CLINICAL REVIEW

Application Type	Original NDA
Application Number	207986
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Division / Office	CDER/OND/OAP/DAIP
Reviewer Name	Mark Needles, M.D.
Review Completion Date	11/19/2015
Established Name	6% ciprofloxacin otic suspension
Proposed Trade Name	OTIPRIO™
Therapeutic Class	Fluoroquinolone Antibacterial
Applicant	Otonomy, Inc.
Formulation	Otic suspension 6% (60 mg/mL) ciprofloxacin
Dosing Regimen	Single intratympanic administration of 0.1 mL (6 mg) into each affected ear
Indication	Treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube placement
Intended Population	Patients 6 months of age or older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend that Otiprio (6% ciprofloxacin otic suspension) be approved for the treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube (TT) placement. Data from two independent, adequate, and well-controlled Phase 3 studies support the efficacy of Otiprio for the proposed indication. Both Phase 3 studies demonstrated that treatment with Otiprio was superior to sham (air injection) when given as a single intratympanic administration of 0.1 mL (6 mg) into each ear at the time of myringotomy and TT placement. Findings from a smaller Phase 1b study also provide supportive evidence for efficacy.

1.2 Risk Benefit Assessment

Two Phase 3 studies, Studies 201-201302 and 201-201303, support the efficacy of Otiprio for the treatment of middle ear effusion in pediatric patients with otitis media requiring TT placement. The primary efficacy endpoint, the proportion of study treatment failures through the Day 15 Visit, favored Otiprio treatment over sham and was statistically significant in both studies. A beneficial effect for Otiprio treatment was noted in the <2 years and >2 years age strata; however, statistical significance was noted in only the younger age stratum, which had the greatest treatment effect. A statistically significant difference favoring Otiprio treatment was noted for the proportion of study treatment failures through the Day 4, Day 8, and Day 29 Visits, as well as for the time to study treatment failure through the Day 15 Visit. A beneficial effect favoring Otiprio treatment was noted for otorrhea-only treatment failure through the Day 15 Visit, but this was not statistically significant in Study 201-201302. A statistically significant difference favoring Otiprio treatment was noted in both studies for the proportion of treatment failures through the Day 4, Day 8, Day 15, and Day 29 Visits due to observed or presumed otorrhea (defined as otorrhea observed by the blinded assessor or antibiotic therapy given for an otorrhea indication). In both studies, a greater proportion of those treated with Otiprio compared to sham had a microbiological response through the Day 15 and Day 29 Visits.

Two Phase 3 studies and a smaller Phase 1 b study (Study 201-201101) support the safety of Otiprio for the treatment of middle ear effusion in pediatric patients, at least 6 months of age, with otitis media requiring TT placement. The same dose as selected for

marketing was evaluated in the two Phase 3 studies, and its use was found to be both safe and well tolerated. Pyrexia was the most frequently reported treatment emergent adverse event (TEAE) in patients treated with Otiprio. Teething, nasopharyngitis, irritability, and rhinorrhea were the most frequent reported TEAEs in patients treated with Otiprio at an incidence higher than sham. Data from the otoscopic examinations (evaluation of health of individual ears and TT patency), the tympanometry assessments (evaluation of middle ear status and TT patency), and the audiometry assessments (evaluation of the possible level of hearing loss) all supported the safety of single intratympanic administration of Otiprio for the proposed treatment indication.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk management strategies other than monitoring and reporting of adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

6% ciprofloxacin otic suspension is a fluoroquinolone antibacterial suspension. Ciprofloxacin is the single active ingredient and like other fluoroquinolones, the mechanism of action is inhibition of DNA gyrase and topoisomerase IV. The product was referred to as OTO-201 during the development process. Otiprio and OTO-201 will be used interchangeably throughout this review to reference the product. Compared to other otic ciprofloxacin preparations, the dosage form, treatment indication, regimen, and route of administration are new.

OTO-201 is a sterile, preservative-free, otic suspension of 6% (60 mg/mL) ciprofloxacin in buffered solution containing a mucoadhesive glycol polymer called poloxamer 407. The poloxamer 407 vehicle in this formulation exhibits thermosensitive properties allowing the product to exist as a liquid at room temperature and transition to a gel after exposure to body temperature in the middle ear. The product is intended as a treatment for pediatric patients, age 6 months and older, with otitis media with middle ear effusion

undergoing TT placement. The recommended dosage regimen, for all patients, is single intratympanic administration of 0.1 mL (6 mg) into each affected ear.

OTO-201 is described by the applicant as a sustained-exposure suspension of ciprofloxacin in poloxamer 407 solution. Specifically, (b) (4)

6% ciprofloxacin otic suspension is formulated for a new route of administration, specifically intratympanic administration. Intratympanic administration is a method of otic administration performed during myringotomy and tympanostomy tube (TT) placement surgery. This route of administration is intended to follow suctioning of middle ear effusion and refers to injecting the drug through the myringotomy site (intratympanic injection) prior to the actual placement of the TT.

Established Name:	6% ciprofloxacin otic suspension
Proposed Trade Name:	OTIPRIO™
Pharmacological Class:	Topical fluoroquinolone antibacterial
Indication:	Treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube placement
Dosing Regimen:	Single intratympanic administration of 0.1 mL (6 mg) into each affected ear
Age Groups:	Pediatric patients 6 months of age or older

2.2 Tables of Currently Available Treatments for Proposed Indications

Otitis media with effusion (OME) is most often seen in children between the ages of 6 months and 4 years with as many as 90% of all children affected at least once by school age.[1] It is a common cause of hearing loss in children, and persistent hearing impairment can impact normal speech, language, and cognitive development. Most episodes of OME are brief and self-limiting; however, spontaneous resolution is unlikely to occur within a year if bilateral and persistent for at least 3 months (chronic OME).[1] Surgical intervention, namely myringotomy surgery with tympanostomy tube (TT) placement, is offered to children with chronic OME especially if accompanied with

hearing difficulties or symptoms impacting the child's behavior and development.[2] Tympanostomy tube otorrhea is the most common complication of tympanostomy tube surgery, occurring in 16% of children within 4 weeks of placement (range, 8.8% to 42.0%).[3] It is difficult to determine clinically if early post-operative drainage is a manifestation of a middle ear infection.

Historically, 40 to 60% of middle ear effusions are sterile in patients with chronic OME.[4-5] Among patients with positive middle ear effusion cultures, the same bacteria responsible for acute otitis media (AOM) are found in OME.[5] The most common bacteria responsible for acute otitis media (AOM) are the following nasopharyngeal pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[6] Patients with AOM with tympanostomy tubes (AOMT) can have external auditory canal pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* implicated because the bacteria can migrate into the middle ear compartment through the non-intact tympanic membrane.[7]

Currently, there are no products that have an FDA approved indication for treatment of patients with otitis media with middle ear effusion undergoing TT placement. Topical antibiotic ear drops with other FDA approved indications - acute otitis media with tympanostomy tubes (AOMT) or acute otitis externa (AOE) – are used off-label for the proposed indication. Ciprodex® (0.3% ciprofloxacin and 0.1% dexamethasone suspension) and Floxin® otic (0.3% ofloxacin solution) are the only available products with FDA-approved indications for the treatment of AOMT.

2.3 Availability of Proposed Active Ingredient in the United States

Ciprofloxacin

- Ciprofloxacin HCl 0.2% otic solution (CETRAXAL®), indicated for the treatment of AOE due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus*
- Ciprofloxacin HCl 0.3% and dexamethasone 0.1% otic suspension (CIPRODEX® Otic Suspension), indicated for the treatment of AOE in pediatric (age 6 months and older), adults, and elderly patients due to susceptible isolates of *S. aureus* and *P. aeruginosa*; and for the treatment of AOMT in pediatric patients (age 6 months and older) due to susceptible isolates of *S. aureus, Streptococcus pneumoniae, Haemophilus influenza*e, *Moraxella catarrhalis*, and *P. aeruginosa*

- Ciprofloxacin HCl 0.2% and hydrocortisone 1% otic suspension (CIPRO HC® OTIC), indicated for the treatment of AOE due to susceptible strains of *P. aeruginosa, S. aureus*, and *Proteus mirabilis*
- Ciprofloxacin HCl 0.3% ophthalmic solution (CILOXAN®), indicated for the treatment of corneal ulcers caused by susceptible strains of *P. aeruginosa*, *Serratia marcescens*, *S. aureus*, *Staphylococcus epidermidis*, *S. pneumoniae*, and viridans group streptococci; and for the treatment of bacterial conjunctivitis caused by susceptible strains of *H. influenzae*, *S. aureus*, *S. epidermidis*, and *S. pneumoniae*
- Ciprofloxacin HCl 0.3% ophthalmic ointment (CILOXAN®), indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of *S. aureus, S. epidermidis, S. pneumonia*, viridans group streptococci, and *H. influenzae*.
- Ciprofloxacin extended-release tablet (CIPRO XR®), indicated for the treatment of uncomplicated and complicated urinary tract infections in adult patients (≥18 years of age)
- Ciprofloxacin tablet and oral suspension (CIPRO®), indicated for the treatment of urinary tract infections in adult patients (≥18 years of age), acute uncomplicated cystitis in adult female patients, chronic bacterial prostatitis in adult patients, lower respiratory tract infections in adult patients, skin and skin structure infections in adult patients, bone and joint infections in adult patients, complicated intraabdominal infections (in combination with metronidazole) in adult patients, infectious diarrhea in adult patients, typhoid fever in adult patients, uncomplicated cervical and urethral gonorrhea in adult patients, complicated urinary tract infections and pyelonephritis in pediatric patients (1 to 17 years of age), post-exposure inhalational anthrax in pediatric (from birth to 17 years of age) and adult patients, and plague in pediatric (from birth to 17 years of age) and adult patients.
- Ciprofloxacin for intravenous infusion (CIPRO® I.V.), indicated for the treatment of urinary tract infections in adult patients (≥18 years of age), lower respiratory tract infections in adults, nosocomial pneumonia in adults, skin and skin structure infections in adults, bone and joint infections in adults, complicated intraabdominal infections in adults (in combination with metronidazole), acute sinusitis in adults, chronic bacterial prostatitis in adults, empiric therapy for febrile neutropenic adults (in combination with piperacillin sodium), complicated urinary tract infections and pyelonephritis in pediatric patients (1 to 17 years of age), post-exposure inhalation anthrax in pediatric (from birth to 17 years of age) and adult patients, and plague in pediatric (from birth to 17 years of age) and adult patients

<u>Other Ototopical Fluoroquinolones</u>

- Ofloxacin 0.3% otic solution (FLOXIN® Otic), indicated for the treatment of otitis externa in pediatric (age 6 months and older) and adults; for the treatment of chronic suppurative otitis media in patients 12 years and older with perforated tympanic membranes; and for the treatment of AOMT in pediatric patients one year of age and older
- Finafloxacin otic suspension (XTORO®), indicated for the treatment of AOE with or without an otowick in patients 1 year of age or older

2.4 Important Safety Issues With Consideration to Related Drugs

There are no specific safety issues with topical fluoroquinolones which need to be addressed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to the development of OTO-201, (b) (4)

OTO-201 has been studied under IND 110244 which was opened on October 18, 2010 with a request for a Pre-IND meeting. The Pre-IND meeting was scheduled to take place on November 22, 2010, but this meeting was cancelled after the applicant received preliminary comments from the Agency on November 16, 2010.

The applicant submitted a Phase 1b clinical study (Study 201-201101) on August 26, 2011 and a teleconference was held with the Agency on September 23, 2011. The protocol was revised by the applicant based on the agreements reached at the teleconference, and a letter authorizing commencement of the study was submitted on October 20, 2011. The following are the pertinent items from the revised protocol that were based on the agreements reached at the teleconference:

- Inclusion of a sham control group
- Time point for the evaluation of safety data prior to enrolling patients into the 12 mg dose cohort
- Performance of audiometry assessments appropriate for age and developmental abilities in all enrolled patients

IND 110244 was placed on full clinical hold on December 13, 2011 due to nonclinical toxicology findings in guinea pigs suggesting the (b) (4) form of poloxamer 407 vehicle was associated with damage to cochlear hair cells and hearing loss. In response to the clinical hold, the applicant conducted additional animal studies and found decreased hearing loss with (b) (4) vehicle compared to the previously tested (b) (4) vehicle. The applicant changed the processing method and the clinical hold was removed on November 30, 2012.

A clinical/nonclinical End-of-Phase 2 meeting took place on September 09, 2013, and two Phase 3 clinical studies (Studies 201-201302 and 201-201303) were submitted on September 27, 2013. The following are the pertinent items included in the protocols that were based on agreements reached at the clinical/nonclinical End-of-Phase 2 meeting:

- Performance of audiometry assessments in at least 30% of patients less than 4 years of age (approximately 60 patients exposed to OTO-201)
- Include the use of systemic antibiotics in the definition of study treatment failure
- Evaluation of microbiological responses through Days 15 and 29
- Evaluation of time-to-study treatment failure through Day 15
- Evaluate the use of systemic antibiotics and missing observations as non-treatment failures in sensitivity analyses

A CMC End-of-Phase 2 meeting took place on September 19, 2013, and agreements were reached in terms of additional tests for drug substance and drug product, as well as an agreement on the stability data needed for the NDA submission.

A Pediatric Study Plan was submitted by the applicant on March 27, 2014. A request for a partial pediatric waiver for patients younger than 6 months of age and a request of a waiver of (b) (4) were included in the NDA submission.

A clinical/nonclinical Pre-NDA meeting was scheduled to take place on October 6, 2014, but this meeting was cancelled after the applicant received preliminary comments from the Agency on October 2, 2014.

A CMC Pre-NDA meeting took place on October 24, 2014, and included discussion in regards to the designation of OTO-201 as an (b) (4) suspension. The rationale for this claim was included in the NDA submission for the Agency to assess during the NDA review.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no meaningful concerns noted by this reviewer regarding the quality and integrity of the datasets. This reviewer reviewed the datasets and the applicant's analyses were verified.

There was no evidence that the studies reviewed were not conducted in accordance with acceptable clinical ethical standards. Clinical site inspections took place at four clinical investigator sites selected for large subject enrollment. Overall the study conduct and applicant's oversight appeared adequate at all four sites. All audited study data were adequately verifiable and appeared reliable as reported in the NDA. No significant deficiencies were observed at three of the audited sites; however, minor isolated discrepancies between source records and eCRF were noted at one site. Discrepancies included concomitant medications not reported to the applicant. These medications (including antibiotics) were in most instances given prior to the study. The amount of data affected was limited and unlikely had a significant impact on the overall study outcome. For further details, please refer to the review by the GCP Reviewer, John Lee, M.D.

3.2 Compliance with Good Clinical Practices

The clinical studies performed under IND 110244 (Studies 201-201101, 201-201302, and 201-201303) were conducted in accordance with the current revision of the Declaration of Helsinki and current International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

The original protocols, protocol amendments, and all supportive information were reviewed and approved by the Institutional Review Board (IRB) or Research Ethics Board (REB) for each of the centers involved in the study. The studies were initiated after full approval of the protocol was obtained from each IRB/REB and a copy of this approval received by the applicant.

3.3 Financial Disclosures

Otonomy has determined there were no financial interests or arrangements to disclose from the investigators in the clinical studies (Studies 201-201101, 201-201302, and 201-201303). Please see Section 9.4 for Clinical Investigator Financial Disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The applicant developed OTO-201 as a sterile, preservative-free, single dose ciprofloxacin suspension for the treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube placement. OTO-201 consists of 6% (60 mg/mL) ciprofloxacin suspension in buffered poloxamer 407 solution. The formulation was developed to allow for sustained exposure of ciprofloxacin in the middle ear compartment following a single intratympanic application at the time of myringotomy and TT placement.

The composition of OTO-201 is summarized in Table 4.1-1. (b) (4) .
Poloxamer 407, at the concentration utilized in the formulation, provides gel forming properties to OTO-201. Specifically, poloxamer 407 allows OTO-201 to exist as a liquid at room temperature (before administration) and transition to a gel at body temperature (upon injection into the middle ear). In order to be consistent with the natural environment of the ear, (b) (4) tromethamine and hydrochloric acid; and (b) (4) .

Table 4.1-1:
Composition of OTO-201 Drug Product

Ingredient	Quality Standard	Function	% w/w	Composition (mg/mL)
Ciprofloxacin	USP	Active ingredient	(b) (4)	60
Poloxamer 407	NF	Gel formation		(b) (4)
Sodium Chloride	USP	(b) (4)		
Tromethamine	USP			
Hydrochloric acid	NF			
Water for injection	USP			
Total			100.0	

Source: Description and Composition of the Drug Product, Module 2, Section 2.3.P, Table 2.

Buffered poloxamer vehicle was used to prepare suspensions containing (b) (4) and 6% ciprofloxacin for the nonclinical studies and the Phase 1b clinical study (Study 201-201101). After completion of the Phase 1b study, the 6% ciprofloxacin suspension in poloxamer 407 was selected for further development and used for the Phase 3 clinical studies (Studies 201-201302 and 201-201303). There were no changes to the formulation of OTO-201 (6% ciprofloxacin) during the clinical development and the same 6% ciprofloxacin formulation used in the Phase 1b and Phase 3 clinical studies is intended for commercial use. For further details, please refer to the review by the CMC Reviewer, Chunchun Zhang, Ph.D.

4.2 Clinical Microbiology

The applicant conducted investigations that supported the in vitro activity of ciprofloxacin against the common pathogens related to otitis media: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Two Phase 3 clinical studies were performed by the applicant and supported the efficacy of OTO-201 for the treatment of otitis media due to *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis.* The clinical efficacy of OTO-201 for the treatment of otitis media due to *S. aureus* or *P. aeruginosa* could only be studied in fewer than 10 patients enrolled into the Phase 3 studies. Please refer to Section 6 of this review for the summary of efficacy results from the Phase 3 studies. Please see the review by the Clinical Microbiology Reviewer, Jalal Sheikh, Ph.D., for further details on the microbiology aspects of OTO-201.

4.3 Preclinical Pharmacology/Toxicology

The applicant conducted nonclinical toxicology studies in guinea pigs. No significant ototoxicity, systemic toxicity, or dermal toxicity (dermal irritation or skin sensitization) was noted following single intratympanic administration of OTO-201 (dose range, 0.06% to 6.0%).

Nonclinical pharmacodynamics studies were performed in chinchillas with otitis media with effusion (OME) induced by *Streptococcus pneumoniae*. Chinchillas treated with a 3 day twice daily regimen of Cetraxal® or a single intratympanic administration of OTO-201 (dose range, 0.06% to 6.0%) had similar reductions in middle ear bacterial load and effusion volumes at 3 days post TT placement compared to untreated chinchillas.

Nonclinical pharmacokinetic studies were performed in guinea pigs to evaluate the middle and inner ear pharmacokinetic profiles of ciprofloxacin following single intratympanic administration of OTO-201. OTO-201 (doses range, 0.06% to 12.0%) provided a comparable middle and inner ear exposure profile to that of a 7 day twice daily regimen of Cetraxal® or Ciprodex®. Please see the review by the Pharmacology Toxicology Reviewer, James Wild, Ph.D., for further details related to the nonclinical toxicology, pharmacodynamics, and pharmacokinetic studies.

