use of OP0201 (IB).

The composition of OP0201 is designed to maximize the lowering of mucosal surface tension. Since the drug product mechanism involves reduction of the interfacial surface tension of the ET, the optimum ratio of DPPC to CP was evaluated by determining the reduction in surface tension at different ratios. An integrated dissolution and surface tension monitoring system was utilized

to measure the surface tension of phosphate buffered saline (pH 7) into which the finished product actuations were fired from the canister. Surface tension lowering of product formulated with DPPC only, CP only, and combined DPPC + CP in 5:1, 10:1, and 20:1 ratios found that the maximum surface tension reduction occurs with combined DPPC + CP at 20:1 ratio. Higher ratios did not result in further significant surface tension reduction and would render the minor CP component difficult to accurately quantify. Hence the DPPC + CP 20:1 ratio was selected for further development.

Refer to Section 4.0 for details on study procedures, dose, and study design justification.

See the IB for further details regarding OP0201.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

3.0 OBJECTIVES AND ENDPOINTS

3.1 Endpoint Rationale

This Phase 2a exploratory study is the first evaluation of OP0201 in treating AOM and in reducing the likelihood of MEE (OME) after AOM. 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. The safety endpoints address the primary objective of safety evaluation. The primary efficacy endpoint family consists of "No bulging of the TM at the Day 4 Visit as assessed by pneumatic otoscopy" and "No MEE (OME) at the Day 12 Visit as assessed by pneumatic otoscopy." No bulging of the TM was chosen because modulating bulging TM, a hallmark sign of AOM, would be the most clinically meaningful demonstration that OP0201 is effective in treating AOM. Clinical experts were surveyed as to what would be considered a clinically meaningful numeric difference between OP0201 and placebo on this endpoint, and consensus indicated that an approximate 0.25 difference in proportions between treatment groups would represent a clinically meaningful benefit in treating AOM. No MEE was chosen because decreasing the likelihood of residual MEE which occurs frequently after completion of a course of antibiotic therapy[(2)] would be the most clinically meaningful demonstration that OP0201 reduces OME which is also associated with a higher likelihood of recurrence of AOM.[(9)] There are no established guidelines for defining a minimal clinical meaningful benefit of treatment for quickly resolving MEE after treating AOM. However, restoration of hearing is dependent on resolving MEE, and in a recent study of children with COME,[(10)] acceptable hearing was observed in 33% of placebo-treated children (age 2 to 8 years) at week 5 and a 0.15 increase in the proportion with hearing resolution was considered clinically meaningful. A significant treatment effect on either AOM treatment or on reduction of the proportion of children with MEE (OME) would constitute a successful study in terms of efficacy.

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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.	• Incidence, seriousness, severity, and relatedness to study treatment of adverse events (AEs) and shifts from baseline (normal, abnormal) in vital signs, physical examination (including visual examination of the nasopharynx and oropharynx), and examination of TM (via otoscopy and endoscopy). • 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.

Secondary	
• 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 Symptoms (AOM-SOS) score, AOM recurrence, and AOM relapse rates).	The following secondary endpoints will be evaluated at the stated visits: • No MEE assessed at the Day 4 Visit and the Day 28 Visit by pneumatic otoscopy. • No bulging of the TM assessed at the Day 12 Visit and the Day 28 Visit by pneumatic otoscopy. • Normal tympanogram (Type A) assessed at the Day 4 Visit, the Day 12 Visit, and the Day 28 Visit 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 by in-clinic AOM-SOS score assessments. • Change from baseline in AOM-SOS score over the planned 10-day treatment period by parent/caregiver diary data. • At least a 50% reduction from baseline in the AOM-SOS score assessed at the Day 4 Visit, the Day 12 Visit, and the Day 28 Visit by in-clinic AOM-SOS score assessments. • AOM treatment failure (clinical failure)* at the Day 12 Visit. • 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. • AOM recurrence defined as those with clinical success# at the Day 12 Visit and who return for an interim/sick visit from Day 17 through Day 28 and have AOM. *Treatment failure (clinical failure) is defined as (1) moderate to severe bulging of the TM (Key Action Statement 1A[11]), or (2) mild bulging of TM and recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B[11]), or (3) mild bulging of the TM and intense erythema of the TM (Key Action Statement 1B[11]). #Clinical success for AOM relapse and AOM recurrence endpoints is defined as (1) no moderate to severe bulging of the TM (Key Action Statement 1A[11]), and (2) no mild bulging of TM and no recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B[11]), and (3) no mild bulging of the TM and no intense erythema of the TM (Key Action Statement 1B[11]).
Other	
• Another objective of this study is to obtain feedback from parents/caregivers on the pMDI	• Parent/caregiver's input on device experience at the Day 12 Visit.

device to optimize design of the device for pivotal studies.	

4.0 STUDY DESIGN

4.1 Overall 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 BID 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). Participants will be followed for up to 20 days after study treatment is discontinued. The total duration of study participation for each Participant is up to 30 days, which includes 4 clinic visits: Visit 1: (Day 1) Screening/Enrollment and initiation of the study treatment and oral antibiotics administration; Visit 2: (Day 4 [+2]); Visit 3: (Day 12 [+2]); and Visit 4: (Day 28 [±2]) Study Exit. On Day 1 potential Participants' parents/legal guardians in attendance at the study center will be told about the study and those Participants whose parents/legal guardian provide written informed consent will be evaluated for study eligibility. Those who meet all inclusion and no exclusion criteria will be enrolled and randomized (1:1 ratio) to receive a total of 20 intranasal doses (over approximately 10 days) with 20 mg per day OP0201 (10 mg BID) or placebo as an adjunct treatment to standard oral antibiotics (amoxicillin-clavulanate given BID for 20 doses).

Parents/caregivers of the Participants will complete an electronic daily diary on all days when study treatment is given (approximately 10 days) to record BID administration of the oral antibiotic and study treatment, and to record daily AOM-SOS scores.

At each study visit, assessments include a physical examination (including visual examination of the nasopharynx and oropharynx) and measurement of vital signs, pneumatic otoscopy to assess TM of each ear, endoscopic examination with image capture of each ear when possible, and tympanogram (to be performed when possible) of each ear. Adverse events and concomitant medication use will be recorded. At the Day 12 Visit, parents/caregivers will complete the Device Experience Questionnaire. The study assessments are summarized in Table 3.

An unscheduled interim/sick visit may occur for safety purposes or if AOM symptoms have relapsed or worsen. Applicable procedures (eg, physical, otoscopy, tympanometry) will be performed and recorded in the electronic case report form (eCRF).

Parents/caregivers will be instructed to contact the Investigators if concerned about the Participant's status. An interim evaluation will be scheduled if a parent/caregiver notifies the Investigators that the Participant shows no improvement, has significantly worsened, or has recurrence of signs and symptoms of AOM or develops symptoms that may be related to the study treatment. If a child failed treatment, based on clinical judgment, after receiving antibiotics and study treatment for at least 48 to 72 hours, and additional antimicrobial therapy is deemed advisable, the child will receive guideline-concordant therapy.[3]

4.2 Scientific Rationale for Study Design

Otitis media is a very common disease seen in pediatric practice and in the US, it is the most common reason children are prescribed antibiotics. Otitis media is a serious condition that can result in life-long adverse consequences including irreversible hearing loss. Morbidity from otitis media is driven by recurrence and/or persistence of otitis media, as well as disease progression that leads to ruptured TM and/or damage to structures of the middle ear. Both intratemporal and intracranial complications can occur resulting in serious consequences and, in rare cases, death. More than $5 billion is spent annually in the US on management of pediatric otitis media (IB).

Novus Therapeutics, Inc. is developing OP0201, a drug-device combination product comprised of 2 surfactant active ingredients DPPC and CP suspended in propellant (HFA-134a) to both treat and prevent otitis media. Both DPPC and CP are highly endogenous surfactants in the human respiratory tract. The product is administered via an intranasal pMDI. Together these 2 active ingredients effectively absorb the mucosal air-liquid interface and reduce the interfacial surface tension and passive opening pressure of the ET to promote “de-sticking” and restoration of physiologic activity of the ET. In the setting of inflammation in the nasopharynx, the ET fails to open as it should and therefore the middle ear is not ventilated.

This study will be conducted in the very young pediatric population (6 to 24 months, inclusive) as the targeted disease occurs more frequently in this age group, and the risk to this population from the compound (given in addition to a course of antibiotics), which is found naturally in human tissues, is considered to be very low. Parents/caregivers will be instructed to contact the Investigators if concerned about the Participant’s status. The use of randomization, a placebo and blinding are employed in this study to eliminate bias in evaluating safety, tolerability, and efficacy.

4.3 Justification for Dose

OP0201 is a local treatment to the nasopharynx and ET. Systemic concentrations of OP0201 would not be possible in guiding dose selection correlated with efficacy, as the components of OP0201 are endogenous to the human body. Furthermore, the drug product is intended to have a local effect at the site of delivery. Thus, a maximum practical dose and dosing interval is proposed for evaluation of OP0201 in humans. Input from expert clinicians indicates that a maximum dosing interval for an infant, child, adolescent, or adult that would be acceptable is BID. Data from the nonclinical pharmacology studies indicated that BID dosing was more efficacious than once daily dosing (see IB Section 4.2.1.3). It has also been determined that the practical maximum number of sprays into each nostril at each dosing interval would be 2 sprays. In vivo studies evaluating the effects of 1 or 2 sprays on reducing surface tension indicate that there is a greater reduction of surface tension after 2 sprays. It is unlikely that patients/caregivers will comply if 3 or more sprays need to be given per nostril per dosing interval. Taking all of the above information into consideration, the maximum number of sprays per nostril in this Phase 2a study is 2 sprays per nostril given BID. An ongoing Phase 1 adult safety study (Novus

Study OP0201-C-002) has established that 2 sprays per nostril 3 times a day (a research dosing interval not considered to be practical for studies in patients) for 14 consecutive days is safe.

4.4 End of Study Definition

A Participant is considered to have completed the study if he/she has completed all visits of the study including the last scheduled procedure shown in Table 3.

The end of the study is defined as the date of the last visit of the last Participant in the study.

4.5 Dose Escalation Criteria

Not applicable.

4.6 Study Stopping Criteria

4.6.1 Stopping Criteria for Individual Participants

Study treatment for any individual Participant will be stopped if the Participant experiences an SAE or a clinically significant possibly study treatment-related AE, which in the opinion of the Principal Investigator, Medical Safety Physician and Sponsor's medical representative, warrants discontinuation of the study for that Participant's wellbeing.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

3. Male and female infants and children aged 6 to 24 months (inclusive).
4. Diagnosis of AOM[11] - moderate to severe bulging of the TM (Key Action Statement 1A[11]), or mild bulging of TM and recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B[11]), or mild bulging of the TM and intense erythema of the TM (Key Action Statement 1B[11]).
5. Score of 5 or more on the 5-question version of the AOM-SOS scale.[12]
6. Intact TM in both ears (eg, no perforation).
7. Written informed consent by the infant/child's parent/legal guardian and their willingness to ensure that study instructions are followed, all study-related visits are attended, that treatment administration is given, and the parent/caregiver assessments are recorded according to the study protocol.
8. Parent/Legal Guardian has a smartphone or internet access to receive the electronic survey.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Allergy to penicillin or cephalosporin.
2. History or presence of immunodeficiency disorders.
3. Antimicrobial therapy within the 3 days (ie, 72 hours) prior to Day 1.
4. Use of intranasal treatments other than intranasal saline within 7 days prior to Day 1.
5. Craniofacial abnormalities (eg, cleft palate or Down's Syndrome) that may interfere with ET function.
6. Disorders with decreased mucociliary clearance or higher viscosity of the mucous (eg, cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome).
7. Clinically relevant blockage of 1 or both nasal passages, as determined by the Investigator's medical judgment.
8. Participants with any condition that would in the Investigator's opinion put the Participant at significant risk, may confound study results, may interfere significantly

with the Participant's participation, or have any factor that may present bias in the Participant selection.