4.4 Clinical Pharmacology

Ciprofloxacin is a fluoroquinolone antibacterial. The mechanism of action of ciprofloxacin is inhibition of enzymes topoisomerase II (also known as DNA gyrase) and topoisomerase IV, which are required for bacterial DNA synthesis. No clinical pharmacology studies were conducted with OTO-201. For further details, please refer to the review by the Clinical Pharmacology Reviewer, Dakshina Chilukuri Ph.D.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5.1-1: Listing of Clinical Trials Relevant to this NDA

Study Identity	Study Objective	Study Design	Treatment Groups	Regimen/ Schedule/ Duration	Study Endpoints	No. of Subjects	Median Age (range)	Region (No. of Centers)
Study 201-201101 IND 110244 Phase1b	In pediatric subjects with bilateral MEE requiring TT placement: *Primary:* Describe the safety and tolerability of 2 dose levels of OTO-201, placebo, and sham *Secondary:* Describe the clinical activity of 2 dose levels of OTO-201, placebo, and sham	Prospective, randomized, double blind, placebo and sham-controlled, sequential dose escalation study Enrolling healthy male and female patients age 6 months to 12 years with a clinical diagnosis of bilateral MEE requiring TT placement	OTO-201: 4 mg OTO-201: 12 mg Placebo: Poloxamer 407 vehicle Sham: Syringe with air	0.2 mL intratymapnic injection into each ear Single dose during myringotomy surgery with TT placement Follow-up to day 29	*1 ^{0} Clinical activity endpoint*: Study treatment failures through Day 4, 8, and 15, and defined as the first occurrence of any of the following post-surgery events: • otorrhea • rescue medication • early termination *Safety Variables*: Frequency of AEs; Results from otoscopic exams, tympanometry, audiometry, vital signs, and physical exam	Randomized: N=83 4 mg: 21 12 mg: 19 Placebo: 22 Sham: 21 Treated: N=83 4 mg: 21 12 mg: 19 Placebo: 22 Sham: 21	1.96 years (0.6 to 10.0)	US (12)

Study Identity	Study Objective	Study Design	Treatment Groups	Regimen/ Schedule/ Duration	Study Endpoints	No. of Subjects	Median Age (range)	Region (No. of Centers)
Study 201-201302 IND 110244 Phase 3	In pediatric subjects with bilateral MEE requiring TT placement: *Primary:* Confirm the effectiveness of OTO-201 *Secondary:* Assess the safety and tolerability of OTO-201	Prospective, randomized, double blind, sham-controlled study Enrolling healthy male and female patients age 6 months to 17 years with a clinical diagnosis of bilateral MEE requiring TT placement	OTO-201: 6 mg Sham: Syringe with air	0.1 mL intratympanic injection into each ear Single dose during myringotomy surgery with TT placement Follow-up to day 29	*1^{0} Efficacy Endpoint*: Study treatment failures through Day 15, and defined as the first occurrence of any of the following events: • otorrhea treatment failure • otic treatment failure • systemic antibiotic treatment failure • lost-to-follow-up treatment failure • missed visit treatment failure *2^{0} Efficacy Endpoint*: Study treatment failure through Days 4, 8, and 29; Time-to-study treatment failure through Day 15; Otorrhea-only treatment failure through Day 15; Microbiological response through Days 15 and 29 *Safety Variables*: Frequency of AEs; Results from otoscopic exams, tympanometry, audiometry, vital signs, and physical exam	Randomized: N=266 6 mg: 179 Sham: 87 Treated: N=265 6 mg: 179 Sham: 86	1.585 years (0.50 to 12.60)	US (25), Canada (4)

Study Identity	Study Objective	Study Design	Treatment Groups	Regimen/ Schedule/ Duration	Study Endpoints	No. of Subjects	Median Age (range)	Region (No. of Centers)
Study 201-201303 IND 110244 Phase 3	In pediatric subjects with bilateral MEE requiring TT placement: *Primary:* Confirm the effectiveness of OTO-201 *Secondary:* Assess the safety and tolerability of OTO-201	Prospective, randomized, double blind, sham-controlled study Enrolling healthy male and female patients age 6 months to 17 years with a clinical diagnosis of bilateral MEE requiring TT placement	OTO-201: 6 mg Sham: Syringe with air	0.1 mL intratympanic injection into each ear Single dose during myringotomy surgery with TT placement Follow-up to day 29	*1^{0} Efficacy Endpoint*: Study treatment failures through Day 15, and defined as the first occurrence of any of the following events: • otorrhea treatment failure • otic treatment failure • systemic antibiotic treatment failure • lost-to-follow-up treatment failure • missed visit treatment failure *2^{0} Efficacy Endpoint*: Study treatment failure through Days 4, 8, and 29; Time-to-study treatment failure through Day 15; Otorrhea-only treatment failure through Day 15; Microbiological response through Days 15 and 29 *Safety Variables*: Frequency of AEs; Results from otoscopic exams, tympanometry, audiometry, vital signs, and physical exam	Randomized: N=266 6 mg: 178 Sham: 88 Treated: N=265 6 mg: 178 Sham: 87	1.535 years (0.51 to 11.63)	US (18), Canada (1)

Source: Adapted from clinical study reports for 201-201101, 201-201302, and 201-201303.

5.2 Review Strategy

The submitted clinical protocols, study reports, and relevant literature were reviewed. The protocol and efficacy data for the Phase 1b study are summarized in Section 5.3.1. For the Phase 3 studies, the protocol is summarized in Section 5.3.2 and the efficacy data summarized in Section 6. All safety data from the Phase 1b and Phase 3 studies are summarized in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 201-201101

A Prospective, Randomized, Double-Blind, Placebo- and Sham-controlled, Multicenter, Phase 1b Study of OTO-201 Given as a Single Intratympanic Injection for Intra-operative Treatment of Middle Ear Effusion in Pediatric Subjects Requiring Tympanostomy Tube Placement

Protocol 201-201101 was a prospective, randomized, double-blind, placebo- and sham-controlled, multicenter, sequential dose escalation Phase 1b study of OTO-201 for the treatment of pediatric patients with bilateral otitis media with middle ear effusion requiring TT placement. In this study, two dose levels of OTO-201 (4 mg and 12 mg) were evaluated in relation to placebo (poloxamer 407 vehicle only) and sham (empty syringe with air). The primary analytic focus for the study was to describe safety and tolerability among the four treatment groups. Clinical activity endpoints were also evaluated in order to provide supportive information related to efficacy of OTO-201. The analytic focus for the clinical activity endpoints was descriptive because the study was not adequately powered for hypothesis testing. Clinical activity data from the Phase 1b study was not integrated with data from the Phase 3 studies because of the small sample size of the Phase 1b study and the differences in the study design and OTO-201 dose.

83 patients were enrolled in the Phase 1b study. All subjects were healthy males (53 patients, 62.7%) or females (31 patients, 37.3%) age 6 months to 12 years with a clinical diagnosis of bilateral middle ear effusion requiring TT placement. A clinical diagnosis was confirmed from otoscopic examination on the day of myringotomy surgery. Cohort 1 consisted of 44 patients who were randomized using a 2:1:1 allocation ratio to receive either a 4 mg dose level of OTO-201, placebo, or sham. Cohort 2 consisted of 39 patients who were randomized using a 2:1:1 allocation ratio to receive either a 12 mg dose level of OTO-201, placebo, or sham. Table 5.3.1-1

summarizes the proportion of patient in each treatment group. Both cohorts were stratified by age (i.e., 6 months -2 years and >2 years) with the median age 2.0 years (range, 0.6 to 10.0). Enrollment of patients into Cohort 2 began after at least 18 patients in Cohort 1 completed the Day 15 visit and no safety issues were identified by the data review group.

Table 5.3.1-1:
Treatment Groups in Study 201-201101

	Cohort 1 N = 44 n (%)	**Cohort 2 N = 39 n (%)**	**Total N = 83 n (%)**
OTO-201 4 mg	21 (47.7%)	NA	21 (25.3%)
OTO-201 12 mg	NA	19 (48.7%)	19 (22.9%)
Placebo	12 (27.3%)	10 (25.6%)	22 (26.5%)
Sham	11 (25.0%)	10 (25.6%)	21 (25.3%)

Source: Adapted from clinical study report for 201-201101, Table 14.1.1.3.

Patients in the 4 mg and 12 mg OTO-201 dose groups (40 patients) were given the respective dose of OTO-201 as single bilateral 0.2 mL intratympanic injections on the day of myringotomy and TT placement (Day 1). Patients in the placebo or sham group received single bilateral 0.2 mL intratympanic injections of either OTO-201 diluent (poloxamer 407 vehicle) or air, respectively. All randomized patients were treated and given the correct randomized treatment. The treating otolaryngologist was unblinded at the time of intra-operative administration due to the appearance of the study drug. The caregivers, patients, and study staff members were blinded to study drug.

During the conduct of Cohort 1, one of the investigators reported difficulty delivering the entire 0.2 mL dose volume of study drug to a single patient. At the completion of Cohort 1, other investigators reported this as well on an informal survey. For approximately half of the remaining patients in Cohort 2, Otonomy instituted a process whereby an unblinded monitor collected the investigator estimates of dose volume administered. The majority were able to receive at least 0.1 mL of study drug.

Patients returned to the study site on Days 4, 8, 15, and 29 for safety assessments and otoscopic examinations. Caregivers were instructed to return to the study site for an unscheduled visit if otorrhea was observed from any ear on or after 3 days postsurgery (Day 4).The presence or absence of otorrhea on external examination was assessed by a blinded assessor at all study visits. Safety assessments in the Phase 1b study included the evaluation of adverse events (all visits) and results from the following assessments: otoscopic examinations (all visits), vital signs (all visits), physical exam

(screening visit before surgery), tympanometry (screening visit before surgery, and Days 4, 8, 15, and 29), and audiometry (screening visit before surgery, and Days 15 and 29). Audiometry assessments consisted of conventional or visual reinforcement audiometry [VRA] assessments (depending on the maturity of the patient) and included air conduction and bone conduction assessments. For patients too young for conventional audiometry assessment (typically below 4 years of age) distortion product optoacoustic emission [DPOAE] assessments were performed.

Reviewer's Comment:
Overall, the safety assessments from the Phase 1b study indicated that OTO-201 was safe and well-tolerated. Please see Section 7 for further review of the safety data.

The primary clinical activity endpoint in the Phase 1b study was the proportion of patients designated as treatment failures through the Day 15 Visit. Patients were categorized as treatment failures if any of the following events occurred through the Day 15 Visit: otorrhea observed by the blinded assessor on or after 3 days postsurgery (Day 4 Visit), use of rescue medications (otic antibiotic drops or systemic antibiotics) prior to otorrhea, or early termination from the study.

After database lock, it was reported that one patient randomized to sham was mistakenly categorized as a non-treatment failure. The patient had received Ciprodex® on Day 10; therefore, the treatment failure status was changed to treatment failure. The applicant compared the analyses of the primary clinical activity endpoint when categorizing and not categorizing the patient as a treatment failure.

Table 5.3.1-2 summarizes, by treatment group, the proportion of patients categorized as treatment failures through Day 15 and the proportion identified with each treatment failure component through Day 15. The results in Table 5.3.1-2 include the one sham patient who had the treatment failure status changed after database lock. Both OTO-201 dose groups had a lower proportion of patients designated as treatment failures through Day 15 compared to patients in the placebo or sham group. Patients who received OTO-201 4 mg or 12 mg had a reduced risk of treatment failure compared to the pooled placebo/sham group at Day 15 (relative risk [95% CI]: 0.31 [0.10, 0.91] and 0.35 [0.12, 1.01], respectively).

Table 5.3.1-2:
Primary Clinical Activity - Treatment Failures through Day 15
by Treatment Group Study 201-201101

	OTO-201 4 mg N = 21	OTO-201 12 mg N = 19	Pooled OTO-201 N = 40	Pooled Placebo N = 22	Pooled Sham N = 21	Total N = 83
Treatment Failure through Day 15						
n (%)	3 (14.3%)	3 (15.8%)	6 (15.0%)	10 (45.5%)	10 (47.6%)	26 (31.3%)
Components of Treatment Failure through Day 15:						
Otorrhea-only	2 (9.5%)	2 (10.5%)	4 (10.0%)	8 (36.4%)	5 (23.8%)	17 (20.5%)
Rescue Medication-only	1 (4.8%)	1 (5.3%)	2 (5.0%)	2 (9.1%)	5 (23.8%)	9 (10.8%)
Early Termination-only	0	0	0	0	0	0

Note: Treatment failure is defined as any otorrhea observed by the blinded assessor, use of rescue medication (otic or systemic antibiotics) prior to otorrhea, or early termination event.
Source: Adapted from clinical study report for 201-201101, Table 14.2.1.1.

Reviewer's Comment:
A similar reduction in the incidence of treatment failure through Day 15 was noted for both OTO-201 doses compared to the pooled placebo/sham group. The proportion of treatment failures was similar between the two control groups. Observations were not meaningfully impacted whether or not the one sham patient had the treatment failure status changed after database lock.

5.3.2 Studies 201-201302 and 201-201303
A Prospective, Randomized, Double-Blind, Sham-controlled, Multicenter, Phase 3 Study of OTO-201 Given as a Single Intratympanic Injection for Intra-operative Treatment of Middle Ear Effusion in Pediatric Subjects Requiring Tympanostomy Tube Placement

Protocols 201-201302 and 201-201303 were two independent, prospective, randomized, double-blind, sham-controlled, multicenter, Phase 3 studies of OTO-201 for the treatment of bilateral middle ear effusion in pediatric patients with otitis media requiring TT placement. The two studies had identical protocols, and one dose level of OTO-201 (6 mg) was evaluated in relation to sham (empty syringe with air). The two Phase 3 studies were conducted in parallel and are the pivotal studies for the evaluation of both efficacy and safety of OTO-201. A more in depth discussion of the two Phase 3 studies follows.

Study Objectives

The primary objective for the Phase 3 trials was to evaluate the effectiveness of OTO-201 (6 mg to each ear) in the treatment of pediatric patients with bilateral middle ear effusion who require tympanostomy tube placement**.** A secondary objective was to assess the safety and tolerability of OTO-201 when administered intra-operatively via intratympanic injection to pediatric patients undergoing myringotomy with tympanostomy tube placement.

Trial Design

Enrollment and Randomization

Studies 201-201302 and 201-201303 were identically designed, prospective, randomized, double-blind, sham-controlled, Phase 3 trials of OTO-201 for the treatment of middle ear effusion in pediatric patients with otitis media requiring TT placement. Study 201-201302 was conducted over an approximate 6.5 month time period, from November 22, 2013, to June 03, 2014, and Study 201-201303 was conducted over an approximate 5.5 month time period, from November 22, 2013, to May 08, 2014. A total of 29 and 19 centers were used for Studies 201-201302 and 201-201303, respectively. Enrolling sites were located at centers located in the U.S. with the exception of 4 centers in Study 201-201302 and 1 center in Study 201-201303 that were located in Canada. Some of the same centers were used for both protocols, but patients were not enrolled in more than one protocol.

Subjects, aged 6 months to 17 years, with bilateral middle ear effusion confirmed via otoscopic exam were randomized to receive a single, intratympanic injection of one dose level of OTO-201 (6 mg) or sham (air from empty syringe) to each ear at the time of myringotomy surgery with TT placement. The investigators planned for 264 patients to be enrolled into each Phase 3 study using a 2:1 allocation ratio stratified by age: 6 months to 2 years or >2 years, with 176 assigned to OTO-201 and 88 assigned to sham. Each Phase 3 study enrolled 266 patients. Only patients with bilateral effusion confirmed on the day of surgery, prior to surgery, were randomized. Patients without bilateral effusion were not randomized and were considered screen failures. Randomization was implemented using a web-based Interactive Web Response System (IWRS). There was no quota regarding the total number of patients randomized to either treatment group or the number randomized to either age stratum.

Blinding

On the day of surgery, the OTO-201 and sham syringes were prepared by a nurse or pharmacist and the syringes covered to maintain the blind in the operating room. The treating otolaryngologist was unblinded at the time of administration because of the

appearance of the treatment. The patients, their caregivers, and study site staff were blinded with respect to what treatment was administered. At the follow up visits to the study site, a blinded assessor performed an external ear examination to evaluate for the presence or absence of otorrhea.

Drug Administration
On the day of myringotomy and TT placement (Day 1), enrolled patients were treated intra-operatively with either OTO-201 (6% ciprofloxacin suspension) or sham (air injection). Randomization and study drug administration occurred on the same day. Patients randomized to the OTO-201 treatment group received a 6 mg dose of OTO-201 to each ear via bilateral intratympanic injections of 0.1 mL of the 6% ciprofloxacin suspension. Patients randomized to the sham treatment group received injections of 0.1 mL of air from an empty syringe. Prior to OTO-201 or sham administration into the middle ear compartment, the middle ear effusion was first suctioned and a culture obtained from each ear. The TT was placed after the administration of OTO-201 or sham. No subsequent doses of either OTO-201 or sham were administered for the remainder of the study.

Dose selection
The 6 mg dose of OTO-201 in a 0.1 mL dosing volume was selected following the completion of the Phase 1b dose-escalation study and agreed to by the Agency at the End-of-Phase 2 meeting held on September 9, 2013. In the Phase 1b study, no safety concerns were identified between the 4 mg or 12 mg OTO-201 doses, and both doses had a similar reduction in the treatment failure rates compared to the placebo and sham groups. Information from a portion of patients in the high-dose (12 mg) cohort indicated that most of the investigators were only able to deliver at least 0.1 mL of study material, but not the entire 0.2 mL dose volume. Nonclinical pharmacokinetic studies in guinea pigs had noted the 6 mg dose of OTO-201 was comparable to the total dose of ciprofloxacin delivered after a 7 day treatment course of CIPRODEX® (5.9 mg).

Diagnostic criteria
Healthy male and female patients aged 6 months to 17 years of age with a clinical diagnosis of bilateral middle ear effusion requiring TT placement and the diagnosis confirmed from otoscopic examination performed on the day of surgery.

Noteworthy Inclusion criteria
Patients were eligible for enrollment if they met the following criteria:

1. Male or female aged 6 months to 17 years.

2. Had a clinical diagnosis of bilateral middle ear effusion requiring tympanostomy tube placement.
3. Patient's caregiver was willing to comply with the protocol and attend all study visits.
4. Patient's caregiver was able to provide written informed consent and Health Insurance Portability and Accountability Act (HIPAA) of 1996 documents before the initiation of any study-related procedures.
5. Patient of appropriate age is able to provide assent for participation in the study.

Noteworthy Exclusion criteria

Patients were not eligible for enrollment if they met the following criteria:

1. Patient had a history of prior ear or mastoid surgery, not including myringotomy or myringotomy with TT placement.
2. Patient was designated for other surgical procedure that would occur concurrently with TT placement, such as, but not limited to adenoidectomy or tonsillectomy.
3. Patient had a history of sensorineural hearing loss.
4. Patient had a history of chronic or recurrent bacterial infections other than otitis media that likely would require treatment with antibiotics during the course of the study.
5. Patient had a tympanic membrane perforation.
6. Patient had a history of known immunodeficiency disease.
7. Patient had an abnormality of the tympanic membrane or middle ear that would preclude precise placement of study drug or intratympanic injection.
8. Patient used topical nonsteroidal otic agents within 1 day of randomization
9. Patient used topical or otic corticosteroids within 3 days of randomization or systemic corticosteroids within 7 days of randomization.
10. There was the presence of any infection requiring systemic antimicrobial or antifungal agents.
11. Patient used topical or systemic antimicrobial or antifungal agents; amoxicillin, Augmentin®, Omnicef®, ceftriaxone, and cephalexin within 3 days of randomization; doxycycline and fluoroquinolones within 7 days and Zithromax® within 14 days of randomization.
12. There was concurrent use of oral anti-inflammatory agents.
13. Patient had a history of allergy to ciprofloxacin or any of the components of OTO-201.
14. Patient had any other clinically significant illness or medical condition that, in the opinion of either the investigator or medical monitor, would prohibit the subject from participating in the study.