9. Persons employed by the Sponsor or Investigator.

5.3 Lifestyle Considerations

Participants must refrain from immersing their head fully under water (eg, swimming) from the time of signed informed consent until after the final follow-up visit (Day 28).

5.4 Screen Failures

Screen failures are defined as Participants whose parents/legal guardian provide written informed consent for their participation in the clinical study but are not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure Participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography (eg, age, gender, race), reasons for screen failure (eg, note which eligibility criteria was not met), and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.4.1 Criteria for Stopping the Study

If 1 or more Participants experience study treatment-related SAEs or 2 or more Participants experience any study treatment-related severe AEs, the study will be stopped.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a Participant according to the study protocol. The study treatment is to be used in accordance with the protocol for Participants who are under the direct supervision of a qualified Investigator.

6.1 Study Treatment(s) Administered

6.1.1 The Drug-device Study Treatment

The study treatment (OP0201 and the placebo) is manufactured using Good Manufacturing Processes (GMP) with development phase appropriate compliance with global Health Authority guidelines[13] by [redacted]. It is considered a drug-device combination product because the drug is expelled from a pressurized canister via an actuating device.

The study treatment is supplied in mechanical packing parts that includes a pressurized canister with a securely attached metering valve where the OP0201 or placebo is contained, an actuator device into which the canister is seated, and an angled tip on the device to deliver the drug to the nostrils. The pressurized canisters are labeled to deliver 100 actuations (sprays) per canister.

Parents/caregivers will be given a demonstration of the administration of the study treatment and will need to be trained on study treatment administration on Day 1, prior to the first dose (which will be given under supervision of the study center staff).

All Medical Device Incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the Investigator throughout the study (see Section 8.4.6).

Participants' parents/caregivers will be trained on the proper administration of the study treatment and antibiotics on Day 1, prior to the first dose. The first dose will be administered under the supervision of the study staff by the parent/caregiver.

6.1.2 OP0201

OP0201 is the active drug. It is a drug-device combination product comprised of DPPC:CP (approximately 20:1 w/w in HFA 134a) for intranasal administration.

Each spray of OP0201 delivers 2.5 mg of active ingredients. Participants randomized to OP0201 will receive 2 sprays per nostril BID (morning and evening, at a total daily dose of 20 mg) for a total of 20 doses.

See the IB for further details regarding OP0201.

6.1.3 Placebo

Placebo is the propellant without any active ingredients (HFA 134a only) and provides a total daily dose of 0 mg.

All Participants will receive the same intranasal dosing regimen of placebo (given as 2 sprays to each nostril BID) for a total of 20 doses.

6.1.4 Standard Antibiotic

Participants will be prescribed a standard 10-day (20 doses) oral antibiotic treatment course of amoxicillin-clavulanate at a total dose of 90 mg/6.4 mg/kg/day administered orally in 2 divided doses (12-hourly).

Children categorized as initial antibiotic treatment failure (no clinical improvement within 48 to 72 hours) will receive appropriate antibiotic therapy which may include intramuscular ceftriaxone 75 mg/kg at the time of treatment failure, and a repeat dose in 48 hours.

6.2 Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only Participants enrolled in the study may receive study treatment and only authorized study center staff may supply study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator, a member of the study center staff, or a pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

On Day 1, Participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the Participant's assignment to study treatment according to the randomization schedule generated prior to the study by the Statistics Department of [redacted]. This is a double-blind study with limited access to the randomization code. OP0201 and placebo will be identical in physical appearance. The specific treatment each Participant will receive (OP0201 or placebo) will not be disclosed to the Investigator, study

center staff, Participant, Sponsor, study vendors, or the Safety Monitoring Committee (SMC). The treatment codes will be held by the Clinical Supplies Department of the Sponsor.

Participants will be randomly allocated in a 1:1 ratio to receive OP0201 or placebo as adjunct treatment to 20 doses of protocol defined oral antibiotic treatment.

Randomization will be stratified by daycare attendance (yes, no) and age (≥6 to <12 months, ≥12 to ≤24 months). Daycare attendance "yes" is defined as exposure to 3 or more children outside of the home for 10 or more hours per week.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any deviations from the protocol defined study treatment regimen must be recorded in the eCRFs.

Parents/caregivers of Participants will be issued a study diary in which they will be instructed to record daily the date and time of study treatment and antibiotic administration. If a study treatment or antibiotic dose is missed or a partial dose is given, this should also be recorded, and the dosing should resume at the next scheduled time.

At the Day 4 Visit and the Day 12 Visit, previously dispensed study treatment and the diary will be retrieved by the Investigator and compliance assessed. Parents/caregivers exhibiting poor compliance as assessed by diary completion should be counseled on the importance of good compliance to the study dosing regimen.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the Participant has received within the 7 days before enrollment (prior therapy) or receives during the study period and after first dose of study treatment (concomitant therapy) must be recorded on the eCRF along with:

- Reason for use.
- Date of administration including start and end date.
- Dosage information including dose, route, and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Excluded Medications

Participants must abstain from taking antimicrobial therapy within the 3 days (ie, 72 hours) prior to Day 1. Excluded medications/therapy is listed below:

- Any intranasal treatments other than saline rinse.

- Any systemic or locally administered drug containing phenylephrine.

The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

6.5.2 Other Concomitant Medications

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required for the wellbeing of the Participant.