15. Patient was a menarcheal or post-menarcheal female.

Schedule

Table 5.3.2-1 summarizes the schedule for the noteworthy procedures performed in the Phase 3 studies. On Day 1, patients underwent myringotomy surgery with TT placement and received intra-operative treatment with OTO-201 (6 mg of the 6% ciprofloxacin suspension) or sham (air injection) via bilateral intratympanic administration. A culture of the middle ear effusion was collected from each ear prior to intratympanic administration. Patients returned to the study site for follow-up assessments on Days 4, 8, 15 and 29 to assess otorrhea presence, tube patency, hearing function, and middle/external ear condition. Caregivers were encouraged to return to the study site for unscheduled visits if otorrhea was observed from any ear on or after 3 days post-surgery (Day 4 Visit), patients experienced an adverse event between scheduled visits, or patients required follow-up for any adverse event prior to the end of study visit (Day 29 Visit).

A blinded assessor performed external ear examinations at all follow-up visits in order to assess for otorrhea and if present, collect a specimen for culture. Otoscopic examinations were performed by an unblinded investigator (i.e., the surgeon who administered OTO-201 or sham) at all follow-up visits to assess the health of individual ears (appearance of the auditory canal and tympanic membrane) and assess the patency of the TT. Tympanometry and audiometry assessments were performed by a licensed audiologist or qualified assistant under the supervision of a licensed audiologist. Tympanometry was performed at the screening, Day 15, and Day 29 Visits to collect objective data regarding middle ear status and TT patency (i.e., equivalent volume, mobility, peak pressure, and compliance of the ear canal and middle ear). Audiometry was performed at the screening, Day 15, and Day 29 Visits to assess hearing function. Conventional audiometry assessments (including air conduction and bone conduction) were performed on all patients mature enough to participate, typically age 4 years and older. Patients who were not mature enough for conventional audiometry (typically less than 4 years of age) underwent visual reinforcement audiometry (VRA) or conditioned play audiometry (CPA) to obtain air and bone conduction at a minimum of at least two frequencies. The most appropriate method (conventional, VRA, CPA) was determined by the audiologist and the same method was intended for all subsequent visits. Patients less than 4 years of age were not required to have audiometry assessments at the Day 15 and Day 29 Visits if at their screening visit they were non-cooperative and/or air conduction (AC) and bone conduction (BC) thresholds could not be obtained at a minimum of two frequencies.

Table 5.3.2-1: Noteworthy Procedures in Studies 201-201302 and 201-201303

Procedure	Screening Visit	Baseline/Study Drug Administration	Follow-up Visit	Follow-up Visit	Follow-up Visit	End-of-Study/Early Termination	Unscheduled Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Unscheduled
	Day -14 to 1	Day 1	Day 4 (+1 day)	Day 8 (-1/+2 days)	Day 15 (-1/+2 days)	Day 29 (±3 days)	N/A
Informed consent	X						
Eligibility criteria	X	X[1]					
Medical History	X						
Physica examination	X						
Vital signs	X					X	
External ear examination for otorrhea (blinded assessor)			X	X	X	X	X
Otoscopic examination (unblinded assessor)	X	X	X	X	X	X	X
Tympanometry	X				X	X	
Audiometry[2]	X				X[2]	X[2]	
Microbiology culture[3]		X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
Adverse event monitoring[4]	X	X	X	X	X	X	X
Urine pregnancy test[5]	X					X	

[1] Eligible patients with bilateral middle ear effusion on day of tympanostomy tube surgery were randomized prior to surgery. Patients without bilateral middle ear effusion on day of surgery were not randomized.
[2] Conventional audiometric assessments were performed on patients mature enough to participate, as determined by the investigator, typically age 4 years and older. In a subset of patients typically younger than 4 years, VRA or CPA was used to obtain air and bone conduction at a minimum of at least two frequencies. The method to collect audiometry data at screening were used for all subsequent visits. At screening, an attempt to collect audiometry data was made for patients not able to conduct conventional audiometry. Audiometry was not collected on Day 15 and 29 for non-cooperative patients who did not have air and bone conduction at a minimum of two frequencies.
[3] On Visit 2, a specimen of effusion should be taken prior to administration of OTO-201 or sham. On Visits 3-6, a specimen will be taken for microbiological culture and sensitivity only if otorrhea is present.
[4] Adverse event information will be collected from the time of screening (Day -14 to 1) until study termination for all subjects randomized.
[5] Urine pregnancy testing was conducted on all female patients aged 9 years or older.
Source: Adapted from clinical study reports for 201-201302 and 201-201303.

Reviewer's Comment:

An agreement at the End-of-Phase 2 meeting was for at least 30% of patients less than 4 years of age (approximately 60 patients exposed to OTO-201) have hearing function assessed with audiometric testing at selected sites across both studies or in one study.

Concomitant medications
Concomitant medications included all prescription drugs, herbal products, vitamins, minerals, and over the counter medications used by subjects within 14 days prior to enrollment and anytime afterward until the end of study visit on Day 29. At the investigator's discretion, concomitant medications were given if deemed necessary for the welfare of the subjects and if not included in any of the following prohibited list:

- Antibiotics, other than OTO-201, topical dermal antibiotics for abrasions, and Ciprodex® not deemed necessary for the welfare of the patients during the study.
- Initiation of nasal, inhaled, or topical corticosteroids during the study was prohibited. Use of one nasal, inhaled, or topical steroid was permitted for patients on a stable dose for a least 1 month prior to screening. Use of more than one nasal, inhaled, or topical steroid was prohibited.
- Ear drops of any kind (other than Ciprodex® for patients who require otic antibiotic treatment).
- Intratympanic injection other than OTO-201.
- Tympanostomy tubes containing antibacterial agents such as antibiotic or silver oxide.
- Other investigational drug(s) or device(s).
- Anti-inflammatory drugs such as aspirin or ibuprofen. Patients may take acetaminophen for pain relief.
- Oxymetazoline nasal spray (Afrin®) used intra-operatively.

Treatment compliance
There were no treatment compliance assessments because the study drug was administered by the clinical investigator as a one-time intra-operative treatment during myringotomy surgery with TT placement. Any deviation in bilateral intratympanic administration was documented.

Rescue medication
On or after 3 days post-surgery (Day 4), patients were eligible to receive treatment with Ciprodex® (4 drops to each ear BID for 7 days) if any ear had otorrhea visible in the auditory canal by the blinded assessor.

Subject completion, discontinuation, or withdrawal
Patients were not considered to have completed the study if they withdrew their consent or were lost to follow-up prior to completing the Day 29 Visit. Regardless of their treatment failure status, all patients were encouraged to return to the study site for their scheduled visits and assessments through Day 29. The investigator could discontinue a patient's participation in the study if a patient experienced an adverse event (AE) that in

the opinion of the investigator required withdrawal from the study, a patient developed a condition that made it unwise to continue with the trial, or a patient (or caregiver) requested an early discontinuation. Patients were discontinued from the Phase 3 studies for the following reasons:

- Withdrawal of consent
- Surgery cancelled
- Lost to follow-up

Treatment failures

Study treatment failures following intra-operative treatment with OTO-201 or sham were determined through Days 4, 8, 15, and 29. Study treatment failures included the following events, whichever occurred first: otorrhea, use of otic antibiotic drops, use of systemic antibiotics, lost-to-follow-up, or missed visit. Patients were study treatment failures due otorrhea if they had otorrhea visible in the auditory canal from any ear by the blinded assessor on or after 3 days post-surgery (Day 4). Patients who were given otic drops or systemic antibiotics prior to confirmation of otorrhea by the blinded assessor were considered study treatment failures due to otic drops or systemic antibiotics, respectively. Patients were study treatment failures due to lost-to-follow-up if at a particular visit they had an unknown treatment failure status because they were lost to follow-up. Patient were considered study treatment failures due to missed visit if they were not lost to follow-up but had a missing treatment failure status for a particular visit because they did not return to the study site for a blinded assessment within the analytic time window. Patients were designated a study treatment failure based on the time point for the earliest occurring event, and were designated a study treatment failure for the remainder of the study.

Study Endpoints

Primary Efficacy Endpoint

- Cumulative proportion of study treatment failures through the Day 15 Visit.

A study treatment failure was defined as the first occurrence of any of the following components:

  - Otorrhea treatment failure – patient with otorrhea observed by the blinded assessor on or after the third day postsurgery (on or after Day 4) through the Day 15 Visit.
  - Otic treatment failure – patient given an otic antibiotic any time postsurgery and either prior to or without confirmation of otorrhea by the blinded assessor through the Day 15 Visit.
  - Systemic antibiotic treatment failure – patient given a systemic antibiotic any time postsurgery and either prior to or without confirmation of otorrhea by the

blinded assessor through the Day 15 Visit.

- Lost to follow up treatment failure – patient at the scheduled Day 15 Visit with an unknown study treatment failure status due to being lost to follow up.
- Missed visit treatment failure – patient, not lost to follow up, who at a particular visit through the Day 15 Visit had a missing treatment failure status because he/she did not return to the clinic for a blinded assessment within the analytic time window and had not yet been identified as a study treatment failure.

Reviewer's Comment:
The presence of otorrhea at least three days after tube placement can be related to an infection (i.e., AOMT) and be an indication for antibiotic therapy. Otorrhea-only treatment failure through Day 15 was evaluated separately as a secondary endpoint. The otorrhea treatment failure component did not include otorrhea prior to the third day postsurgery because post-surgical drainage can occur for up to three days after tube placement and its presence not related to an infection. The definition of study treatment failure included patients prescribed otic or systemic antibiotics because either could be given for an indication in the absence of otorrhea (i.e., occluded TT, granuloma, or sinus infection) and their use could prevent the development of otorrhea.

Secondary Efficacy Endpoints

- Cumulative proportion of study treatment failures through the Day 4 Visit (Visit 3).
- Cumulative proportion of study treatment failures through the Day 8 Visit (Visit 4).
- Cumulative proportion of study treatment failures through the Day 29 Visit (Visit 6).
- Time-to-study treatment failure through the Day 15 Visit (Visit 5).
- Cumulative proportion of otorrhea-only treatment failures as described above through the Day 15 Visit (Visit 5).
- Microbiological response through the Day 15 Visit (Visit 5) and Day 29 Visit (Visit 6).

A microbiological response was defined as either:

- Microbiological response without presumption – patients who had a postbaseline bacteriology sample collected that confirmed eradication of the baseline bacterial pathogen.
- Microbiological response with presumption – patients who did not have a postbaseline bacteriology sample collected, but had presumed eradication of the baseline bacterial pathogen because they were not identified as a study treatment failure.

The assessment for microbiological response was conducted in patients with a positive baseline bacteriology sample for *Streptococcus pneumoniae, Haemophilus influenzae,*

Moraxella catarrhalis, Staphylococcus aureus, or *Pseudomonas aeruginosa* in at least one ear.

Post hoc Efficacy Endpoints

The post hoc efficacy endpoints were added after database lock and included endpoints evaluating the occurrence of observed/presumed otorrhea.

- Cumulative proportion of treatment failures due to observed/presumed otorrhea through the Day 4, Day 8, Day 15, and Day 29 Visits.

A study treatment failure due to observed/presumed otorrhea was defined as either:

  - Observed otorrhea – otorrhea observed by the blinded assessor on or after the third day postsurgery (on or after Day 4).
  - Presumed otorrhea – use of otic or systemic antibiotics prescribed for otorrhea (defined as otorrhea, ear drainage, ear infection, effusion, otitis externa, or otitis media).

- Microbiological response by the Day 15 and Day 29 Visits using observed/presumed otorrhea treatment failure when evaluating presumed response.

Microbiological response for the post hoc efficacy endpoint was defined as either:

  - Microbiological response without presumption – patients who had a postbaseline bacteriology sample collected that confirmed eradication of the baseline bacterial pathogen.
  - Microbiological response with presumption – patients who did not have a postbaseline bacteriology sample collected, but had presumed eradication of the baseline bacterial pathogen because they were not identified as a study treatment failure due to observed/presumed otorrhea.

Safety Endpoints

- Adverse Events (AEs)
- Otoscopic examinations
- Tympanometry assessments
- Audiometry assessments
- Vital sign measurements
- Physical examination

Statistical Analysis Plan

Determination of Sample Size

Several assumptions were made by the investigators to estimate the sample size for the Phase 3 studies. After accounting for sampling variability in the Phase 1b study, the investigators assumed a smaller treatment effect would be observed in the Phase 3 studies than observed in the Phase 1b study. The investigators estimated that 5% of

patients in each of the Phase 3 study would have an unknown Day 15 treatment failure status due lost-to-follow-up or missed visits. A dilution of the estimated treatment effect was incorporated after assuming that patients with an unknown treatment failure status would be analyzed as study treatment failures for the primary analysis. It was anticipated that 60% of the total sample size would consist of patients aged 6 months to 2 years, while the remaining 40% of subjects would be older than 2 years of age. In the Phase 1b study, there was a 50:50 mix of patients in each age stratum and though both groups were observed to benefit from OTO-201 treatment, the data suggested a larger treatment effect for younger patients.

For each Phase 3 study, the overall study treatment failure rates in the OTO-201 and sham groups were estimated to be 25% and 46%, respectively. The investigators estimated an odds ratio (OR) of 0.37 favoring OTO-201 treatment over sham. The Cochran-Mantel-Haenszel (CMH) test conducted at the two-tailed 0.05 alpha level adjusted for age and a 2:1 allocation ratio was used to estimate power and sample size. With a sample size of 264 patients planned for each Phase 3 study (176 assigned to OTO-201 and 88 to sham), the studies would have the power of 93% to reject the null hypothesis of no difference. The planned sample size would have the power of 88% if the lost-to-follow up rate increased to 10% and the power would increase if the mix of younger patients was greater than 60%.

Analysis Sets

- **Full Analysis Set (FAS):** The FAS consisted of the Intent-to-Treat (ITT) population where all randomized patients were analyzed in the group to which they were randomized regardless of the actual treatment received. The FAS was used for the efficacy analysis unless otherwise noted.
- **Per-Protocol set:** The per-protocol population was a subset of the ITT population that included all randomized patients without major protocol deviations who had external ear examinations for otorrhea conducted by the blinded assessor at Days 4, 8, and 15 (Visits 3, 4, and 5, respectively). Major protocol deviations were identified prior to blind break and database lock. The per-protocol analysis set was used for the sensitivity analysis of the primary efficacy endpoint.
- **Microbiologically Evaluable Set (MES):** The MES was a subset of the FAS that consisted of patients who had a baseline bacteriology sample positive for either *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus*, or *Pseudomonas aeruginosa* in at least one ear. The MES was used for the microbiologic response analyses.

- **Safety Analysis Set:** The safety analysis set included all patients who received actual treatment with either OTO-201 or sham. Patients were analyzed in the group to which they received actual treatment regardless of their randomized assignment. The safety analyses set was used for the safety analyses unless otherwise noted.

Primary Efficacy Analysis
The frequency (n) and percentage (%) of patients who were study treatment failures through the Day 15 Visit in the OTO-201 and sham groups were compared using a Cochran-Mantel-Haenszel (CMH) test stratified by the two age strata (6 months to 2 years and greater than 2 years). The CMH test was conducted at a two-tailed Type I error rate of 0.05. Estimates of the strength of association were presented using adjusted odds-ratio (OR) and adjusted relative risk (RR) with their associated 95% confidence intervals (CI). Overall risk differences, and for each age stratum, were also presented.

Secondary Efficacy Analysis
The frequency (n) and percentage (%) of patients who were study treatment failures through the Day 4, Day 8, and Day 29 Visits as well as those who were otorrhea-only treatment failures through the Day 15 Visit were analyzed in the same manner as the primary efficacy endpoint.

The time-to-study treatment failure through the Day 15 visit was presented by treatment group using Kaplan-Meier survival analysis estimates and log-rank test adjusted for age. The actual study day of failure in patients who received the study drug was calculated as the date of failure − date of study drug administration + 1. The actual study day of failure in patients who were randomized but did not receive study drug was calculated as date of failure – date of randomization + 1. Patients who were identified as study treatment failures due to lost-to-follow-up were censored at the date of last contact. In patients who were identified as study treatment failures due to missed visits, the study date for the first missed visit was the date of failure.

The frequency (n) and percentage (%) of patients with microbiological responses through the Day 15 and Day 29 Visits were tabulated using the MES population. The overall microbiological responses through the relevant time points were presented by treatment group and the proportion of patients with and without a presumed microbiological response. For patients in the MES population without a post baseline culture, study treatment failure due to any of the 5 treatment failure categories (otorrhea treatment failure, otic treatment failure, systemic antibiotic treatment failure, lost-to-

follow-up treatment failure, or missed visit treatment failure) was used to evaluate presumed microbiological responses in the secondary efficacy analysis.

The frequency (n) and percentage (%) of patients who had otorrhea-only treatment failures through the Day 4, Day 8, and Day 29 Visits were presented in the sensitivity analysis. The sensitivity analysis also included the frequency (n) and percentage (%) of patients who were study treatment failures due to the other treatment failure categories through the Day 4, Day 8, Day 15, and Day 29 Visits.

Post hoc Efficacy Analysis
The frequency (n) and percentage (%) of patients who had treatment failures due to observed/presumed otorrhea through the Day 4, Day 8, Day 15, and Day 29 Visits were analyzed in the same manner as the primary efficacy endpoint. After accounting for patients with observed/presumed otorrhea treatment failures, the frequency (n) and percentage (%) of patients with otic-only treatment failures and systemic antibiotic-only treatment failures through the Day 4, Day 8, Day 15, and Day 29 Visits were tabulated.

For patients in the MES population without a post baseline culture, the post hoc efficacy analysis used observed/presumed otorrhea treatment failure through the Day 15 and 29 Visits to evaluate presumed microbiological responses through the relevant time points. The frequency (n) and percentage (%) of patients with microbiological responses through the Day 15 and Day 29 Visits were presented in the same manner as the secondary analysis; however, observed/presumed otorrhea treatment failure through the relevant time points were used to evaluate presumed microbiological responses in the post hoc efficacy analysis.

Safety Analysis
Safety assessments through Day 29 included tabulation of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) for each treatment group by severity and relationship to study drug. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term. Changes from screening with respect to otoscopic examinations (i.e., the description of auditory canal, tympanic membrane, and TT patency), tympanometry assessments (i.e., category of tympanic tube patency and type of tympanogram), audiometry assessments (i.e., Pure Tone Average, bone conduction and air-bone gap), and vital sign measurements were tabulated in the safety analysis and each age stratum. Physical examination data at baseline was presented as individual subject line listings. The Safety Analysis Set was used for the safety analysis and defined as all randomized patients who received at least one OTO-201 or sham

injection. Patients in the safety analysis were analyzed according to the actual treatment they received regardless of their randomized assignment.