6.6 Dose Modification

Dose modifications are not planned in this study.

6.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to Participants after they leave the study.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a clinically significant finding is identified, the Investigator or qualified designee will determine if the Participant should continue with the study treatment and if any change in Participant management is needed, and/or if they should remain in the study. Any new clinically relevant finding should be reported as an AE.

7.1 Discontinuation of Study Treatment

The Investigator may use their discretion in deciding whether to discontinue the Participant from the study. If the Participant is discontinued from the study early, see Table 3 for data to be collected at the time of study discontinuation. The reason that the study treatment is stopped should be documented on the appropriate eCRF.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants who meet any of the following criteria should not receive further study treatment and should be exited from the study. See Table 3 for data to be collected at the time of Study Exit.

- Investigator or Sponsor (or its designee) decides to discontinue Participants from the study for safety, behavioral, compliance, or administrative reasons.
- Parent/legal guardian of Participant indicates that they no longer want the Participant to participate in the study. If the parent/legal guardian of the Participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Notification of early Participant withdrawal from the study and the reason for discontinuation will be clearly documented and noted in the eCRF. If the Participant exits the study prior to the Day 28 Study Exit visit, all of the Day 28 final measurements should be performed and recorded on the appropriate eCRF.

7.3 Lost to Follow-up

A Participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a Participant fails to return to the study center for a required study visit:

- The study center must attempt to contact the parent/caregiver of the Participant and reschedule the missed visit as soon as possible and counsel the parent/caregiver of the

Participant on the importance of maintaining the assigned visit schedule and ascertain whether or not he/she wishes the Participant to continue in the study.

- Before a Participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the parent/caregiver of the Participant (where possible, 3 telephone calls and, if necessary, a certified letter to the Participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the Participant's medical record.
- Should the Participant continue to be unreachable, he/she will be considered to have withdrawn from the study and not returning for scheduled visits.

8.0 STUDY ASSESSMENTS AND PROCEDURES

This section provides a high-level summary of the study assessments to be performed. For details as to when these assessments are performed see Table 3.

- Study procedures and their timing are summarized in Table 3.
- Protocol waivers or exemptions are not allowed.
- Safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the Participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Table 3, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential Participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all Participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the Participant's routine clinical management (eg, audiology hearing test) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in Table 3.

8.1 Efficacy Assessments

Pneumatic otoscopy* to evaluate each TM for:

- TM: intact, perforated
- Color (check all that apply): gray, pink, pale yellow, white, amber, blue
- Translucency: translucent, opaque, semi-opaque
- Mobility: none, 1+, 2+, 3+, 4+
- Air fluid interface: yes, no
- Distinct erythema: yes, no
- Position: neutral, retracted, 1+ bulging, 2+ bulging, 3+ bulging
- Otorrhea: no, serous, purulent

*Note: Trained otoscopists who have undergone comprehensive educational program (ePROM, enhancing proficiency in otitis media) for training in the diagnosis of AOM will perform the otoscopy assessments in this study. This training includes training on cerumen removal, which is required (as needed) prior to performing pneumatic otoscopy.

Tympanometry will be performed, when possible, to assess middle ear function (ie, TM mobility, ET function) by measuring the amount of sound energy reflected back when a small probe is placed in each ear canal. The output of the right ear and left ear tympanometry will be a

tympanogram tracing recorded using a 226 Hz probe tone and a positive (+300 decaPascals [daPa]) to negative (-600 daPa) air-pressure sweep at fast speed. Each tympanogram will be classified as Type A (normal), Type B (abnormal), or Type C (abnormal).

AOM-SOS score will be recorded daily by parent/caregiver during the 10-day course of study treatment and antibiotics, and recorded in-clinic at Day 4, Day 12, and Day 28.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in Table 3.

8.2.1 Physical Examinations

- A complete physical examination will be performed to assess any physical abnormalities and will include, at a minimum, assessment of the following body systems: overall status of the skin, head, neck, trunk, eyes, ears, heart, and lungs (eg, breathing sounds), abdomen, extremities, and lymph nodes.
- Physical examination will also include visual examination of the nasopharynx and oropharynx using a light source (for local effects).
- Height and weight will be measured and recorded on Day 1.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Temperature (as Celsius or Fahrenheit degrees) will be assessed and method obtained recorded.
- Respiration rate (per minute) will be measured by counting at least 30 seconds and multiplying accordingly.
- Pulse rate (beats/minute) will be assessed after the Participant has been at rest (seated) for approximately 5 minutes in a quiet setting without distractions with a completely automated device. Manual techniques will be used only if an automated device is not available. A total of 1 pulse reading should be recorded.

8.2.3 Otoscopy

Pneumatic otoscopy and an endoscope-iPhone application that captures a video segment will be performed to assess the appearance of the TM.

8.2.4 Acute Otitis Media Symptom Burden

Parents/caregivers will record the AOM symptom burden daily during the 10-day course of study treatment and antibiotics using the 5-question version of the AOM-SOS Scale. Each of the following 5 questions will be rated on a 6-point Likert scale (0 [no], 1 [almost none], 2 [a little], 3 [some], 4 [a lot], and 5 [an extreme amount]) (total score ranges from 0 to 25): (1) Over the past 12 hours, has your child been tugging, rubbing, or holding the ear(s) more than usual?,

(2) Over the past 12 hours, has your child been crying more than usual?, (3) Over the past 12 hours, has your child been more irritable or fussy than usual?, (4) Over the past 12 hours, has your child been having more difficulty sleeping than usual?, (5) Over the past 12 hours, has your child been having fever or feeling warm to touch?

8.3 Other Assessments

1. Otalgia (per Investigator judgment in consultation with parent/caregiver): yes, no. Information used by the Investigator to confirm diagnosis. Data will be collected in the eCRF and summarized.
2. Endoscopic examination with image capture of each ear when possible, using an endoscope iPhone application (Pitt CMU iTM). Information used by the Investigator to confirm agreement of findings with Sub-investigators. Data will not be collected in the eCRF or analyzed.
3. Parent/caregiver's input on Device Experience Questionnaire. Data will be collected in the eCRF and summarized in data listings.

8.4 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

Adverse events will be reported by the parent/caregiver of the Participant.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the Participant to discontinue the study treatment or study (see Section 7.0).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the time of signed informed consent obtained until the Study Exit.

All AEs will be collected from the time of signed informed consent obtained until the Study Exit.

Medical occurrences that begin before the start of study treatment but after obtaining signed informed consent will be recorded as pretreatment-emergent AEs in the AE section of the eCRF.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, within 30 days of Study Exit, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the parent/caregiver of the Participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each Participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the Participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of Participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.4.5 Adverse Events of Special Interest

Not applicable.

8.4.6 Medical Device Incidents (Including Malfunctions)

Instructions for documenting Medical Device Incidents are provided in Appendix 4.

Medical devices are being provided for use in this study for delivering the study treatment via pMDI. In order to fulfill regulatory reporting obligations worldwide, the Investigator is

responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.4.3 and Appendix 3 of the protocol.

8.4.6.1 Time Period for Detecting Medical Device Incidents

- Medical Device Incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a Participant has discontinued from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting Medical Device Incidents is provided in Appendix 4.

8.4.6.2 Follow-up of Medical Device Incidents

- All Medical Device Incidents involving an AE will be followed and reported in the same manner as other AEs (see Appendix 3). This applies to all Participants, including those who discontinue study treatment.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.4.6.3 Prompt Reporting of Medical Device Incidents to Sponsor

- Medical Device Incidents will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a Medical Device Incident.
- The Medical Device Incident Report Form will be sent to the Sponsor by email.
- The same individual will be the contact for the receipt of medical device reports and SAE.

8.4.6.4 Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB.

8.5 Treatment of Overdose

It is unknown what dose of study treatment within a 24-hour time period would be considered an overdose. Both active ingredients in the study treatment are endogenous to the human respiratory system in very large quantities compared with the maximum study treatment dose of 20 mg per day of surfactant. Even if a Participant were to be administered an entire canister of the study treatment into the nostrils in 1 day, the total exposure to the active pharmaceutical ingredient would be 250 mg (up to approximately 35 mg/kg for a 6 to 24-month old child who usually weighs approximately 7 to 13 kg), which is far less than exposures on a mg/kg basis for approved surfactant products that are usually given over 1 to 2 days (see Table 4 of the IB).

HFA-134a is not endogenous to the human respiratory system. Symptoms potentially related to misuse or inhalation abuse are: anesthetic effects, light-headedness, dizziness, confusion, incoordination, drowsiness, unconsciousness, irregular heartbeat with a strange sensation in the chest, heart thumping, apprehension, feeling of fainting, dizziness, or weakness. Vapors are heavier than air and can cause suffocation by reducing oxygen available for breathing. However, the maximum amount of 10 mL of HFA-134a per study treatment canister would not be sufficient exposure to be considered an overdose. If symptoms described above were experienced with a suspected HFA-134a overdose, the suggested treatment would be to deliver oxygen and other necessary supportive care per the Investigator's judgment.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the Participant for any AE/SAE for at least 2 days.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.6 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary objective of this study is to demonstrate safety, tolerability, and efficacy of intranasal OP0201 compared with placebo in accelerating AOM resolution by reducing and/or eliminating MEE or in reducing the likelihood of MEE (OME) in infants and children and accordingly reducing the likelihood of AOM recurrences during follow-up when given as an adjunct treatment to oral antibiotics.

The primary efficacy endpoint family consists of 2 endpoints: (1) no bulging of the TM at the Day 4 Visit as assessed by pneumatic otoscopy, the most influential outcome in the overall assessment of efficacy of OP0201 as a treatment for AOM, and (2) no MEE at the Day 12 Visit as assessed by pneumatic otoscopy, the most influential outcome in the overall assessment of efficacy of OP0201 as a treatment to prevent OME. The hypothesis set is as follows:

Null hypothesis (AOM treatment):

There is no difference between treatment groups in proportion of Participants with no bulging of the TM at the Day 4 Visit.

Alternative hypothesis (AOM treatment):

There is a difference between treatment groups in proportion of Participants with no bulging of the TM at the Day 4 Visit.

Null hypothesis (OME reduction):

There is no difference between treatment groups in proportion of Participants with no MEE at the Day 12 Visit.

Alternative hypothesis (OME reduction):

There is a difference between treatment groups in proportion of Participants with no MEE at the Day 12 Visit.

9.2 Power Calculation

The power calculation is based on a 2-sided Pearson chi square test of each of the 2 endpoints in the primary efficacy endpoint family and control of Type 1 error using the step-up Hochberg procedure.[(14)] The minimally important difference in proportions for both endpoints is approximately 0.25. With 70 Participants randomized per treatment group, and assuming a 12% dropout rate with dropouts counted as failures, this Phase 2a study will have 87% power to detect a treatment effect in at least 1 of the 2 endpoints assuming 40% of placebo-treated Participants will have no bulging TM at Day 4 and 30% of placebo-treated Participants will have no MEE at Day 12.

9.3 Populations for Analyses

Four populations will be considered. The screened population will be all Participants whose parent/legal guardian signs the ICF. Safety data and secondary efficacy endpoints will be analyzed using the safety population defined as all Participants who received at least 1 intranasal spray of study treatment. The intent-to-treat (ITT) population is defined as all randomized Participants and will be used to assess the primary efficacy endpoint family. The per-protocol population is defined as the subset of the ITT population who have no protocol violations affecting the primary efficacy endpoint family and will be used to confirm results from the primary efficacy endpoint family.