6 Review of Efficacy

Efficacy Summary

Two Phase 3 studies demonstrated the efficacy of Otiprio for the treatment of middle ear effusion in pediatric patients with otitis media requiring TT placement. The cumulative proportion of study treatment failures through Day 15 was the primary efficacy endpoint, and defined as the occurrence of any of the following events: otorrhea as determined by a blinded assessor, use of otic or systemic antibiotics for any reason, missed visits, or lost-to-follow-up. A statistically significant difference favoring Otiprio treatment was observed in both Phase 3 studies for the primary efficacy endpoint. Various sensitivity analyses using the per-protocol population or assuming systemic antibiotic use and missing observations were non-treatment failure events did not impact the overall observations. In terms of the cumulative proportion of study treatment failures through Days 4, 8, 15, and 29, a statistically significant difference favoring Otiprio treatment was maintained at all the time points in both Phase 3 studies. A beneficial effect favoring Otiprio treatment was also noted in the subset of patients with a positive baseline microbiology culture. Though there was some variability related to the degree of treatment effect for the various endpoints evaluated, an overall beneficial effect was observed with Otiprio treatment compared to sham in both Phase 3 studies.

6.1 Indication for Studies 201-201302 and 201-201303

Intra-operative treatment of pediatric patients with bilateral otitis media with middle ear effusion requiring tympanostomy tube placement.

6.1.1 Methods

The review of efficacy relied on the data from the two identically designed, prospective, randomized, double blind, sham-controlled Phase 3 studies: Protocols 201-201302 and 201-201303. Please see Section 5.3 for description of the clinical trial design for the two Phase 3 studies. Supportive efficacy data from the Phase 1b study (Protocol 201-201101) is not included in this section of the review, but can be found with a protocol description in Section 5.3. Clinical study reports, clinical protocols, and literature references were submitted by the applicant.

6.1.2 Demographics

Table 6.1.2-1 summarizes the demographic characteristics from the two Phase 3 studies. A total of 266 patients were enrolled into each study. Study 201-201302 consisted of 160 males (60.2%) and 106 females (39.8%). There were 144 males (54.1%) and 122 females (45.9%) in Study 201-201303. The mean age was 2.4 years (range 0.5 to 12.6 years) and 2.5 years (range 0.5 to 11.6 years) in Studies 201-201302 and 201-201303, respectively. Patients ages 6 months to 2 years accounted for 60.9% and 61.7% of the total population in Studies 201-201302 and 201-201303, respectively.

Table 6.1.2-1:
Demographic Characteristics by Study (Full Analysis Set)

	Study 201-201302			Study 201-201303		
	OTO-201 6 mg N=179	**Sham N=87**	**Total N=266**	**OTO-201 6 mg N=178**	**Sham N= 88**	**Total N=266**
Sex – n(%)						
Male	104 (58.1%)	56 (64.4%)	160 (60.2%)	96 (53.9%)	48 (54.5%)	144 (54.1%)
Female	75 (41.9%)	31 (35.6%)	106 (39.8%)	82 (46.1%)	40 (40.5%)	122 (45.9%)
Age (years)						
Mean years (SD)	2.392 (2.0710)	2.463 (2.1176)	2.416 (2.0826)	2.279 (1.9010)	2.863 (2.5942)	2.472 (2.1677)
Median (years)	1.510	1.610	1.585	1.500	1.585	1.535
Min, max (years)	0.50, 12.60	0.51, 11.25	0.50, 12.60	0.51, 10.88	0.58, 11.63	0.51, 11.63
Age stratum – n(%)						
6 months to 2 years	109 (60.9%)	53 (60.9%)	162 (60.9%)	111 (62.4%)	53 (60.2%)	164 (61.7%)
> 2 years	70 (39.1%)	34 (39.1%)	104 (39.1%)	67 (37.6%)	35 (39.8%)	102 (38.3%)
Race – n(%)						
White	148 (82.7%)	69 (79.3%)	217 (81.6%)	140 (78.7%)	72 (81.8%)	212 (79.7%)
Black or African American	20 (11.2%)	13 (14.9%)	33 (12.4%)	23 (12.9%)	10 (11.4%)	33 (12.4%)
Asian	2 (1.1%)	0	2 (0.8%)	2 (1.1%)	2 (2.3%)	4 (1.5%)
Native American/Canadian	1 (0.6%)	0	1 (0.4%)	1 (0.6%)	1 (1.1%)	2 (0.8%)
Native Hawaiian or Other Pacific Islander	0	0	0	2 (1.1%)	0	2 (0.8%)
Not Applicable	1 (0.6%)	1 (1.1%)	2 (0.8%)	1 (0.6%)	2 (2.3%)	3 (1.1%)
Other	7 (3.9%)	4 (4.6%)	11 (4.1%)	9 (5.1%)	1 (1.1%)	10 (3.8%)
Ethnicity – n(%)						
Hispanic or Latino	24 (13.4%)	11 (12.6%)	35 (13.2%)	16 (9.0%)	10 (11.4%)	26 (9.8%)
Not Hispanic or Latino	149 (83.2%)	70 (80.5%)	219 (82.3%)	162 (91.0%)	75 (85.2%)	237 (89.1%)
Not Reported	2 (1.1%)	3 (3.4%)	5 (1.9%)	0	1 (1.1%)	1 (0.4%)
Unknown	4 (2.2%)	3 (3.4%)	7 (2.6%)	0	2 (2.3%)	2 (0.8%)

Source: Adapted from clinical study reports for 201-201302 and 201-201303, Table 14.1.1.

Reviewer's Comment:
As summarized in Table 6.1.2-1, the demographic characteristics were well-balanced across the two Phase 3 studies. Demographic characteristics were also well-balanced between treatment groups in each Phase 3 study.

Table 6.1.2-2 summarizes the demographic characteristics in the pooled treatment groups across both Phase 3 studies. A total of 357 and 175 patients were randomized into the OTO-201 and sham groups, respectively. The OTO-201 group consisted of 200 males (56.0%) and 157 females (44.0%). There were 104 males (59.4%) and 71 females (40.6%) in the sham group. The mean age for patients randomized to the OTO-201 group was 2.3 years (range 0.5 to 12.6 years) and the mean age for patients randomized to the sham group was 2.7 years (range 0.5 to 11.6 years). Across the two Phase 3 studies, patients ages 6 months to 2 years accounted for 61.6% and 60.6% of the population randomized to OTO-201 and sham, respectively.

Table 6.1.2-2:
Demographic Characteristics by Treatment Group
Studies 201-201302 and 201-201303 Pooled (Full Analysis Set)

	OTO-201 6mg N=357	**Sham N=175**	**Total N=532**
Sex – n(%)			
Male	200 (56.0%)	104 (59.4%)	304 (57.1%)
Female	157 (44.0%)	71 (40.6%)	228 (42.9%)
Age (years)			
Mean years (SD)	2.336 (1.9861)	2.664 (2.3709)	2.444 (2.1238)
Median (years)	1.51	1.59	1.55
Min, max (years)	0.50, 12.60	0.51, 11.63	0.50, 12.6
Age stratum – n(%)			
6 months to 2 years	220 (61.6%)	106 (60.6%)	326 (61.3%)
> 2 years	137 (38.4%)	69 (39.4%)	206 (38.7%)
Race – n(%)			
White	288 (80.7%)	141 (80.6%)	429 (80.6%)
Black or African American	43 (12.0%)	23 (13.1%)	66 (12.4%)
Asian	4 (1.1%)	2 (1.1%)	6 (1.1%)
Native American/Canadian	2 (0.6%)	1 (0.6%)	3 (0.6%)
Native Hawaiian or Other Pacific Islander	2 (0.6%)	0	2 (0.4%)
Not Applicable	2 (0.6%)	3 (1.7%)	5 (0.9%)
Other	16 (4.5%)	5 (2.9%)	21 (3.9%)
Ethnicity – n(%)			
Hispanic or Latino	40 (11.2%)	21 (12.0%)	61 (11.5%)
Not Hispanic or Latino	311 (87.1%)	145 (82.9%)	456 (85.7%)
Not Reported	2 (0.6%)	4 (2.3%)	6 (1.1%)
Unknown	4 (1.1%)	5 (2.9%)	9 (1.7%)

Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 5.

Reviewer's Comment:
Demographic characteristics were well-balanced between the two treatment groups in the integrated data across both Phase 3 studies.

Baseline Microbiological Status
Table 6.1.2-3 summarizes the baseline microbiological status for patients in each of the Phase 3 studies and for the pooled treatment groups across both Phase 3 studies. Results are listed by treatment group in each Phase 3 study and for the pooled treatment groups across both Phase 3 studies. A positive baseline microbiological status was defined as a positive baseline culture for either *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis, Staphylococcus aureus*, or *Pseudomonas aerugino*sa. 23.7% and 21.1% of patients had a positive microbiological culture from at least one ear in Studies 201-201302 and 201-201303, respectively. In each Phase 3 study, *H. influenzae* followed by *S. pneumoniae* and *M. catarrhalis* were the most common pathogens cultured in the OTO-201 and sham treatment groups.

Table 6.1.2-3: Baseline Microbiological Status by Study and Treatment Group (Full Analysis Set)

	Study 201-201302			Study 201-201303			Pooled		
	OTO-201 6 mg N=179	Sham N=87	Total N=266	OTO-201 6 mg N=178	Sham N= 88	Total N=266	OTO-201 6 mg N=357	Sham N= 175	Total N=532
Baseline microbiology results – n (%)[1]									
Positive[2]									
Both Ears	17 (9.5%)	11 (12.6%)	28 (10.5%)	7 (3.9%)	6 (6.8%)	13 (4.9%)	24 (6.7%)	17 (9.7%)	41 (7.7%)
At Least One Ear[3]	41 (22.9%)	22 (25.3%)	63 (23.7%)	29 (16.3%)	27 (30.7%)	56 (21.1%)	70 (19.6%)	49 (28.0%)	119 (22.4%)
***S. pneumoniae* – positive**									
Both Ears	2 (1.1%)	2 (2.3%)	4 (1.5%)	6 (3.4%)	1 (1.1%)	7 (2.6%)	8 (2.2%)	3 (1.7%)	11 (2.1%)
At Least One Ear	10 (5.6%)	6 (6.9%)	16 (6.0%)	10 (5.6%)	6 (6.8%)	16 (6.0%)	20 (5.6%)	12 (6.9%)	32 (6.0%)
***H. influenzae* – positive**									
Both Ears	10 (5.6%)	9 (10.3%)	19 (7.1%)	1 (0.6%)	4 (4.5%)	5 (1.9%)	11 (3.1%)	13 (7.4%)	24 (4.5%)
At Least One Ear	26 (14.5%)	15 (17.2%)	41 (15.4%)	13 (7.3%)	12 (13.6%)	25 (9.4%)	39 (10.9%)	27 (15.4%)	66 (12.4%)
***M. catarrhalis* – positive**									
Both Ears	0	0	0	0	1 (1.1%)	1 (0.4%)	0	1 (0.6%)	1 (0.2%)
At Least One Ear	8 (4.5%)	3 (3.4%)	11 (4.1%)	6 (3.4%)	5 (5.7%)	11 (4.1%)	14 (3.9%)	8 (4.6%)	22 (4.1%)
***S. aureus* – positive**									
Both Ears	4 (2.2%)	1 (1.1%)	5 (1.9%)	0	0	0	4 (1.1%)	1 (0.6%)	5 (0.9%)
At Least One Ear	5 (2.8%)	1 (1.1%)	6 (2.3%)	1 (0.6%)	3 (3.4%)	4 (1.5%)	6 (1.7%)	4 (2.3%)	10 (1.9%)
***P. aeruginosa* – positive**									
Both Ears	0	0	0	0	0	0	0	0	0
At Least One Ear	1 (0.6%)	0	1 (0.4%)	0	2 (2.3%)	2 (0.8%)	1 (0.3%)	2 (1.1%)	3 (0.6%)
Not positive[4]	135 (75.4%)	63 (72.4%)	198 (74.4%)	147 (82.6%)	61 (69.3%)	208 (78.2%)	282 (79.0%)	124 (70.9%)	406 (76.3%)
Unknown[5]	3 (1.7%)	2 (2.3%)	5 (1.9%)	2 (1.1%)	0	2 (0.8%)	5 (1.4%)	2 (1.1%)	7 (1.3%)

[1] Baseline was defined as the last measurement taken on or prior to the day of study drug administration.
[2] "Positive" indicates that the baseline microbiology culture was positive for at least 1 of the following 5 organisms: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Pseudomonas aeruginosa*.
[3] "At Least one ear" includes "One ear" and "Both ears"
[4] "Not Positive" indicates that the baseline microbiology culture grew either no organism or grew organism(s) that were not *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, or *P. aeruginosa*. Patients in this category had a baseline microbiology

culture result for at least 1 ear and did not have a positive baseline microbiology culture in any ear. Patients with missing baseline microbiology cultures for both ears were not included in this category.

[5] "Unknown" indicates that the baseline microbiology culture results were not recorded (or missing) for both ears.

Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 6.

Reviewer's Comment:

The baseline microbiological characteristics were similar between the two treatment groups in Study 201-201302. The proportion of patients with a positive baseline microbiology culture was greater in the sham group compared to the OTO-201 group In Study 201-201303. There were a greater proportion of sham patients compared to OTO-201 patients with a positive baseline microbiology culture in the integrated data across both Phase 3 studies; however, the difference was less prominent than observed in Study 201-201303.

6.1.3 Subject Disposition

Table 6.1.3-1 summarizes for each Phase 3 study the proportion of patients in each analysis population and the subject disposition.

Table 6.1.3-1:
Subject Disposition by Study (Full Analysis Set)

	Study 201-201302			Study 201-201303		
	OTO-201 6 mg	**Sham**	**Total**	**OTO-201 6 mg**	**Sham**	**Total**
	N=179 n (%)	N=87 n (%)	N=266 n (%)	N=178 n (%)	N=88 n (%)	N=266 n (%)
Analysis populations[1]						
Full Analysis Set (ITT population)[2]	179 (100%)	87 (100%)	266 (100%)	178 (100%)	88 (100%)	266 (100%)
Received study drug	178 (99.4%)	87 (100%)	265 (99.6%)	177 (99.4%)	88 (100%)	265 (99.6%)
Did not receive study drug	1 (0.6%)	0	1 (0.4%)	1 (0.6%)	0	1 (0.4%)
Per-Protocol Set[3]	148 (82.7%)	70 (80.5%)	218 (82.0%)	159 (89.3%)	74 (84.1%)	233 (87.6%)
Microbiologically Evaluable Set[4]	41 (22.9%)	22 (25.3%)	63 (23.7%)	29 (16.3%)	27 (30.7%)	56 (21.1%)
Safety Analysis Set[5]	179	86	265	178	87	265
Study Completion through Visit 6/Day 29						
Completed	176 (98.3%)	86 (98.9%)	262 (98.5%)	176 (98.9%)	88 (100%)	264 (99.2%)
Discontinued	3 (1.7%)	1 (1.1%)	4 (1.5%)	2 (1.1%)	0	2 (0.8%)
Reason for Premature Discontinuation[6]						
Adverse event	0	0	0	0	0	0
Condition	0	0	0	0	0	0
Withdrawal of consent	1 (33.3%)	0	1 (20%)	0	0	0
Surgery Cancelled	0	0	0	1 (50%)	0	1 (50%)
Lost to follow-up	2 (66.7%)	1 (100%)	3 (60%)	1 (50%)	0	1 (50%)

[1] Percentages were calculated using the number of subjects in the Full Analysis Set.
[2] The Full Analysis Set includes all randomized subjects, categorized by randomized treatment.
[3] The Per-Protocol Set included all randomized subjects without major protocol deviations and who had external examination of the ears for otorrhea at Visits 3, 4, and 5.
[4] The Microbiologically Evaluable Set included all randomized subjects whose baseline bacteriology sample was positive for at least 1 of the following organisms: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Pseudomonas aeruginosa*.
[5] The Safety Analysis Set included all treated subjects, categorized by actual treatment administered.

[6] The denominator is the total number of patients who discontinued the study. There were a total of 4 patients in Study 201-201302 (3 for OTO-201 and 1 for sham) and 2 patients in Study 201-201303 (1 for OTO-201 and none for sham) who discontinued prematurely from the study.
Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 4.

6 patients in Studies 201-201302 and 201-201303 were discontinued prematurely from the study, all for reasons other than AEs. 1 patient in Study 201-201302 and 1 patient in Study 201-201303 were both randomized to the OTO-201 group, and both exited the study before any treatment was administered. The caregiver of the former patient withdrew consent at the operating room doors, while the latter patient had the surgery cancelled. 3 patients in Study 201-201302 (2 randomized to OTO-201 and 1 randomized to sham) and 1 patient in Study 201-201303 (randomized to OTO-201) were lost to follow up because they did not attend the Day 29 Visit.

Reviewer's Comment:
The most frequent reason for discontinuation was lost to follow up. In the integrated data across both Phase 3 studies, 1.12% of OTO-201 patients and 0.6% of sham patients were lost to follow up.

Protocol Deviations in Study 201-201302
48 of the randomized patients were excluded from the per-protocol analysis set for having a major protocol deviation or for not having an external examination of the ears for otorrhea by the blinded assessor at Visit 3 (Day 4), Visit 4 (Day 8), and Visit 5 (Day 15).

The following were the reasons for exclusion (some patients had more than one protocol deviation):

- Procedure or Visit out of window – 41 patients
  These patients were not examined for otorrhea by the blinded assessor within the analytical time windows for the Day 4, Day 8, and Day 15 Visits.
- Site personnel/assessor error (inadvertently unblinded) – 7 patients
  In these patients, the study site personnel/assessor was inadvertently unblinded, the blinded assessor served as the patient's unblinded assessor at an earlier visit, or the assessor was unblinded during surgery.
- Incorrect treatment given – 2 patients
  One patient randomized to the sham group and one patient randomized to the OTO-201 group was given OTO-201 treatment and no treatment instead.
- Exclusion criterion – 1 patient

One patient randomized to sham was given Zithromax® 7 days prior to randomization (exclusion criterion included doses within 14 days of randomization).

Protocol Deviations in Study 201-201303

33 of the randomized patients were excluded from the per-protocol analysis set for having a major protocol deviation or for not having an external examination of the ears for otorrhea by the blinded assessor at Visit 3 (Day 4), Visit 4 (Day 8), and Visit 5 (Day 15).

The following were the reasons for exclusion:

- Procedure or Visit out of window – 23 patients
  These patients were not examined for otorrhea by the blinded assessor within the analytical time windows for the Days 4, 8, and 15 Visits.
- Site personnel/assessor error (inadvertently unblinded) – 6 patients
  In these patients, the study site personnel/assessor was inadvertently unblinded, the blinded assessor served as the patient's unblinded assessor at an earlier visit, or the assessor was unblinded during surgery.
- Incorrect treatment given – 4 patients
  Two patients randomized to the OTO-201 group were instead given sham treatment and no treatment, respectively. Two patients randomized to the sham group were instead given OTO-201 treatment.

6.1.4 Analysis of Primary Endpoint(s)

Table 6.1.4-1 summarizes the results from the applicant's primary efficacy analysis of study treatment failures through Day 15. Results are summarized by treatment group for each Phase 3 study and for the combined Phase 3 studies. The data from the applicant's analysis was verified by this reviewer and the Statistics Reviewer, Mushfiqur Rashid, Ph.D.