9.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the Participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary efficacy endpoints.

In general, categorical variables (including binary outcomes) will be summarized as frequencies and percentages and will be analyzed using logistic regression to control for covariates, including the randomization stratifiers. Continuous variables will be summarized by numbers of observations, means, measures of variances, percentiles, and ranges and will be analyzed using general linear models to control for covariates. All statistical tests will be 2-sided with 0.05 significance levels.

9.4.1 Efficacy Analyses

The analysis of the primary efficacy endpoint family will compare the 2 treatment groups (OP0201, placebo) with respect to the proportion of Participants with no bulging of the TM at the Day 4 Visit as well as the proportion of Participants with no MEE at the Day 12 Visit using the ITT population for which Participants 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. A sensitivity analysis will be done that defines the endpoints as no bulging of the TM at the Day 4 Visit and no recurrence of bulging TM throughout the remainder of the study, and no MEE at the Day 12 Visit and no recurrence of MEE throughout the remainder of the study. Sensitivity analyses will also be done using the per-protocol population. Treatment groups will be statistically compared using generalized estimating equations (GEE), if possible, with an alternative method (eg, logistic regression) at each visit as an alternative if GEE convergence cannot be achieved. Randomization stratifiers (daycare attendance [yes, no] and age group [≥6 to <12 months, ≥12 to ≤24 months]) and degree of TM bulging at baseline will be covariates. Tympanic membrane bulging at baseline will also be evaluated as a potential effect modifier.

The step-up Hochberg procedure will be used to control the familywise Type 1 error. Specifically, the endpoint with the highest p-value will be tested first at 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 1 of the 2 endpoints in the primary efficacy endpoint family is significant

Descriptive statistics will be provided for the primary efficacy endpoint family by the following sub-groups: age stratum (≥6 to <12 months, ≥12 to ≤24 months), race (Caucasian, non-Caucasian), gender (male, female), laterality of disease (unilateral, bilateral), 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 (yes, no), and daycare attendance stratum defined as exposure to 3 or more children outside of the home for 10 or more hours per week (yes, no).

All secondary efficacy endpoints will be evaluated in the safety population, without adjustment for multiplicity; therefore, p-values for these endpoints will be used only to aid in decision-making regarding whether any should be elevated in importance in future studies. These endpoints are:

- No MEE assessed at the Day 4 Visit and the Day 28 Visit by pneumatic otoscopy.
- No bulging of the TM assessed at the Day 12 Visit and the Day 28 Visit by pneumatic otoscopy.
- Normal tympanogram (Type A) assessed at the Day 4 Visit, the Day 12 Visit, and the Day 28 Visit 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 by in-clinic AOM-SOS score assessments.
- Change from baseline in AOM-SOS score over the planned 10-day treatment period by parent/caregiver diary data.
- At least a 50% reduction from baseline in the AOM-SOS score assessed at the Day 4 Visit, the Day 12 Visit, and the Day 28 Visit by in-clinic AOM-SOS score assessments.
- AOM treatment failure (clinical failure)* at the Day 12 Visit.
- 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.
- AOM recurrence defined as those with clinical success# at the Day 12 Visit and who return for an interim/sick visit from Day 17 through Day 28 and have AOM.

*Treatment failure is defined as (1) moderate to severe bulging of the TM (Key Action Statement 1A[11]), or (2) mild bulging of TM and recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B[11]), or (3) mild bulging of the TM and intense erythema of the TM (Key Action Statement 1B[11]).

#Clinical success for AOM relapse and AOM recurrence endpoints is defined as (1) no moderate to severe bulging of the TM (Key Action Statement 1A[11]), and (2) no mild bulging of the TM

and no recent (less than 48 hours) onset of ear pain (otalgia) (Key Action Statement 1B[11]), and (3) no mild bulging of the TM and no intense erythema of the TM (Key Action Statement 1B[11]).

For the AOM cure endpoint, a sensitivity analysis will be done where AOM cure will be defined as AOM-SOS score = 0.

Treatment groups will be statistically compared on proportions using GEE (or an alternative method), and analyses of differences in means will be done using either general linear models or mixed models for repeated measures to control for covariates.

9.4.2 Safety Analyses

Safety will be assessed by incidence, seriousness, severity, and relatedness to study treatment of AEs and shifts from baseline (normal, abnormal) in vital signs, physical examination, and examination of the nasopharynx and oropharynx for local effects.

The Medical Dictionary for Regulatory Activities will be used to code AEs to system organ class (SOC) and preferred term. An AE that began or worsened in severity after first dose of study treatment and no later than 2 calendar days after the last dose of study treatment will be considered a treatment-emergent adverse event (TEAE).

Treatment-emergent adverse event incidence will be tabulated by primary SOC and by preferred term within each primary SOC. Summary tables will be provided for all TEAEs, serious AEs, treatment-related TEAEs and all AEs leading to discontinuation of study treatment.

No formal testing of treatment group differences will be performed for AEs.

Shifts from baseline in vital signs, physician examination, nasopharynx and oropharynx examination results will be summarized for each visit.

9.5 Interim Analyses

No interim analysis is planned.