Table 6.1.4-1:
Primary Efficacy – Study Treatment Failures through Day 15
by Study and Treatment Group (Full Analysis Set)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6mg N = 179	Sham N = 87	OTO-201 6mg N = 178	Sham N = 88	OTO-201 6mg N = 357	Sham N =179
Cumulative proportion of Study Treatment Failures[a] through Day 15						
n (%)	44 (24.6%)	39 (44.8%)	38 (21.3%)	40 (45.5%)	82 (23.0%)	79 (45.1%)
OR (95% CI)[b]	0.388 (0.2232, 0.6758)		0.299 (0.1689, 0.5287)		0.341 (0.2294, 0.5082)	
RR (95% CI)[b]	0.548 (0.3901, 0.7709)		0.463 (0.3258, 0.6590)		0.506 (0.3960, 0.6457)	
Risk Difference (95% CI)[c]	-0.202 (-0.3245, -0.0804)		-0.241 (-0.3613, -0.1209)		-0.222 (-0.3074, -0.1361)	
p-value[d]	<0.001		<0.001		<0.001	

[a] A study treatment failure was defined as the occurrence of any of the following events: otorrhea treatment failure, otic treatment failure, systemic antibiotic treatment failure, lost-to-follow-up treatment failure, or missed visit treatment failure.
[b] The odds ratio (OR), relative risk (RR), and corresponding 95% confidence intervals (95% CI) for OTO-201 6 mg versus sham were adjusted for age strata.
[c] All risk differences and the corresponding 95% CIs were not adjusted for age strata. Risk differences were estimated by the proportion of patients with treatment failure in the OTO-201 6 mg group – the proportion of patients with treatment failure in the sham group.
[d] p-values were derived from a Cochran-Mantel-Haenszel test stratified by age strata (6 months through 2 years and >2 years).
Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 7.

Reviewer's Comment:
Both Phase 3 studies had a greater proportion of patients with study treatment failure through Day 15 in the sham group compared to the OTO-201 group. A statistically significant difference favoring OTO-201 treatment was apparent in each study.

Per-Protocol Analyses

Table 6.1.4-2 summarizes the results from the applicant's primary efficacy analysis in the Per-Protocol analysis set. The per-protocol analysis included all randomized patients from the ITT population who did not have major protocol deviations and had a blinded assessor perform external ear examinations for otorrhea at the Day 4, Day 8, and Day 15 Visits. The data from the applicant's analysis was verified by this reviewer and the Statistics Reviewer, Mushfiqur Rashid, Ph.D.

Table 6.1.4-2:
Primary Efficacy - Study Treatment Failures through Day 15 by Study and Treatment Group (Per-Protocol Analysis Set)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6mg N = 148	Sham N = 70	OTO-201 6mg N = 159	Sham N = 74	OTO-201 6mg N = 307	Sham N =144
Cumulative proportion of Study Treatment Failures[a] through Day 15						
n (%)	18 (12.2%)	27 (38.6%)	27 (17.0%)	29 (39.2%)	45 (14.7%)	56 (38.9%)
OR (95% CI)[b]	0.211 (0.1040, 0.4293)		0.284 (0.1483, 0.5455)		0.249 (0.1545, 0.4019)	
RR (95% CI)[b]	0.321 (0.1919, 0.5355)		0.428 (0.2787, 0.6565)		0.377 (0.2716, 0.5245)	
Risk Difference (95% CI)[c]	-0.264 (-0.3897, -0.1385)		-0.222 (-0.3477, -0.0965)		-0.242 (-0.3312, -0.1534)	
p-value[d]	<0.001		<0.001		<0.001	

[a] A study treatment failure was defined as the occurrence of any of the following events: otorrhea treatment failure, otic treatment failure, systemic antibiotic treatment failure, lost-to-follow-up treatment failure, or missed visit treatment failure.

[b] The odds ratio (OR), relative risk (RR), and corresponding 95% confidence intervals (95% CI) for OTO-201 6 mg versus sham were adjusted for age strata.

[c] All risk differences and the corresponding 95% CIs were not adjusted for age strata. Risk differences were estimated by the proportion of patients with treatment failure in the OTO-201 6 mg group - the proportion of patients with treatment failure in the sham group.

[d] p-values were derived from a Cochran-Mantel-Haenszel test stratified by age strata (6 months through 2 years and >2 years).

Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 8.

Reviewer's Comment:

Each Phase 3 study had a statistically significant difference favoring OTO-201 treatment when evaluating the primary efficacy endpoint in the per-protocol population.

Sensitivity Analyses

Table 6.1.4-3 summarizes the results from the applicant's sensitivity analyses of the primary efficacy endpoint. The sensitivity analyses were conducted to assess whether the use of systemic antibiotics or missing observations impacted the interpretation of the results. Specifically, patients in the three sensitivity analyses were not categorized as study treatment failures if identified as systemic antibiotic treatment failures, lost-to-follow-up treatment failures, or missed visit treatment failures, respectively. The data from the applicant's sensitivity analyses was verified by this reviewer.

Table 6.1.4-3:
Primary Efficacy – Sensitivity Analyses of Study Treatment Failures through Day 15 by Study (Full Analysis Set)

	Study 201-201302		Study 201-201303	
	OTO-201 6mg N = 179	Sham N = 87	OTO-201 6mg N = 178	Sham N = 88
Cumulative proportion of study treatment failures through Day 15				
Sensitivity - Exclude systemic antibiotic treatment failure from definition				
n (%)	42 (23.5%)	35 (40.2%)	32 (18.0%)	37 (42.0%)
OR (95% CI)	0.447 (0.2558, 0.7819)		0.273 (0.1512, 0.4946)	
RR (95% CI)	0.583 (0.4054, 0.8393)		0.421 (0.2861, 0.6193)	
Risk Difference (95% CI)	-0.168 (-0.2880, -0.0474)		-0.241 (-0.3582, -0.1231)	
p-value	0.004		<0.001	
Sensitivity - Exclude lost-to-follow-up treatment failure from definition				
n (%)	43 (24.0%)	39 (44.8%)	37 (20.8%)	40 (45.5%)
OR (95% CI)	0.375 (0.2147, 0.6546)		0.285 (0.1599, 0.5065)	
RR (95% CI)	0.536 (0.3804, 0.7551)		0.451 (0.3161, 0.6424)	
Risk Difference (95% CI)	-0.208 (-0.3299, -0.0862)		-0.247 (-0.3666, -0.1268)	
p-value	<0.001		<0.001	
Sensitivity - Exclude missed visit treatment failure from definition				
n (%)	29 (16.2%)	30 (34.5%)	29 (16.3%)	35 (39.8%)
OR (95% CI)	0.349 (0.1892, 0.6448)		0.268 (0.1465, 0.4890)	
RR (95% CI)	0.470 (0.3055, 0.7228)		0.403 (0.2682, 0.6062)	
Risk Difference (95% CI)	-0.183 (-0.2963, -0.0693)		-0.235 (-0.3506, -0.1190)	
p-value	<0.001		<0.001	

Note: A study treatment failure was defined as the occurrence of any of the following events: otorrhea treatment failure, otic treatment failure, systemic antibiotic treatment failure, lost-to-follow-up treatment failure, or missed visit treatment failure. Patients in each specified treatment failure group were not categorized as study treatment failures unless they subsequently became a study treatment failure by some other treatment failure event.

Note: The odds ratio (OR), relative risk (RR), and corresponding 95% CIs (confidence interval) for OTO-201 vs. sham are adjusted for age strata.

Note: All risk differences and the corresponding 95% CIs are not adjusted for age strata. Risk difference is estimated by the difference between the proportion of patients with treatment failure in the OTO-201 6 mg group and the sham group.
Note: The p-values were derived from a Cochran-Mantel-Haenszel test stratified by age strata.
Source: Adapted from clinical study reports for 201-201302 and 201-201303, Table 14.2.2, Table 14.2.3, and Table 14.2.4.

Reviewer's Comment:
Each Phase 3 study had a statistically significant difference favoring OTO-201 treatment when assuming patients prescribed systemic antibiotics were non-treatment failures. Additionally, each Phase 3 study had a statistically significant difference favoring OTO-201 treatment when assuming patients with missing observations due to being lost-to-follow-up or missed visits were non-treatment failures.

Age Group Analyses
Table 6.1.4-4 summarizes the results from the applicant's primary efficacy analysis in the two age strata, age 6 months through 2 years and age >2 years. The data from the applicant's analysis was verified by this reviewer and the Statistics Reviewer, Mushfiqur Rashid, Ph.D.

Table 6.1.4-4:
Study Treatment Failures through Day 15
by Age Group, Study and Treatment Group (Full Analysis Set)

Age Group: 6 months through 2 years						
	Study 201-201302		**Study 201-201303**		**Pooled**	
	OTO-201 6mg N = 109	**Sham N = 53**	**OTO-201 6mg N = 111**	**Sham N = 53**	**OTO-201 6mg N = 220**	**Sham N = 106**
Cumulative proportion of Study Treatment Failures[a] through Day 15						
n (%)	33 (30.3%)	28 (52.8%)	28 (25.2%)	33 (62.3%)	61 (27.7%)	61 (57.5%)
OR (95% CI)[b]	0.388 (0.1971, 0.7627)		0.204 (0.1014, 0.4123)		0.283 (0.1742, 0.4598)	
RR (95% CI)[b]	0.573 (0.3911, 0.8396)		0.405 (0.2763, 0.5941)		0.482 (0.3683, 0.6304)	
Risk Difference (95% CI)[c]	-0.226 (-0.3852, -0.0659)		-0.370 (-0.5239, -0.2169)		-0.298 (-0.4093, -0.1871)	
p-value[d]	0.005		<0.001		<0.001	

Age Group: >2 years						
	Study 201-201302		**Study 201-201303**		**Pooled**	
	OTO-201 6mg N = 70	**Sham N = 34**	**OTO-201 6mg N = 67**	**Sham N = 35**	**OTO-201 6mg N = 137**	**Sham N = 69**
Cumulative proportion of Study Treatment Failures[a] through Day 15						
n (%)	11 (15.7%)	11 (32.4%)	10 (14.9%)	7 (20.0%)	21 (15.3%)	18 (26.1%)
OR (95% CI)	0.390 (0.1486, 1.0229)		0.702 (0.2415, 1.0388)		0.513 (0.2521, 1.0438)	
RR (95% CI)	0.486 (0.2344, 1.0063)		0.746 (0.3111, 1.7904)		0.588 (0.3359, 1.0278)	
Risk Difference (95% CI)	-0.166 (-0.3453, 0.0125)		-0.051 (-0.2084, 0.1069)		-0.108 (-0.2275, 0.0123)	
p-value	0.051		0.514		0.063	

[a] A study treatment failure was defined as the occurrence of any of the following events: otorrhea treatment failure, otic treatment failure, systemic antibiotic treatment failure, lost-to-follow-up treatment failure, or missed visit treatment failure.
[b] The odds ratio (OR), relative risk (RR), and corresponding 95% confidence intervals (95% CI) for OTO-201 6 mg versus sham were adjusted for age strata.
[c] All risk differences and the corresponding 95% CIs were not adjusted for age strata. Risk differences were estimated by the proportion of patients with treatment failure in the OTO-201 6 mg group – the proportion of patients with treatment failure in the sham group.
[d] p-values were derived from a Cochran-Mantel-Haenszel test stratified by age strata (6 months through 2 years and >2 years).
Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 18.

Reviewer's Comment:
Across both age strata, the sham groups in both Phase 3 studies had a greater proportion of patients with study treatment failure through Day 15 compared to the OTO-201 groups. A statistically significant difference between the two treatment groups favoring OTO-201 treatment was noted in the younger age strata in both Phase 3 studies, especially Study 201-201303. A statistically significant difference was not apparent in the older age strata in either Phase 3 study.

6.1.5 Analysis of Secondary Endpoints

Study Treatment failures through Days 4, 8, and 29
Table 6.1.5-1 summarizes the results from the applicant's secondary efficacy analysis of study treatment failures through Days 4, 8, and 29. The data from the applicant's analysis was verified by this reviewer and the Statistics Reviewer, Mushfiqur Rashid, Ph.D.

Table 6.1.5-1:
Secondary Efficacy - Study Treatment Failures through Days 4, 8, and 29 by Study and Treatment Group (Full Analysis Set)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88	OTO-201 6 mg N = 357	Sham N = 175
Cumulative proportion of Study Treatment Failures[a]						
Through Day 4						
n (%)	16 (8.9%)	21 (24.1%)	9 (5.1%)	25 (28.4%)	25 (7.0%)	46 (26.3%)
OR (95% CI)[b]	0.302 (0.1474, 0.6207)		0.118 (0.0510, 0.2741)		0.199 (0.1161, 0.3408)	
RR (95% CI)[b]	0.370 (0.2047, 0.6701)		0.174 (0.0858, 0.3524)		0.264 (0.1689, 0.4125)	
Risk Difference (95% CI)[c]	-0.152 (-0.2512, -0.0528)		-0.234 (-0.3331, -0.1340)		-0.193 (-0.2632, -0.1224)	
p-value[d]	<0.001		<0.001		<0.001	
Through Day 8						
n (%)	27 (15.1%)	31 (35.6%)	25 (14.0%)	32 (36.4%)	52 (14.6%)	63 (36.0%)
OR (95% CI)	0.314 (0.1712, 0.5765)		0.263 (0.1414, 0.4906)		0.289 (0.1870, 0.4459)	
RR (95% CI)	0.423 (0.2716, 0.6599)		0.380 (0.2437, 0.5936)		0.402 (0.2935, 0.5505)	
Risk Difference (95% CI)	-0.205 (-0.3190, -0.0920)		-0.223 (-0.3359, -0.1105)		-0.214 (-0.2943, -0.1344)	
p-value	<0.001		<0.001		<0.001	
Through Day 29						
n (%)	58 (32.4%)	48 (55.2%)	58 (32.6%)	51 (58.0%)	116 (32.5%)	99 (56.6%)
OR (95% CI)	0.380 (0.2224, 0.6475)		0.302 (0.1718, 0.5324)		0.344 (0.2338, 0.5061)	
RR (95% CI)	0.587 (0.4439, 0.7772)		0.554 (0.4260, 0.7199)		0.571 (0.4713, 0.6921)	
Risk Difference (95% CI)	-0.228 (-0.3527, -0.1027)		-0.254 (-0.3777, -0.1297)		-0.241 (-0.3288, -0.1527)	
p-value	<0.001		<0.001		<0.001	

[a] A study treatment failure was defined as the occurrence of any of the following events: otorrhea treatment failure, otic treatment failure, systemic antibiotic treatment failure, lost-to-follow-up treatment failure, or missed visit treatment failure. Patients identified as a study treatment failure were considered study treatment failures for the remainder of the study.

[b] The odds ratio (OR), relative risk (RR), and corresponding 95% confidence intervals (95% CI) for OTO-201 6 mg versus sham were adjusted for age strata.

[c] All risk differences and the corresponding 95% CIs were not adjusted for age strata. Risk differences were estimated by the proportion of patients with treatment failure in the OTO-201 6 mg group – the proportion of patients with treatment failure in the sham group.

[d] p-values were derived from a Cochran-Mantel-Haenszel test stratified by age strata (6 months through 2 years and >2 years).

Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 8.

Reviewer's Comment:
In both Phase 3 studies, the proportion of patients with study treatment failure through Days 4, 8, and 29 were greater in the sham group compared to the OTO-201 group. Statistically significant differences favoring OTO-201 treatment were apparent in each study as well as the integrated data across both studies.

Study treatment failures due to otorrhea-only through Day 15
Table 6.1.5-2 summarizes the results from the applicant's secondary efficacy analysis of otorrhea-only treatment failures through Day 15. The data from the applicant's analysis was verified by this reviewer.

Table 6.1.5-2:
Secondary Efficacy - Study Treatment Failures due to Otorrhea-only through Day 15 by Study and Treatment Group (Full Analysis Set)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88	OTO-201 6 mg N = 357	Sham N = 175
Cumulative proportion of Study Treatment Failures due to Otorrhea-only[a]						
Through Day 15						
n (%)	13 (7.3%)	10 (11.5%)	12 (6.7%)	24 (27.3%)	25 (7.0%)	34 (19.4%)
OR (95% CI)[b]	0.601 (0.2517, 1.4361)		0.179 (0.0830, 0.3848)		0.303 (0.1734, 0.5300)	
RR (95% CI)[b]	0.632 (0.2894, 1.3800)		0.243 (0.1285, 0.4585)		0.358 (0.2214, 0.5778)	
Risk Difference (95% CI)[c]	-0.042 (-0.1194, 0.0347)		-0.205 (-0.3054, -0.1052)		-0.124 (-0.1886, -0.0599)	
p-value[d]	0.250		<0.001		<0.001	

[a] Study treatment failure due to otorrhea through Day 15 was defined as otorrhea visible on the external ear examination by the blinded assessor on or after the third post-surgery day (Day 4) through the Day 15 Visit.
[b] The odds ratio (OR), relative risk (RR), and corresponding 95% confidence intervals (95% CI) for OTO-201 6 mg versus sham were adjusted for age strata.
[c] All risk differences and the corresponding 95% CIs were not adjusted for age strata. Risk differences were estimated by the proportion of patients with treatment failure in the OTO-201 6 mg group – the proportion of patients with treatment failure in the sham group.
[d] p-values were derived from a Cochran-Mantel-Haenszel test stratified by age strata (6 months through 2 years and >2 years).
Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 11.

Reviewer's Comment:
The sham group in both Phase 3 studies had a greater proportion of patients with study treatment failure due to otorrhea-only through Day 15 compared to the OTO-201 group. Statistically significant differences favoring OTO-201 treatment were apparent in Study

201-201303 and in the integrated data across both studies. A statistically significant difference was not noted between the two treatment groups in Study 201-201302. The sham group in Study 201-201303 had over twice as many patients with otorrhea-only treatment failure through Day 15 compared to Study 201-201302. This observation may be due to the larger number of otic antibiotics-only treatment failures in the sham group in Study 201-201302 compared to Study 201-201303. By the Day 15 Visit, these patients were already designated as study treatment failures.

Component of study treatment failure through Days 4, 8, 15, and 29

Table 6.1.5-3 summarizes the results from the applicant's analysis of cumulative proportions of study treatment failures due to each treatment failure component. A patient was defined as a study treatment failure from the time point of the earliest occurring treatment failure component and considered a study treatment failure due to that component for the remainder of the study. Other treatment failure components occurring after a patient was identified as study treatment failure were not included in this analysis. The data from the applicant's analysis was verified by this reviewer.