9.6 Safety Monitoring Committee

An SMC will be established for the purpose of monitoring the safety of Participants in this study. The SMC will review blinded safety data for all Participants when approximately 25% of enrolled Participants have completed Day 12. 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 separate charter document.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
ANOVA	Analysis of variance
AOM	Acute otitis media
AOM-SOS	Acute Otitis Media Severity of Symptoms
BID	Twice daily
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CP	Cholesteryl palmitate
CRF	Case report form
DPPC	Dipalmitoylphosphatidylcholine
eCRF	Electronic case report form
ET	Eustachian tube
ETD	Eustachian tube dysfunction
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Processes
HFA-134a	Hydrofluoroalkane-134a
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
MEE	Middle ear effusion
OME	Otitis media with effusion
pMDI	Pressurized metered dose inhaler
SAE	Serious adverse event
SMC	Safety Monitoring Committee
SOC	System organ class
TEAE	Treatment-emergent adverse events
TM	Tympanic membrane

Abbreviation	Definition
w/w	Weight/weight

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to Participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 5). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the Participant's parent/legal guardian and answer all questions regarding the study.
- The parent/legal guardian of the Participant must be informed that participation is voluntary. The Participant's parent/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center.
- The research record must include a statement that written informed consent was obtained before the Participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the Participant's parent/legal guardian.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any Participant records or datasets that are transferred to the Sponsor will contain the identifier only; Participant names or any information which would make the Participant identifiable will not be transferred.
- The Participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the Participant.
- The Participant must be informed that his/her research records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Administrative Structure

See Section 9.6 for information regarding the SMC.

Medical Monitor

[redacted]

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. The study will be registered on clinicaltrials.gov and appropriate reporting to ensure compliance with clinicaltrials.gov will be met.

Data Quality Assurance

- All Participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, daily diary data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Monitoring will be carried out as determined by the risk assessment process conducted on the study.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of Participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's Participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes

to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the Participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of Participants by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice. Novus Therapeutics, Inc. as the Sponsor, has proprietary interest in the study and thus will be involved in reviewing, at a minimum, any abstract or manuscript prior to submission in order to allow the Sponsor to protect proprietary information and to provide comments. For this study, authorship and abstracts or manuscript composition will reflect joint cooperation between the Investigator and Novus Therapeutics, Inc. personnel. Authorship will be (1) established prior to the writing of abstracts or manuscripts, (2) determined by mutual agreement and (3) in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Events

Adverse Event Definition
• An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a Participant. • An AE that occurs after informed consent is signed and prior to exposure to study treatment is a pretreatment AE. • An AE that first occurs or worsens in severity after informed consent is signed and occurs after administration of study treatment, whether or not considered related to the study treatment, is a TEAE.

Events Meeting the Adverse Event Definition
• Any safety assessments (eg, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the Participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the Participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the Participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the Participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the Participant's medical records in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all Participant identifiers, with the exception of the Participant number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- Whether the AE resolved or improved with stopping use of the investigational product. Judgment should be used if multiple products are discontinued at the same time.
- Positive rechallenge.
- Positive dechallenge (resolution upon stopping suspect study treatment, in the absence of other intervention or treatment).
- The causal relationship between at study treatment and the AE will be assessed using 1 of the following categories:

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

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section).
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a Participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator by telephone.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor/SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Appendix 4 Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study (see Section 6.1) for the list of Sponsor medical devices.

Medical Device Incident Definition

- A Medical Device Incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a Participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness.
- Permanent impairment of body function or permanent damage to body structure.
- Condition necessitating medical or surgical intervention to prevent 1 of the above.
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents

- A Participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A Participant's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A Participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting

- Any Medical Device Incident occurring during the study will be documented in the Participant's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the eCRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE eCRF page will be completed as described in Appendix 3.
- The eCRF will be completed as thoroughly as possible and signed by the Investigator before transmittal to the Sponsor or designee.
- It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

Appendix 5 Signature of Investigator

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 NO: OP0201-C-006

VERSION: Amendment 3

This protocol is a confidential communication of Novus Therapeutics, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Sponsor or CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Appendix 6 Protocol Amendment History

Amendment 2 (05 June 2019)

Overall Rationale for the Amendment:

Novus Therapeutics filed the original protocol to the US Food and Drug Administration (FDA) Investigational New Drug (IND) application on 21 January 2019. On 22 March 2019 the Biometric team (ie, Biostatisticians) at FDA sent an email communication to Novus with some suggested changes to this exploratory study, which this amendment addresses. These changes include (1) use of a hierarchical gatekeeping procedure for testing the primary and key secondary efficacy endpoints, (2) use of a sensitivity analysis of the primary efficacy endpoint in which responders must have no bulging of the tympanic membrane (TM) at the Day 4 Visit and no recurrence of bulging TM through the remainder of the study, (3) a clear definition of clinical success at the Day 12 Visit for the acute otitis media (AOM) relapse and AOM recurrence efficacy endpoints, and (4) a clear definition of treatment failure (clinical failure) in Section 6.1.4. In addition, the sample size for the study has been increased to approximately 140 Participants planned for enrollment to improve the likelihood of detecting the minimum clinically important difference between treatment groups. Relevant changes to the power calculation have been made due to the change in sample size.

Table 5 Description of Changes in Amendment 2

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Rationale and Section 2.1 Study Rationale	Updated to state that AOM resolution for primary and secondary efficacy endpoints will be determined by no bulging of the tympanic membrane rather than by a reduced proportion of children with bulging tympanic membrane(s).	To define AOM resolution for primary and secondary efficacy endpoints based on no bulging of the tympanic membrane as this is how AOM resolution is standardly assessed by clinicians. To define a minimum clinically important difference in the proportions between treatment groups for the primary efficacy endpoint.
Section 1.1 Overall Design, Number of Participants and Statistical Methods	Updated time window from at least 72 hours to at least 48 to 72 hours after which concordant	To address FDA request to further clarify description of treatment failure.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design Section 9.0 Statistical Considerations (9.1 Statistical Hypothesis, 9.2 Power Calculation, 9.3 Populations for Analyses, 9.4 Statistical Analyses [9.4.1 Efficacy and 9.4.2 Safety Analyses])	antibiotic therapy will be administered in case of treatment failure. Updated number of study Participants from approximately 50 to approximately 140. Updated relevant statistical sections.	To ensure that study will have 80% power to detect an approximate 0.25 difference (based on a 40% placebo response rate) in proportions for the primary efficacy endpoint using a 2-sided significance level of 0.05. Relevant changes to the power calculation have been made due to the change in sample size. Definitions for safety population, intent-to-treat population, per-protocol population, and treatment-emergent adverse events have been updated to align with the Statistical Analysis Plan. To include a hierarchical gatekeeping procedure for testing the primary and key secondary efficacy endpoints. To update text for sensitivity and subgroup analyses. To align definitions of efficacy endpoints to match Section 1.1 and Section 3.0 (see below).
Section 1.1 Objectives and Endpoints and Section 3.0 Study Objectives and Endpoints	Updated objectives and endpoints.	To provide rationale for choice of primary and key secondary efficacy endpoints. To define AOM resolution based on no bulging of the tympanic membrane and to define OME prevention based on no MEE. To more clearly define efficacy endpoints based on a consistent convention to state the variable being assessed, timepoint at

Section # and Name	Description of Change	Brief Rationale
		which variable will be assessed and how variable will be assessed. To remove proportion of Participants with AOM, OME or no MEE on Days 4, 12 and 28 as this was inadvertently listed as a secondary endpoint. To address FDA request to define clinical success at the Day 12 Visit for the AOM relapse and AOM recurrence efficacy endpoints. All reference to AOM-SOS score was removed from 3 secondary endpoints. Definitions of "treatment failure at Day 12 Visit" and "clinical success" relating to the AOM recurrence and relapse efficacy endpoints are now anchored to the entry criteria definition of AOM, which is: "moderate to severe bulging of the TM, or mild bulging of TM and recent (less than 48 hours) onset of ear pain (otalgia), or mild bulging of the TM and intense erythema of the TM."
Section 5.1 Inclusion Criteria	Added the term "otalgia" to describe ear pain.	To ensure consistency with data field captured in the eCRF.
Section 6.1.1 The Drug-device Study Treatment	Updated 60 actuations per canister to 100 actuations per canister.	Additional dose content uniformity (DCU) test data supports the OP0201 canister can deliver up to 100 actuations per canister.

Section # and Name	Description of Change	Brief Rationale
Section 6.1.4 Standard Antibiotic	Updated description for treatment failure.	To address FDA request to further clarify description for treatment failure.
Section 6.4 Study Treatment Compliance	Updated on Days 4 and 12 to at the Day 4 Visit and the Day 12 Visit.	To ensure consistent format within document.
Section 8.1 Efficacy Assessment Section 8.3 Other Assessments	Deleted other assessments from Section 8.1 Efficacy Assessments and added Section 8.3 Other Assessments.	Other assessments including otalgia, endoscopic examination with iPhone application and parent/caregiver Device Experience Questionnaire were inadvertently listed under Section 8.1 Efficacy Assessments. Assessments have been moved to newly created Section 8.3 Other Assessments.
Section 9.4.3 Other Analyses	Deleted this section.	No analysis will be included in the execution of the Statistical Analysis Plan for the parent/caregiver Device Experience Questionnaire.
Section 10.0 References	Francis et al, 2018 citation added to reference list.	Reference added to support rationale for key secondary endpoint.

Amendment 1 (8 March 2019)

Overall Rationale for the Amendment:

The purpose of Protocol Amendment 1 is to provide clarification and updates to the original version of the protocol.

Table 6 Description of Changes in Amendment 1

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Overall Design	Tympanometry assessment changed to when possible	Satellite sites to be added cannot perform the tympanometry assessment due to unavailability of tympanometry diagnostic tool
Section 1.1 Number of Investigators and Study Centers	Up to 3 satellite sites to be added	To support enrollment
Section 1.1 Safety Monitoring Committee	Changed wording to indicate that SMC will meet when approximately 25% of Participants have completed D12	To account for slower enrollment than planned
Section 1.3 Schedule of Activities	Tympanometry assessment changed to when possible	Satellite sites to be added cannot perform the tympanometry assessment due to unavailability of tympanometry diagnostic tool
Section 1.3 Schedule of Activities	Removed in clinic for safety observation	Participants enrolled at the satellite sites may be observed for safety in Participant's home
Section 4.1 Overall Design	Tympanometry assessment changed to when possible	Satellite sites to be added cannot perform the tympanometry assessment due to unavailability of tympanometry diagnostic tool
Section 5.1 Inclusion Criteria	Re-ordered inclusion	Ensure consistency with data fields captured in eCRF
Section 5.1 Inclusion Criteria	Added criteria that parent/legal guardian have a smartphone or	Electronic survey is mandatory for Participants

Section # and Name	Description of Change	Brief Rationale
	internet access to receive the electronic survey	
Section 6.1.1 The Drug-device Study Treatment	Removed in clinic for first dose administration	Participants enrolled at the satellite sites will be administered the first dose in Participant's home
Section 6.5 Concomitant Therapy	Removed time of administration	Ensure consistency with data fields captured in eCRF
Section 8.1 Efficacy Assessments	Added semi-opaque to translucency category of pneumatic otoscopy	Ensure consistency with data fields captured in eCRF
Section 8.1 Efficacy Assessments	Tympanometry assessment changed to when possible	Satellite sites to be added cannot perform the tympanometry assessment due to unavailability of tympanometry diagnostic tool
Section 8.2.2 Vital Signs	Changed time at rest to approximately 5 minutes	Given age of Participants it is realistically difficult to have them sit still for exactly 5 minutes as originally specified
Section 8.2.2 Vital Signs	Removed television and cellphones as prohibited distractions	Given age of Participants, using a cellphone or iPad will assist in keeping them at rest
Section 9.6 Safety Monitoring Committee	Change wording to indicate that SMC will meet when approximately 25% of Participants have completed D12	To account for slower enrollment than planned
Section 9.4.1 Efficacy Analysis	Descriptive statistics updated to primary and key secondary efficacy endpoints. Gender and race were removed from the sub-groups	To streamline the number of planned subgroup analyses