Table 6.1.5-3:
Components of Study Treatment Failure
by Study, Treatment Group and Time point (Full Analysis Set)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88	OTO-201 6mg N = 357	Sham N = 175
Overall cumulative proportion of Study Treatment Failures[1]						
Through Day 4	16 (8.9%)	21 (24.1%)	9 (5.1%)	25 (28.4%)	25 (7.0%)	46 (26.3%)
Through Day 8	27 (15.1%)	31 (35.6%)	25 (14.0%)	32 (36.4%)	52 (14.6%)	63 (36.0%)
Through Day 15	44 (24.6%)	39 (44.8%)	38 (21.3%)	40 (45.5%)	82 (23.0%)	79 (45.1%)
Through Day 29	58 (32.4%)	48 (55.2%)	58 (32.6%)	51 (58.0%)	116 (32.5%)	99 (56.6%)
Cumulative proportion of Study Treatment Failures due to:						
Otorrhea-only						
Through Day 4	8 (4.5%)	7 (8.0%)	6 (3.4%)	17 (19.3%)	14 (3.9%)	24 (13.7%)
Through Day 8	11 (6.1%)	8 (9.2%)	9 (5.1%)	21 (23.9%)	20 (5.6%)	29 (16.6%)
Through Day 15	13 (7.3%)	10 (11.5%)	12 (6.7%)	24 (27.3%)	25 (7.0%)	34 (19.4%)
Through Day 29	15 (8.4%)	12 (13.8%)	22 (12.4%)	29 (33.0%)	37 (10.4%)	41 (23.4%)
Otic Antibiotics-only						
Through Day 4	2 (1.1%)	12 (13.8%)	1 (0.6%)	5 (5.7%)	3 (0.8%)	17 (9.7%)
Through Day 8	4 (2.2%)	15 (17.2%)	4 (2.2%)	5 (5.7%)	8 (2.2%)	20 (11.4%)
Through Day 15	10 (5.6%)	15 (17.2%)	9 (5.1%)	7 (8.0%)	19 (5.3%)	22 (12.6%)
Through Day 29	15 (8.4%)	17 (19.5%)	12 (6.7%)	9 (10.2%)	27 (7.6%)	26 (14.9%)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88	OTO-201 6mg N = 357	Sham N = 175
Systemic Antibiotics-only						
Through Day 4	1 (0.6%)	0	0	1 (1.1%)	1 (0.3%)	1 (0.6%)
Through Day 8	2 (1.1%)	1 (1.1%)	3 (1.7%)	3 (3.4%)	5 (1.4%)	4 (2.3%)
Through Day 15	3 (1.7%)	4 (4.6%)	6 (3.4%)	3 (3.4%)	9 (2.5%)	7 (4.0%)
Through Day 29	6 (3.4%)	6 (6.9%)	9 (5.1%)	6 (6.8%)	15 (4.2%)	12 (6.9%)
Lost-to-follow-up-only						
Through Day 4	1 (0.6%)	0	1 (0.6%)	0	2 (0.6%)	0
Through Day 8	1 (0.6%)	0	1 (0.6%)	0	2 (0.6%)	0
Through Day 15	1 (0.6%)	0	1 (0.6%)	0	2 (0.6%)	0
Through Day 29	1 (0.6%)	0	1 (0.6%)	0	2 (0.6%)	0
Missed Visits-only						
Through Day 4	4 (2.2%)	2 (2.3%)	1 (0.6%)	2 (2.3%)	5 (1.4%)	4 (2.3%)
Through Day 8	9 (5.0%)	7 (8.0%)	8 (4.5%)	3 (3.4%)	17 (4.8%)	10 (5.7%)
Through Day 15	17 (9.5%)	10 (11.5%)	10 (5.6%)	6 (6.8%)	27 (7.6%)	16 (9.1%)
Through Day 29	21 (11.7%)	13 (14.9%)	14 (7.9%)	7 (8.0%)	35 (9.8%)	20 (11.4%)

Note: A patient was defined as a study treatment failure from the earliest time point of the 5 events as described in the statistical analysis plan and was considered a study treatment failure for the remainder of the study.

Note: A patient receiving otic antibiotic drops or systemic antibiotics on the same day as confirmation of otorrhea by the blinded assessor was considered a study treatment failure due to otorrhea if they had not yet been identified as a study treatment failure.

Note: The table above does not include any subsequent or other treatment failure events that may occur after a patient is designated a study treatment failure.

Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 14.

Reviewer's Comment:

Both sham groups in the two Phase 3 studies had a greater proportion of patients identified as study treatment failure due to otorrhea-only, otic antibiotics-only, systemic antibiotics-only, or missed visit-only through all of the time points compared to their respective OTO-201 group. The proportion of patients identified as study treatment failure due to lost-to-follow-up-only through all the time points was comparable between the two treatment groups. Otorrhea-only treatment failure through all of the time points (except at Day 15 in the OTO-201 group) was the most common study treatment failure component in the integrated analysis across both studies.

In Studies 201-201302 and 201-201303, the frequency of otorrhea-only, otic antibiotics-only, and systemic antibiotics-only treatment failures were comparable among patients in either of the OTO-201 groups; however, differences were observed among patients in the two sham groups. Through all of the time points, there were more study treatment failures due to otic antibiotics-only in Study 201-201302 and more study treatment

failures due to otorrhea-only in Study 201-201303. Despite not having confirmation of otorrhea by the blinded assessor, most of the sham group patients who did receive otic antibiotics in Study 201-201302 were prescribed therapy for an otorrhea indication (presumed otorrhea). A further analysis of the proportions of patients given antibiotic therapy for a non-otorrhea indication is presented later in this review (see Section 6.1.6, Table 6.1.6-2).

The OTO-201 and sham groups within each Phase 3 study had comparable proportions of patients who were identified as missed visit-only treatment failures; however, the proportions in Study 201-201302 were greater than Study 201-201303. Missed visit-only treatment failures through Day 15 accounted for 10.2% (27 patients) of the ITT population in Study 201-201302 and 6.0% (16 patients) of the population in Study 201-201303. The majority of patients identified with this endpoint had their missed visit rescheduled and the planned study assessments completed 1 to 2 days outside the analytic time window (range -1 to 6 days). All but 1 patient in Study 201-201302 and 3 patients in Study 201-20303 completed the planned assessments for the Day 15 Visit. The differences in the proportion of study treatment failures in the OTO-201 and sham groups were not meaningfully impacted if assuming the missed visit-only treatment failures were non-treatment failures until the occurrence of some other treatment failure component.

Microbiological responses through Days 15 and 29

Table 6.1.5-4 summarizes the results from the applicant's secondary efficacy analysis of microbiological responses with and/or without presumption through the Day 15 and 29 Visits. The data from the applicant's analysis was verified by this reviewer.

Table 6.1.5-4:
Secondary Efficacy - Microbiological Responses by Study, Treatment Group and Time point (Microbiologically Evaluable Set)

	Study 201-201302			Study 201-201303			Pooled		
	OTO-201 6mg N = 41	Sham N = 22	Total N = 63	OTO-201 6mg N = 29	Sham N = 27	Total N = 56	OTO-201 6mg N =70	Sham N = 49	Total N = 119
Microbiological response (total)[1]									
Through Day 15	33 (80.5%)	9 (40.9%)	42 (66.7%)	24 (82.8%)	13 (48.1%)	37 (66.1%)	57 (81.4%)	22 (44.9%)	79 (66.4%)
Through Day 29	31 (75.6%)	7 (31.8%)	38 (60.3%)	21 (72.4%)	10 (37.0%)	31 (55.4%)	52 (74.3%)	17 (34.7%)	69 (58.0%)
Microbiological response without presumption only[2]									
Through Day 15	3 (7.3%)	2 (9.1%)	5 (7.9%)	5 (17.2%)	1 (3.7%)	6 (10.7%)	8 (11.4%)	3 (6.1%)	11 (9.2%)
Through Day 29	4 (9.8%)	2 (9.1%)	6 (9.5%)	5 (17.2%)	1 (3.7%)	6 (10.7%)	9 (12.9%)	3 (6.1%)	12 (10.1%)
Microbiological response with presumption only[3]									
Through Day 15	30 (73.2%)	7 (31.8%)	37 (58.7%)	19 (65.5%)	12 (44.4%)	31 (55.4%)	49 (70.0%)	19 (38.8%)	68 (57.1%)
Through Day 29	27 (65.9%)	5 (22.7%)	32 (50.8%)	16 (55.2%)	9 (33.3%)	25 (44.6%)	43 (61.4%)	14 (28.6%)	57 (47.9%)

Note: The Microbiological Evaluable Set included patients with a positive baseline bacteriology sample for *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis, Staphylococcus aureus*, or *Pseudomonas aeruginosa* in at least 1 ear.

[1] Microbiological response (total) included patients in the MES who had microbiological responses either with or without presumption during the relevant time points.

[2] Microbiological response without presumption included patients in the MES who had negative post-baseline cultures

[3] Microbiological response with presumption included patients in the MES who had no post-baseline culture collected and were not study treatment failures during the relevant time points. A study treatment failure was defined as the occurrence of any of the following events: otic treatment failure, systemic antibiotic treatment failure, otorrhea treatment failure, lost-to-follow-up treatment failure, or missed visit treatment failure.

Source: Adapted from clinical study reports for 201-201302 and 201-201303, Table 14.2.11.

Reviewer's Comment:

In each Phase 3 study, there were a greater proportion of patients in the OTO-201 group compared to the sham group who had microbiological responses with and/or without presumption through Days 15 and 29.

Time to Study Treatment failure through the Day 15 Visit

In each Phase 3 study, the time to study treatment failure through the Day 15 Visit was significantly different between the two treatment groups using a log-rank test adjusted for age ($p<0.001$). There were too few events in either treatment group to estimate the median time to study treatment failure, but the data suggested sham patients compared to OTO-201 patients were more likely to fail earlier. By Day 4, the probability of failure among the two sham groups compared to the two OTO-201 groups was 0.1600 and 0.0534, respectively. By Day 6, the probability of failure was 0.2629 and 0.0675 among the two sham groups and the two OTO-201 groups, respectively.

6.1.6 Other Endpoints

Study treatment failures due to observed/presumed otorrhea-only through Days 4, 8, 15, and 29

Table 6.1.6-1 summarizes the results from the applicant's post-hoc efficacy analysis of observed/presumed otorrhea-only treatment failures through Days 4, 8, 15, and 29. The data from the applicant's analysis was verified by this reviewer.

Table 6.1.6-1:
Post hoc Efficacy - Study Treatment Failures due to Observed/Presumed Otorrhea-only through Days 4, 8, 15, and 29 by Study and Treatment Group (Full Analysis Set)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88	OTO-201 6 mg N = 357	Sham N = 175
Study Treatment Failures due to Observed/Presumed Otorrhea-only[a]						
Through Day 4						
n (%)	11 (6.1%)	16 (18.4%)	7 (3.9%)	21 (23.9%)	18 (5.0%)	37 (21.1%)
OR (95% CI)[b]	0.279 (0.1210, 0.6414)		0.109 (0.0424, 0.2784)		0.180 (0.0970, 0.3323)	
RR (95% CI)[b]	0.334 (0.1640. 0.6812)		0.160 (0.0718, 0.3548)		0.235 (0.1395, 0.3968)	
Risk Difference (95% CI)[c]	-0.122 (-0.2111, -0.0338)		-0.199 (-0.2928, -0.1058)		-0.161 (-0.2256, -0.0964)	
p-value[d]	0.002		<0.001		<0.001	
Through Day 8						
n (%)	14 (7.8%)	20 (23.0%)	12 (6.7%)	25 (28.4%)	26 (7.3%)	45 (25.7%)
OR (95% CI)	0.278 (0.1316, 0.5870)		0.156 (0.0714, 0.3401)		0.211 (0.1236, 0.3613)	
RR (95% CI)	0.340 (0.1817, 0.6374)		0.231 (0.1241, 0.4305)		0.280 (0.1806, 0.4354)	
Risk Difference (95% CI)	-0.152 (-0.2484, -0.0549)		-0.217 (-0.3178, -0.1155)		-0.184 (-0.2545, -0.1142)	
p-value	<0.001		<0.001		<0.001	

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6 mg N = 179	**Sham N = 87**	**OTO-201 6 mg N = 178**	**Sham N = 88**	**OTO-201 6 mg N = 357**	**Sham N = 175**
Through Day 15						
n (%)	21 (11.7%)	22 (25.3%)	17 (9.6%)	29 (33.0%)	38 (10.6%)	51 (29.1%)
OR (95% CI)	0.379 (0.1918, 0.7477)		(0.0934, 0.3784)		0.268 (0.1649, 0.4345)	
RR (95% CI)	0.464 (0.2732, 0.7883)		0.283 (0.1673, 0.4800)		0.361 (0.2496, 0.5234)	
Risk Difference (95% CI)	-0.136 (-0.2383, -0.0328)		-0.234 (-0.3413, -0.1268)		-0.185 (-0.2595, -0.1104)	
p-value[d]	0.004		<0.001		<0.001	
Through Day 29						
n (%)	27 (15.1%)	26 (29.9%)	30 (16.9%)	36 (40.9%)	57 (16.0%)	62 (35.4%)
OR (95% CI)	0.399 (0.2117, 0.7503)		0.258 (0.1402, 0.4755)		0.319 (0.2065, 0.4943)	
RR (95% CI)	0.505 (0.3182, 0.8010)		0.404 (0.2712, 0.6013)		0.446 (0.3302, 0.6036)	
Risk Difference (95% CI)	-0.148 (-0.2576, -0.0385)		-0.241 (-0.3571, -0.1240)		-0.195 (-0.2750, -0.1142)	
p-value	0.004		<0.001		<0.001	

[a] A study treatment failure due to observed/presumed otorrhea was defined as either: 1) observed otorrhea – study treatment failure due to observed otorrhea by the blinded assessor or, 2) presumed otorrhea – study treatment failure due to antibiotic treatment (either otic or systemic antibiotics) if the antibiotic was prescribed for otorrhea (defined as otorrhea, ear drainage, ear infection, effusion, otitis externa, or otitis media).

[b] The odds ratio (OR), relative risk (RR), and corresponding 95% confidence intervals (95% CI) for OTO-201 6 mg versus sham were adjusted for age strata.

[c] All risk differences and the corresponding 95% CIs were not adjusted for age strata. Risk differences were estimated by the proportion of patients with treatment failure in the OTO-201 6 mg group – the proportion of patients with treatment failure in the sham group.

[d] p-values were derived from a Cochran-Mantel-Haenszel test stratified by age strata (6 months through 2 years and >2 years).

Note: This table does not include patients who may have had observed/presumed otorrhea after they were identified a study treatment failures due to other treatment failure components.

Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Table 15.

Reviewer's Comment:

In both Phase 3 studies, the proportion of patients with study treatment failures due to observed/presumed otorrhea through Days 4, 8, 15, and 29 were greater in the sham group compared to the OTO-201 group. Many of the patients in Study 201-201302, particularly those in the sham group, were given antibiotic therapy for an otorrhea indication (presumed otorrhea). Among patients identified with either observed or presumed otorrhea, a statistically significant difference favoring OTO-201 treatment was apparent in each study. Of note, analysis of just patients with observed otorrhea treatment failure through Day 15 did not achieve statistical significance difference in

Study 201-201302 (See Section 6.1.5, Table 6.1.5-2).

Any observed otorrhea, observed/presumed otorrhea, or otic/systemic antibiotics through Days 4, 8, 15, and 29

As mentioned earlier, the cumulative proportion of otorrhea-only treatment failures and observed/presumed otorrhea-only treatment failures included only the patients categorized as study treatment failures due to the specified treatment failure component (See Table 6.1.5-3 and Table 6.1.6-1, respectively). The results presented by the applicant did not include patients categorized as study treatment failures due to otic antibiotics, systemic antibiotics, or missed visits who subsequently developed observed otorrhea or observed/presumed otorrhea. This reviewer used the datasets provided by the applicant to account for these patients when tabulating the number of patients who had any occurrence of observed otorrhea or observed/presumed otorrhea during the study. Table 6.1.6-2 summarizes by study, treatment group, and time point the cumulative proportion of patients with any observed otorrhea (otorrhea treatment failures), any observed/presumed otorrhea (observed/presumed otorrhea treatment failures), or any use of otic/systemic antibiotics not related to observed/presumed otorrhea. The analysis was performed by this reviewer to determine if the previously reported differences between the OTO-201 and sham groups would be affected.

Table 6.1.6-2:
Any Treatment Failure Component by Study, Treatment Group and Time point (Full Analysis Set)

	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88	OTO-201 6 mg N = 357	Sham N = 175
Any Observed Otorrhea[1]						
Through Day 4	8 (4.5%)	8 (9.2%)	6 (3.4%)	17 (19.3%)	14 (3.9%)	25 (14.3%)
Through Day 8	11 (6.1%)	12 (13.8%)	9 (5.1%)	21 (23.9%)	20 (5.6%)	33 (18.9%)
Through Day 15	14 (7.8%)	14 (16.1%)	12 (6.7%)	25 (28.4%)	26 (7.3%)	39 (22.3%)
Through Day 29	17 (9.5%)	18 (20.7%)	23 (12.9%)	30 (34.1%)	40 (11.2%)	48 (27.4%)
Any Observed/Presumed Otorrhea[2]						
Through Day 4	11 (6.1%)	16 (18.4%)	7 (3.9%)	21 (23.9%)	18 (5.0%)	37 (21.1%)
Through Day 8	14 (7.8%)	21 (24.1%)	12 (6.7%)	25 (28.4%)	26 (7.3%)	46 (26.3%)
Through Day 15	23 (12.8%)	23 (26.4%)	17 (9.6%)	29 (33.0%)	40 (11.2%)	52 (29.7%)
Through Day 29	29 (16.2%)	29 (33.3%)	30 (16.9%)	36 (40.9%)	59 (16.5%)	65 (37.1%)
Any Otic/Systemic Antibiotics not related to observed/presumed otorrhea[3]						
Through Day 4	0	3 (3.4%)	0	2 (2.3%)	0	5 (2.9%)
Through Day 8	3 (1.7%)	4 (4.6%)	4 (2.2%)	4 (4.5%)	7 (2.0%)	8 (4.6%)
Through Day 15	5 (2.8%)	7 (8.0%)	10 (5.6%)	6 (6.8%)	15 (4.2%)	13 (7.4%)
Through Day 29	10 (5.6%)	9 (10.3%)	15 (8.4%)	9 (10.2%)	25 (7.0%)	18 (10.3%)

[1] "Any Observed Otorrhea" include patients who had otorrhea observed by the blinded assessor on or after the third day postsurgery (on or after Day 4). This group includes patients who were study treatment failures due to otorrhea-only through the relevant time points as well as patients who had the event after they were already identified as study treatment failures due to other treatment failure components.
[2] "Any Observed/Presumed Otorrhea" include patients who had either: 1) observed otorrhea - observed otorrhea by the blinded assessor, or 2) presumed otorrhea – antibiotic treatment (either otic or systemic antibiotics) prescribed for otorrhea (defined as otorrhea, ear drainage, ear infection, effusion, otitis externa, or otitis media). This group includes patients who were study treatment failures due to observed/presumed otorrhea-only through the relevant time points as well as patients who had the event after they were already identified as study treatment failures due to other treatment failure components.
[3] "Any Otic/Systemic antibiotics not related to observed/presumed otorrhea" include patients who were given otic or systemic antibiotics prior to having observed or presumed otorrhea.
Source: Clinical reviewer's calculations.

Reviewer's Comment:
In each Phase 3 study, the proportion of patients with any observed otorrhea, observed/presumed otorrhea, or use of otic/systemic antibiotics not related to observed/presumed otorrhea was greater in the sham group compared to the OTO-201 group through all of the time points. No meaningful differences appreciated when the two former endpoints were compared to the proportions reported for the otorrhea-only and the observed/presumed otorrhea-only treatment failure endpoints (See Table 6.1.5-3 and Table 6.1.6-1, respectively).

Microbiological responses through Days 15 and 29, otorrhea defined as observed/presumed otorrhea

Table 6.1.6-3 summarizes the results from the applicant's post-hoc efficacy analysis of microbiological responses with and/or without presumption through the Day 15 and 29 Visits. The data from the applicant's analysis was verified by this reviewer. Please see Table 6.1.5-4 for results related to the proportion of patients who had microbiological responses without presumption through Days 15 and 29.

Table 6.1.6-3:
Post-hoc Efficacy - Microbiological Responses by Study, Treatment Group and Time point, Otorrhea Defined as Observed/Presumed Otorrhea (Microbiologically Evaluable Set)

	Study 201-201302			Study 201-201303			Pooled		
	OTO-201 6mg N = 41	Sham N = 22	Total N = 63	OTO-201 6mg N = 29	Sham N = 27	Total N = 56	OTO-201 6mg N =70	Sham N = 49	Total N = 119
Microbiological response (total)[1]									
Through Day 15	38 (92.7%)	11 (50.0%)	49 (77.8%)	29 (100%)	14 (51.9%)	43 (76.8%)	67 (95.7%)	25 (51.0%)	92 (77.3%)
Through Day 29	37 (90.2%)	10 (45.5%)	47 (74.6%)	27 (93.1%)	12 (44.4%)	39 (69.6%)	64 (91.4%)	22 (44.9%)	86 (72.3%)
Microbiological response with presumption only[2]									
Through Day 15	35 (85.4%)	9 (41.0%)	44 (69.8%)	24 (82.8%)	13 (48.1%)	37 (66.1%)	59 (84.3%)	22 (44.9%)	81 (68.1%)
Through Day 29	33 (80.5%)	8 (36.4%)	41 (65.1%)	22 (75.9%)	11 (40.7%)	33 (58.9%)	55 (78.6%)	19 (38.8%)	74 (62.2%)

Note: The Microbiologically Evaluable Set (MES) included patients with a positive baseline bacteriology sample for *Streptococcus pneumonia*, *Haemophilus influenzae*, *Moraxella catarrhalis, Staphylococcus aureus,* or *Pseudomonas aeruginosa* in at least 1 ear.

[1] Microbiological response (total) included patients in the MES who had microbiological responses either with or without presumption during the relevant time points.

[2] Microbiological responses with presumption included patients in the MES who had no post-baseline culture collected and were not treatment failures due to observed/presumed otorrhea during the relevant time points. Study treatment failure due to observed/presumed otorrhea was defined as either: 1) observed otorrhea – study treatment failure due to otorrhea observed by the blinded assessor, or 2) presumed otorrhea – study treatment failure due to antibiotic treatment (otic or systemic antibiotics) if the antibiotic was prescribed for otorrhea (defined as otorrhea, ear drainage, ear infection, effusion, otitis externa, or otitis media).

Source: Adapted from clinical study reports for 201-201302 and 201-201303, Table 14.2.11B.

Reviewer's Comment:

There were a greater proportion of patients in the OTO-201 group compared to the sham group who had microbiological responses with and/or without presumption through Days 15 and 29. This observation was noted in each individual study and the integrated data across both studies.

6.1.7 Subpopulations

Subgroup analyses of the efficacy endpoints were conducted by age stratum (6 months through 2 years and >2 years), sex, race, ethnicity, baseline microbiology culture status/pathogen type, and baseline effusion type. Overall, the results from each Phase 3 study indicated a treatment effect favoring OTO-201 in all of the subgroups analyzed. However, some variability was observed in the degree of treatment effect in some of the subgroups across both Phase 3 studies. In particular, a greater treatment effect was observed in the younger age stratum (6 months through 2 years) for the primary efficacy endpoint. A greater treatment effect in the younger age stratum was not a significant issue to the program because OTO-201 is proposed for a pediatric indication that predominantly affects young children. Please see Section 6.1.4 (Table 6.1.4-4) for analyses of the primary efficacy endpoint for the two age strata.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dose of OTO-201 is 6 mg (0.1 mL dosing volume) administered to each affected ear. The 6 mg (0.1 mL) dose is recommended in the label because of the efficacy results demonstrated in the two Phase 3 studies using the 6 mg (0.1 mL) dose and supported in a smaller Phase 1b study using a 4 mg (0.2 mL) and 12 mg (0.2 mL) dose. The two OTO-201 doses in the Phase 1b study had a similar reduction in treatment failures compared to treatment with placebo and sham; however, many of the investigators were only able to delivery at least 0.1 mL of study drug. Based on these findings, the 6 mg (0.1 mL) dose was selected for the two Phase 3 studies and the efficacy of OTO-201 was confirmed in both studies.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Clinical failures with or without a persistent pathogen through Day 15

Table 6.1.10-1 summarizes the results of an additional analysis of the primary efficacy endpoint based on baseline microbiological status. Clinical failures in Table 6.1.10-1 refer to study treatment failures through Day 15; and the persistent pathogen category refer to only the proportion of clinical failures that had the same pathogen type on both a baseline and postbaseline culture by the Day 15 Visit. Patients with a positive baseline microbiological status had a positive baseline culture for at least one of the following pathogens: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus* or *Pseudomonas aeruginosa*. The analysis was performed by this reviewer to evaluate the number of patients with a presumed bacterial etiology for the baseline middle ear effusion and determine the proportion that developed clinical failures with or without a persistent pathogen.

Table 6.1.10-1:
Clinical Failures with or without a Persistent Pathogen through Day 15
by Baseline Microbiological Status
Studies 201-201302 and 201-201303 Pooled (Full Analysis Set)

Baseline Pathogen	OTO-201 6mg N=357			Sham N=175		
	Total N	Clinical Failures n (%)	Persistent Pathogen[3] n (%)	Total N	Clinical Failures n (%)	Persistent Pathogen[3] n (%)
Positive[1]	70	21 (30.0%)	0	49	30 (61.2%)	15 (30.6%)
Streptococcus pneumoniae	20	9 (45.0%)	0	12	10 (83.3%)	6 (50.0%)
Haemophilus influenzae	39	8 (20.5%)	0	27	16 (59.3%)	7 (25.9%)
Moraxella catarrhalis	14	6 (42.9%)	0	8	4 (50.0%)	2 (25.0%)
Staphylococcus aureus	6	2 (33.3%)	0	4	2 (50.0%)	1 (25.0%)
Pseudomonas aeruginosa	1	1 (100%)	0	2	0	0
Negative[2]	232	46 (19.8%)	N/A	98	40 (40.8%)	N/A
Unknown[3]	5	2 (40.0%)	N/A	2	0	N/A

Note: Total N equals the number of patients with the specified baseline culture result.
[1] "Positive" refers to patients who had a positive baseline microbiology culture from at least one ear. A positive baseline microbiology culture was defined as growth of at least 1 of the

following 5 pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis, Staphylococcus aureus* or *Pseudomonas aeruginosa*. Patients with multiple pathogens at baseline are included in the rows for each pathogen.

[2] "Negative" refers to patients who had negative baseline microbiology cultures from both ears.

[3] "Unknown" refers to patients who did not have baseline microbiology culture from both ears.

Note: Clinical failures refer to study treatment failures through Day 15 and defined as the occurrence of any of the following events: use of otic antibiotic, use of systemic antibiotic, otorrhea observed by the blinded assessor, lost-to-follow-up, or missed visit.

Note: Persistent Pathogen refers to patients who had a positive baseline culture and later the same pathogen identified on a post-baseline culture collected anytime through the Day 15 Visit.

Source: Clinical reviewer's calculations.

Reviewer's Comment:

There were fewer clinical failures among patients in the OTO-201 group compared to the sham group regardless of the baseline pathogen type, with the exception of Pseudomonas aeruginosa. None of the patients with a positive baseline culture in the OTO-201 group had a post-baseline culture positive for the same pathogen type by the Day 15 Visit. This may suggest that the clinical failures in the OTO-201 group were not necessarily related to incomplete bacterial eradication at the time of myringotomy with TT placement. In contrast, 30.6% of patients in the sham group had the same pathogen type (especially Streptococcus pneumoniae) identified on their post-baseline culture. Of note, less than 3% of patients in either the OTO-201 or sham group had a baseline culture positive for Staphylococcus aureus and/or Pseudomonas aeruginosa.

Baseline and Post-baseline microbiological status in patients with any observed/presumed otorrhea through Day 15

Table 6.1.10-2 summarizes the baseline and post-baseline microbiological status in the subset that had any observed/presumed otorrhea through Day 15. The proportion of patients with any observed/presumed otorrhea was evaluated earlier in this review (See Table 6.1.6-2). The purpose of this additional analysis was to determine the proportion of patients who had any observed/presumed otorrhea through Day 15 after a presumed bacterial etiology or were a presumed bacterial etiology at the time of observation. This reviewer conducted the analysis using the datasets provided by the applicant.

Table 6.1.10-2:
Baseline and Post-baseline Microbiological Status in Patients with Any Observed/Presumed Otorrhea through Day 15
Studies 201-201302 and 201-201303 Pooled

Pathogen	Any Observed/Presumed Otorrhea through Day 15			
	OTO-201 6mg N=40		Sham N=52	
	Baseline culture	Post-baseline culture	Baseline culture	Post-baseline culture
Microbiological status – n (%)				
Positive[1]	12 (30.0%)	2 (5.0%)	27 (51.9%)	32 (61.5%)
Streptococcus pneumoniae	6 (15.0%)	2 (5.0%)	10 (19.2%)	10 (19.2%)
Haemophilus influenzae	6 (15.0%)	0	13 (25.0%)	20 (38.5%)
Moraxella catarrhalis	2 (5.0%)	0	4 (7.7%)	13 (25.0%)
Staphylococcus aureus	1 (2.5%)	1 (2.5%)	2 (3.8%)	4 (7.7%)
Pseudomonas aeruginosa	1 (2.5%)	0	0	0
Unknown[2]	0	11 (27.5%)	0	9 (17.3%)

Note: Sample sizes (N) presented for OTO-201 6 mg and Sham represent the number of patients with any observed/presumed otorrhea by the Day 15 Visit. This group included patients with any observed or presumed otorrhea by Day 15, regardless if they were already designated as study treatment failures due to some other treatment failure component.
Note: Baseline culture refers to the microbiology cultures collected at the time of myringotomy surgery (prior to OTO-201 or sham administration). Post-baseline culture refers to post-surgery microbiology cultures collected through the Day 15 Visit
[1] "Positive" refers to patients who had a microbiology culture from at least one ear positive for one or more of the following pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis, Staphylococcus aureus* or *Pseudomonas aeruginosa*. Patients with multiple pathogens at baseline and/or postbaseline are included in the row for each pathogen.
[2] "Unknown" refers to patients who did not have a baseline microbiology culture from both ears or did not have a post-baseline microbiology culture from at least one ear.
Source: Clinical reviewer's calculations

Reviewer's Comment:
The number of patients with any observed/presumed otorrhea through Day 15 was smaller in the OTO-201 group compared to sham; and from this set, there were a smaller proportion of patients in the OTO-201 group who had a positive baseline or post-baseline microbiological culture through Day 15. This observation was noted for each pathogen type, with the exception of Pseudomonas aeruginosa. A negative culture may indicate a non-bacterial etiology (i.e., viral) for the observed/presumed otorrhea

and this was more apparent in the patients in the OTO-201 group who had any observed/presumed otorrhea through Day 15.

7 Review of Safety

Safety Summary

One Phase 1b and two Phase 3 studies demonstrated the safety of Otiprio for the treatment of pediatric patients with otitis media with middle ear effusion requiring TT placement. A 4 mg (0.2 mL) and 12 mg (0.2 mL) dose of Otiprio was evaluated in the Phase 1b study, while a 6 mg (0.1 mL) dose was evaluated in the Phase 3 studies (same as selected for marketing). The majority of TEAEs associated with intratympanic administration of Otiprio were minor, mild or moderate in severity, and self-limited. There were no deaths, life-threatening TEAEs, or TEAEs leading to study discontinuation in any of the clinical studies. No meaningful impact to hearing function, middle ear function, or tube patency was observed by Day 29 in any of the clinical studies.

7.1 Methods

Healthy pediatric patients with bilateral middle ear effusion requiring tympanostomy tube placement were enrolled into the Phase 1b and Phase 3 studies. Patients enrolled into the Phase 1b study received intraoperative treatment with OTO-201 (4 mg or 12 mg), sham (empty syringe), or placebo (poloxamer 407 vehicle), while patients in the Phase 3 studies received intraoperative treatment with OTO-201 6 mg or sham. After treatment on Day 1, patients in the Phase 1b and Phase 3 studies returned to the study site for safety assessments on Days 4, 8, 15, and 29. The following safety assessments were performed in all three clinical studies: adverse events, vital signs, physical examinations, otoscopic examinations, tympanometry, and audiometry. Additional information related to the study designs for the Phase 1b and Phase 3 studies can be found in Section 5.3.1 and Section 5.3.2, respectively.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 7.1.1-1: Summary of Completed Clinical Studies for OTO-201

Study Identifier	Study Design	Study Population	Regimen/Schedule/ Duration	Treatment (N)	Safety assessments
Study 201-201101 **IND 110244** **Phase1b**	Prospective, randomized, double blind, placebo and sham-controlled, sequential dose escalation study	Healthy male and female patients age 6 months to 12 years with a clinical diagnosis of bilateral MEE requiring TT placement and a confirmed diagnosis on the day of surgery	0.2 mL intratymapnic injection into each ear Single dose during myringotomy surgery with TT placement Follow-up to day 29	• OTO-201 4mg (N=21) • OTO-201 12mg (N=19) • Placebo (N=22) • Sham (N=21)	• Adverse Events • Otoscopic exams • Tympanometry • Audiometry • Vital signs • Physical exam
Study 201-201302 **IND 110244** **Phase 3**	Prospective, randomized, double blind, sham-controlled	Healthy male and female patients age 6 months to 17 years with a clinical diagnosis of bilateral MEE requiring TT placement and a confirmed diagnosis on the day of surgery	0.1 mL intratymapnic injection into each ear Single dose during myringotomy surgery with TT placement Follow-up to day 29	• OTO-201 6mg (N=179) • Sham (N=86)	• Adverse Events • Otoscopic exams • Tympanometry • Audiometry • Vital signs • Physical exam
Study 201-201303 **IND 110244** **Phase 3**	Prospective, randomized, double blind, sham-controlled	Healthy male and female patients age 6 months to 17 years with a clinical diagnosis of bilateral MEE requiring TT placement and a confirmed diagnosis on the day of surgery	0.1 mL intratymapnic injection into each ear Single dose during myringotomy surgery with TT placement Follow-up to day 29	• OTO-201 6mg (N=178) • Sham (N=87)	• Adverse Events • Otoscopic exams • Tympanometry • Audiometry • Vital signs • Physical exam

Source: Adapted from clinical study reports for 201-201101, 201-201302, and 201-201303

7.1.2 Categorization of Adverse Events

The routine clinical testing required to establish the safety of intratympanic administration of OTO-201 was adequately addressed in the design and conduct of the Phase 1b and two Phase 3 studies.

All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse events were pooled for the two Phase 3 studies (Study 201-201302 and 201-201303) because both studies were identically designed and there were a small number of reported adverse events. In addition, the OTO-201 dose (6 mg) and dosing volume (0.1 mL) evaluated in the Phase 3 studies were the same as selected for marketing.

The safety data from the Phase 1b study (Study 201-201101) will not be pooled with the data from the Phase 3 studies because of the small number of enrolled patients and the different design of the study. Unlike the Phase 3 studies, the doses and dosing volume used in the Phase 1b study were not selected for marketing.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 7.2.1-1 summarizes the cumulative patient exposure to each treatment group in the Phase 1b and Phase 3 studies.

Table 7.2.1-1:
Cumulative Patient Exposure
Studies 201-201101, 201-201302, and 201-201303

Treatment	Number of Subjects
OTO-201[a] (any dose)	397
OTO-201 4 mg	21
OTO-201 6 mg	357
OTO-201 12 mg	19
Placebo (vehicle only)	22
Sham[b] (air injection)	194

[a] 397 patients were randomized to OTO-201, but 2 patients were not treated and 1 patient was treated with Sham instead. The total number of patients exposed to OTO-201 was still 397 because 3 patients randomized to sham were treated with OTO-201 instead.
[b] 196 patients were randomized to sham, but 3 patients were treated with OTO-201 instead. The total number of patients exposed to Sham was 194 because 1 patient randomized to OTO-201 was treated with Sham instead.
Source: IND 110244 Development Safety Update Report (DSUR) SN0055 submitted 04/28/15, Table 1.

7.2.2 Explorations for Dose Response

Two dose levels of OTO-201, 4 mg and 12 mg, were evaluated in the Phase 1b study. The Cochran-Armitage test for a dose response trend (with pooled control group at dose level 0) was conducted and the analysis indicated that as the dose level increased, the proportion of subjects designated as treatment failure generally decreased (Day 4, p-value = 0.0102; Day 8, p-value = 0.065; Day 15, p-value = 0.021). No meaningful differences in safety findings observed between the two doses.

The Phase 3 studies evaluated only one dose level of OTO-201.

7.2.3 Special Animal and/or In Vitro Testing

Adequate nonclinical investigations of OTO-201 were performed and submitted in the original NDA 207986. Ototoxicity, systemic toxicity, local tolerance (dermal toxicity or delayed-hypersensitivity), antigenicity, and tube patency were assessed for OTO-201 in a guinea pig model. Please see the Pharmacology Toxicology review by James Wild, Ph.D., for further details.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of OTO-201 was adequately addressed in the design and conduct of the Phase 1b and two Phase 3 studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

Adequate nonclinical studies with OTO-201 were submitted in this original NDA 207986. There is minimal systemic absorption of this low-dose topical product. For further details, please refer to the review by the Pharmacology Toxicology Reviewer, James Wild, Ph.D.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported in the Phase 1b and two Phase 3 studies are consistent with those reported with other topical otic fluoroquinolones. The assessment of these adverse events within the clinical trials was adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during any of the following clinical studies involving OTO-201: the Phase 1b study (Study 201-201101) and the two Phase 3 studies (Studies 201-201302 and 201-201303).

7.3.2 Nonfatal Serious Adverse Events

Table 7.3.2-1 summarizes the 4 serious adverse events reported in the Phase 1b and Phase 3 studies. In Study 201-201101, one patient in the 4 mg OTO-201 group experienced one serious adverse event, chemical poisoning, from ingesting a dishwashing detergent tablet. In Study 201-201302, three patients in the OTO-201 group experienced three serious adverse events; one had gastroenteritis and two had bronchiolitis. There were no serious adverse events reported in Study 201-201303.

Table 7.3.2-1:
Summary of Serious Adverse Events
Studies 201-201101, 201-201302, and 201-201303 (Safety Analysis Set)

System Organ Class Preferred Term	OTO-201 4 mg N = 21	OTO-201 6 mg N = 357	OTO-201 12 mg N = 19	Placebo N = 22	Sham N = 194
Infections and Infestations	--	3	--	--	--
Bronchiolitis	--	2	--	--	--
Gastroenteritis	--	1	--	--	--
Injury, Poisoning and Procedural Complications	1	--	--	--	--
Chemical Poisoning	1	--	--	--	--

Source: IND 110244 Development Safety Update Report (DSUR) SN0055 submitted 04/28/15, Table 13.

7.3.3 Dropouts and/or Discontinuations

One patient in the Phase 1b study was prematurely discontinued from the study. This patient was in Cohort 2, had received sham treatment, and had completed assessments up to and including the Day 15 Visit. The patient did not return to the study site for the Day 29 Visit and was categorized as lost-to-follow-up through Day 29. No other dropouts occurred during the Phase 1b study.

6 patients were prematurely discontinued from the two Phase 3 studies, all for reasons other than AEs. Please see Section 6.1.3 for additional information regarding dropouts in the Phase 3 studies.

7.3.4 Significant Adverse Events

Please see Section 7.4.1 for Common Adverse Events. No other significant adverse events were identified.

7.3.5 Submission Specific Primary Safety Concerns

The major safety concerns of local delivery of OTO-201 to the otic compartment were possible local AEs (i.e., middle ear appearance and tube patency) and effects on hearing function (i.e., middle and inner ear function). Otoscopic exams, tympanometry, and audiometry assessments were performed to assess for these potential safety issues. Please see Section 7.4.7 for Otoscopic Examinations, Section 7.4.8 for Tympanometry, and Section 7.4.9 for Audiometry findings.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 7.4.1-1 summarizes the common TEAEs reported during the Phase 1b study, and defined as TEAEs experienced by at least 2 subjects in any treatment group.

Table 7.4.1-1:
Treatment Emergent Adverse Events Experienced by at least 2 Subjects in Any Treatment Group Study 201-201101

Preferred term	OTO-201			Pooled Placebo N=22	Pooled Sham N=21	Total N=83
	4 mg N=21	12 mg N=19	All N=40			
Pyrexia	0	4 (21.1%)	4 (10%)	1 (4.5%)	2 (9.5%)	7 (8.4%)
Upper respiratory tract infection	3 (14.3%)	0	3 (7.5%)	2 (9.1%)	1 (4.8%)	6 (7.2%)
Diarrhea	1 (4.8%)	2 (10.5%)	3 (7.5%)	0	0	3 (3.6%)
Otorrhea	1 (4.8%)	1 (5.3%)	2 (5.0%)	7 (31.8%)	8 (38.1%)	17 (20.5%)
Cough	0	2 (10.5%)	2 (5.0%)	1 (4.5%)	0	3 (3.6%)
Ear infection	1 (4.8%)	1 (5.3%)	2 (5.0%)	3 (13.6%)	2 (9.5%)	7 (8.4%)
Ear pain	0	1 (5.3%)	1 (2.5%)	0	2 (9.5%)	3 (3.6%)
Headache	0	0	0	0	2 (9.5%)	2 (2.4%)

MedDRA Version 15.0
Source: Adapted from clinical study report for 201-201101, Table 12-2.

Reviewer's Comment:
In the Phase 1b study, treatment emergent adverse events reported by 2 or more patients in any treatment group and more frequently in the OTO-201 group (4 mg or 12 mg dose) were pyrexia, upper respiratory tract infection, diarrhea, and cough.

Table 7.4.2-2 summarizes the common TEAEs reported during in the Phase 3 studies, and defined as TEAEs experienced by at least 3% of patients in the OTO-201 group.

Table 7.4.1-2:
Treatment Emergent Adverse Events Experienced at rates ≥ 3% in OTO-201 patients Studies 201-201302 and 201-201303 (Safety Analysis Set)

Preferred term	OTO-201 6 mg N=357	Sham N=173	Total N=530
Pyrexia	40 (11.2%)	20 (11.6%)	60 (11.3%)
Teething	24 (6.7%)	8 (4.6%)	32 (6.0%)
Upper Respiratory Tract Infection	23 (6.4%)	12 (6.9%)	35 (6.6%)
Procedural Pain	19 (5.3%)	15 (8.7%)	34 (6.4%)
Nasopharyngitis	18 (5.0%)	6 (3.5%)	24 (4.5%)
Cough	17 (4.8%)	11 (6.4%)	28 (5.3%)
Irritability	17 (4.8%)	5 (2.9%)	22 (4.2%)
Ear Pain	14 (3.9%)	6 (3.5%)	20 (3.8%)
Nasal congestion	12 (3.4%)	5 (2.9%)	17 (3.2%)
Rhinorrhea	12 (3.4%)	3 (1.7%)	15 (2.8%)
Vomiting	11 (3.1%)	5 (2.9%)	16 (3.0%)

MedDRA Version 16.1
Source: Adapted from Summary of Clinical Safety, Module 2, Section 2.7.4, Table 8.

Reviewer's Comment:
In the Phase 3 studies, treatment emergent adverse events reported by at least 3% of patients in the OTO-201 group and more frequently in the OTO-201 group were teething, nasopharyngitis, irritability, and rhinorrhea.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were not needed for this topical fluoroquinolone product.

7.4.3 Vital Signs

Patients in the Phase 1b study underwent systolic blood pressure, diastolic blood pressure, and pulse rate measurements at all visits to the study site. There were no clinically significant changes in vital signs, no patterns in vital signs suggestive of treatment-related effect, and no vital sign values reported as AEs.

Patients in the Phase 3 studies had blood pressure and pulse rate measured at the baseline and the Day 29 Visits. No overall clinically relevant differences in vital sign changes from baseline to the Day 29 Visit were observed between OTO-201 and sham treatment groups. Findings were similar to that observed in the Phase 1b study.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in either the Phase 1b study or the two Phase 3 studies.

7.4.5 Special Safety Studies/Clinical Trials

Please see Section 7.4.7 for Otoscopic Examinations, Section 7.4.8 for Tympanometry, and Section 7.4.9 for Audiometry findings.

7.4.6 Immunogenicity

Not applicable.

7.4.7 Otoscopic Examinations

Otoscopic examinations were performed in the Phase 1b and Phase 3 studies to assess the health of individual ears (from the appearance of the auditory canal and tympanic membrane) and assess patency of the TT. There was no evidence in the Phase 1b study that OTO-201 was associated with a worsening of otoscopic exam findings. In the Phase 3 studies, worsening findings were infrequent at post-treatment visits and less common in the OTO-201 group compared to the sham group.

Table 7.4.7-1 summarizes TT patency assessments in the Phase 3 studies at the first and final post-treatment visits (Day 4 and Day 29, respectively).

Table 7.4.7-1:
Summary of Tube Patency by Treatment Group and Visit
Studies 201-201302 and 201-201303 (Safety Analysis Set)

Visit Category	Subjects with	OTO-201 6 mg N=357 n/nn (%)	Sham N=173 n/nn (%)	Total N=530 n/nn (%)
Day 4				
Patent	Both Tubes	331/354 (93.5%)	166/172 (96.5%)	497/526 (94.5%)
Blocked	At least One Tube	23/354 (6.5%)	6/172 (3.5%)	29/526 (5.5%)
	Both Tubes	3/354 (0.8%)	1/172 (3.5%)	4/526 (0.8%)
Extruded	At least One Tube	0	0	0
	Both Tubes	0	0	0
Day 29				
Patent	Both Tubes	333/354 (94.1%)	162/171 (94.7%)	495/525 (94.3%)
Blocked	At least One Tube	18/354 (5.1%)	7/171 (4.1%)	25/525 (4.8%)
	Both Tubes	2/354 (0.6%)	1/171 (0.6%)	3/525 (0.6%)
Extruded	At least One Tube	3/354 (0.8%)	1/171 (0.6%)	4/525 (0.8%)
	Both Tubes	1/354 (0.3%)	0	1/525 (0.2%)

Note: Percentages are based on the number of patients with nonmissing data for at least 1 ear at the visit analyzed.
Source: Adapted from Summary of Clinical Safety, Module 2, Section 2.7.4, Table 15.

Reviewer's Comment:
A greater proportion of patients in the OTO-201 group had at least one TT blocked at the Day 4 Visit compared to the sham group. By the Day 29 Visit, the proportion of patients with at least one TT blocked was similar between the OTO-201 and sham groups. Bilateral blocked TTs or extruded tubes were infrequent in either treatment group or time points.

7.4.8 Tympanometry

Tympanometry assessments were performed in the Phase 1b and Phase 3 studies to provide objective data regarding middle ear status and TT patency (from measurements of equivalent volume, mobility, peak pressure, and compliance of the ear canal and middle ear). The majority of ears had a tympanometry category of B with a large canal volume, consistent with the presence of the TT and normal middle ear function. Results in the OTO-201 and control groups were similar. No safety issues were identified from the tympanometry data.

7.4.9 Audiometry

Audiometry assessments were conducted in the Phase 1b and Phase 3 studies to evaluate hearing function. All patients in the Phase 1b study underwent audiometry assessments appropriate for their age and developmental abilities. No safety concerns with regards to possible hearing loss were noted in the Phase 1b study.

Audiometry assessments in the Phase 3 studies were not required in patients <4 years of age if they were non-cooperative with the audiometry testing at the screening visit. Table 7.4.9-1 summarizes the number of patients in the overall and the <4 years of age populations who underwent audiometry assessments in the combined Phase 3 studies.

Table 7.4.9-1:
Summary of Audiometry Assessment Completion for the Overall Population and Patients <4 Years Old by Treatment Group and Visit
Studies 201-201302 and 201-201303 (Safety Analysis Set)

Overall population:			
Visit	**OTO-201 6 mg N = 357**	**Sham N = 173**	**Total N=530**
Baseline[a]	310 (86.8%)	151 (87.3%)	461 (87.0%)
Day 15	226 (63.3%)	108 (62.4%)	334 (63.0%)
Day 29	223 (62.5%)	107 (61.8%)	330 (62.3%)
All Visits	211 (59.1%)	101 (58.4%)	312 (58.9%)
Patients <4 years of age			
Visit	**OTO-201 6 mg N = 296**	**Sham N = 139**	**Total N=435**
Baseline[a]	249 (84.1%)	117 (84.2%)	366 (84.1%)
Day 15	168 (56.8%)	74 (53.2%)	242 (55.6%)
Day 29	162 (54.7%)	73 (52.5%)	235 (54.0%)
All Visits	153 (51.7%)	67 (48.2%)	220 (50.6%)

[a] Baseline was defined as the least measurement taken on or prior to the day of administration. Per protocol, this evaluation was not required for patients <4 years of age.
Source: Summary of Clinical Safety, Module 2, Section 2.7.4, Table 16.

In the Phase 3 studies, analysis of shifts in the air conduction (AC) and bone conduction (BC) revealed that the majority of ears had normal AC results or their results had shifted to normal by the Day 29 Visit. All patients in the OTO-201 group and all but 1 in the sham group had normal BC at all visits. Shifts in pure tone average (PTA) indicating worsening of hearing were infrequent in the OTO-201 and sham groups in each Phase 3 study. An effusion was often observed on otoscopic examination in the few patients with shifts in PTA. Bone conduction averages (BCA) were normal for a majority of ears in both treatment groups at all visits.

Reviewer's Comment:
As noted in Table 7.4.9-1, the number of patients less than 4 years of age with full audiometry testing in the Phase 3 studies met the minimum target number agreed upon at the End-of-Phase 2 meeting (approximately 60 patients exposed to OTO-201). Overall, audiometry changes consistent with worsening hearing from baseline were infrequent among ears in the OTO-201 or sham groups in the Phase 1b and Phase 3 studies.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

OTO-201 in the Phase 1b study was administered as either a single 4 mg (0.2 mL) or 12 mg (0.2 mL) dose into each ear. Information from a portion of patients in the high-dose (12 mg) cohort indicated that a majority received at least 0.1 mL of study materials, but not the targeted 0.2 mL dose volume. Assuming at least 0.1 mL of OTO-201 was administered into each ear in both OTO-201 cohorts, patients in the Phase 1b study received at least 2-4 mg and 6-12 mg of OTO-201. No safety concerns resulting from either dose were noted from the safety assessments, including from TEAEs, from hearing function testing, and from tympanometry.

OTO-201 in the Phase 3 studies was administered to patients as a single 6 mg (0.1 mL) dose into each ear and dose dependency for adverse events was not applicable in these studies.

7.5.2 Time Dependency for Adverse Events

The majority of TEAEs in the Phase 1b and Phase 3 studies were minor, occurred early after treatment, and self-limited. An exploration of time dependency for adverse events was not conducted.

7.5.3 Drug-Demographic Interactions

The safety analysis in the Phase 1b and Phase 3 studies stratified by age, sex, and race did not reveal clinically meaningful safety risks following intratympanic administration of OTO-201. Data were consistent with those from the overall safety population.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

In the combined Phase 3 studies, a review of adverse events in the group of patients who took additional antibiotics did not reveal a notably higher incidence of TEAEs than patients in the sham group who took additional antibiotics. No concerns were identified in the analysis of “antibiotic-emergent” adverse events where the timing of the receipt of concomitant antibiotic and the timing of the adverse event were taken into account. Drug interactions are unlikely to occur because of the limited systemic exposure to OTO-201 following single intratympanic administration. Specific drug interaction studies were not conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Menarcheal and post-menarcheal females were excluded from the clinical studies of OTO-201. There have been no adequate and well-controlled studies in pregnant or lactating women.

7.6.3 Pediatrics and Assessment of Effects on Growth

OTO-201 is proposed for a pediatric indication, specifically in children age 6 months and older. Assessment of effects on growth is unnecessary in the case of limited, low-dose exposure to a topical fluoroquinolone product such as this.

A partial pediatric waiver request for studies in patients younger than 6 months of age was included in the NDA submission. The rationale for the waiver was that it is impossible or highly impracticable to include patients less than 6 months of age in the clinical studies of otitis media with effusion requiring tympanostomy tube placement. Children less than 6 months of age generally have not manifested the signs and symptoms long enough to diagnose chronic OME. Further, tympanostomy tube placement is typically not indicated and rarely performed in patients less than 6 months of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

OTO-201 is designed for single intratympanic administration during myringotomy surgery with TT placement. The potential for overdose, drug abuse, withdrawal, or rebound are not expected concerns because OTO-201 is administered as a single dose by a trained clinician and in a controlled setting.

7.7 Additional Submissions / Safety Issues

The 120 day Safety Update was submitted on June 25, 2015. Per Otonomy:
2 new feasibility studies, Studies 201-201404 and (b) (4), have been conducted with OTO-201 since the NDA was submitted on February 25, 2015. The design of the two studies is summarized in Table 7.7-1.

Table 7.7-1:
Summary of the OTO-201 Studies Conducted Since NDA 207986 Submission

Study Identify	Study Design	Indication	Setting/ Treatment	Treatment Duration	Treated Subjects
201-201404[a]	Phase 3b, open-label, uncontrolled	Pediatric patients with otitis media undergoing TT placement	Surgical unit/ 6 mg OTO-201	Single bilateral administration through the tube post-myringotomy and suction	N = 33
(b) (4)					

[a] Study data have been analyzed, but report is not final

(b) (4)

Supportive Clinical Safety Information - Study 201-201404

This study was conducted in pediatric patients with bilateral middle ear effusion and evaluated the safety and feasibility of bilateral OTO-201 administration through the lumen of the TT during surgery. Patients/caregivers at 2 weeks post-administration were given the option of a single blood draw to measure the plasma ciprofloxacin concentration.

No deaths, serious adverse events, or dropouts due to an adverse event were reported in Study 201-201404. Plasma samples were obtained from two patients and both samples were below the limit of quantitation (i.e., <0.500 ng/mL). No overall differences were reported in results of vital sign evaluations, otoscopic examinations, and tympanometry for Study 201-201404 compared to the Phase 3 studies (Studies 201-201302 and 201-201303). Table 7.7.2 summarizes the adverse events reported in at least 2 patients in Study 201-201404 or reported in at least 3% of OTO-201 patients in Studies 201-201302 and 201-201303.

Table 7.7-2:
Adverse Events Reported in Study 201-201404

System Organ Class Preferred Term	OTO-201 6 mg N=33
Any TEAE	21 (63.6%)
Infections and infestations	12 (36.4%)
Upper respiratory tract infection	3 (9.1%)
Nasopharyngitis	7 (21.2%)
General disorders and administration site conditions	4 (12.1%)

System Organ Class Preferred Term	OTO-201 6 mg N=33
Pyrexia	4 (12.1%)
Irritability	0 (0.0%)
Gastrointestinal disorders	1 (3.0%)
Teething	1 (3.0%)
Vomiting	1 (3.0%)
Respiratory, thoracic and mediastinal disorders	4 (12.1%)
Cough	1 (3.0%)
Nasal congestion	2 (6.1%)
Rhinorrhea	0 (0.0%)
Injury, poisoning and procedural complications	0 (0.0%)
Procedural pain	0 (0.0%)
Ear and labyrinth disorders	7 (21.2%)
Ear pain	6 (12.1%)
Otorrhea	2 (6.1%)

Note: AE terms included in this table include events reported in at least 3% of OTO-201 treated patients in the combined Phase 3 studies or in at least 2 subjects treated in Study 201-201404.
Source: Adapted from 120-Day Safety Update Report SD004 submitted 06/25/15, Table 3.

Reviewer's Comment:
The adverse events reported in Study 201-201404 are consistent with those observed in the Phase 1b and the Phase 3 studies (Studies 201-201101, 201-201302, and 201-201303). Teething and nasopharyngitis were reported in Study 201-201404, but not irritability or rhinorrhea. No new safety issues were identified.

Study (b) (4)
(b) (4)

(b) (4)
. The study was completed but the data have not been analyzed.

8 Postmarket Experience

OTO-201 is not marketed in any country, and there are no post-marketing data to report.

9 Appendices

9.1 Literature Review/References

An independent literature review did not produce any additional significant information regarding OTO-201. Below is a list of the specific references cited in Section 2.2.

References

1. American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, American Academy of Pediatrics Subcommittee on Otitis Media with Effusion. “Otitis Media with Effusion.” *Pediatrics*, 2004; 113(5): 1412-29.

2. American Academy of Otolaryngology--Head and Neck Surgery. “Clinical Practice Guideline: Tympanostomy Tubes in Children.” *Otolaryngology—Head and Neck Surgery*, 2013; 149(1S): S1-S35.

3. Kay DJ, Nelson M, Rosenfeld RM. “Meta-analysis of tympanostomy tube sequelae.” *Otolaryngology-Head and Neck Surgery,* 2001; 124:374-80.

4. Coates H, Thornton R, Langlands J, Filion P, Keil AD, Vijayasekaran S, Richmond P. “The role of chronic infection in children with otitis media with effusion: Evidence for intracellular persistence of bacteria.” *Otolaryngology-Head and Neck Surgery,* 2008; 138:778-81.

5. Jung H, Lee SK, Cha SH, Byun JY, Park MS, Yeo SG. “Current bacteriology of chronic otitis media with effusion: high rate of nosocomial infection and decreased antibiotic sensitivity.” *Journal of Infection,* 2009; 59:308-16.

6. Pelton SI, Leibovitz E. “Recent Advances in Otitis Media.” *The Pediatric Infectious Disease Journal*, 2009; 28:S133-S137.

7. Roland PS, Parry DA, Stroman DW. “Microbiology of Acute Otitis Media with Tympanostomy Tubes.” *Otolaryngology-Head and Neck Surgery*, 2005; 133:585-95.

9.2 Labeling Recommendations

(b) (4)

5 pages of draft labeling have been withheld immediately following this page

9.3 Advisory Committee Meeting

Not applicable.

9.4 Clinical Investigator Financial Disclosure

Application Number: 207986

Submission Date(s): February 25, 2015

Applicant: Otonomy, Inc.

Product: 6% ciprofloxacin otic suspension

Reviewer: Mark Needles, M.D.

Date of Review: 11/19/2015

Covered Clinical Study (Name and/or Number):
201-201101, 201-201302, and 201-201303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Study 201-201101: 12 investigators Study 201-201302: 28 investigators Study 201-201303: 19 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: ____		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) ___		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant determined there were no financial interests or arrangements to disclose from the investigators in Studies 201-201101, 201-201302, and 201-201303.

1 See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK S NEEDLES
11/19/2015

THOMAS D SMITH
11/20/2015