CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207986Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

CLINICAL STUDIES

NDA #:	207986
Drug Name:	OTO-201 (6% ciprofloxacin otic suspension)
Indication(s):	Intra-operative treatment of middle ear effusion in pediatric subjects requiring tympanostomy tube placement
Applicant:	Otonomy, Inc.
Submission Date(s):	February 25, 2015
Review Priority:	Standard
PDUFA Date:	December 25, 2015
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Mushfiqur Rashid, Ph.D.
Concurring Reviewers:	Karen Higgins, Sc.D.
Medical Division:	Division of Anti-infective Products
Clinical Team:	Mark Needles, M.D. and Thomas Smith, M.D.
Project Manager:	Jane Dean
Keywords:	Sham-controlled, Confidence Interval, Cochran-Mantel-Haenszel test, Sensitivity Analyses

Addendum to the Statistical review:

In this submission, the applicant was seeking approval to market OTIPRIO (OTO-201), a 6% Ciprofloxacin otic suspension (OTO-201) for the treatment of middle ear effusion (MEE) in pediatric patients (aged 6 months to 17 years) with otitis media who are undergoing tympanostomy tube (TT) placement. The statistical review was posted in DARRTS on November 20, 2015. There were typos in row 5 Table 9 of the review. The corrected (with highlighted row 5) Table 9 is provided below:

Table 9: Components of Study Treatment Failure by Study, Treatment Group and Time point (Full Analysis Set)

	Study 201-201302		Study 201-201303	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88
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%)
Through Day 8	11 (6.1%)	8 (9.2%)	9 (5.1%)	21 (23.9%)
Through Day 15	13 (7.3%)	10 (11.5%)	12 (6.7%)	24 (27.3%)
Through Day 29	15 (8.4%)	12 (13.8%)	22 (12.4%)	29 (33.0%)
Otic Antibiotics-only				
Through Day 4	2 (1.1%)	12 (13.8%)	1 (0.6%)	5 (5.7%)
Through Day 8	4 (2.2%)	15 (17.2%)	4 (2.2%)	5 (5.7%)
Through Day 15	10 (5.6%)	15 (17.2%)	9 (5.1%)	7 (8.0%)
Through Day 29	15 (8.4%)	17 (19.5%)	12 (6.7%)	9 (10.2%)
Systemic Antibiotics-only				
Through Day 4	1 (0.6%)	0	0	1 (1.1%)
Through Day 8	2 (1.1%)	1 (1.1%)	3 (1.7%)	3 (3.4%)
Through Day 15	3 (1.7%)	4 (4.6%)	6 (3.4%)	3 (3.4%)
Through Day 29	6 (3.4%)	6 (6.9%)	9 (5.1%)	6 (6.8%)
Lost-to-follow-up-only				
Through Day 4	1 (0.6%)	0	1 (0.6%)	0
Through Day 8	1 (0.6%)	0	1 (0.6%)	0
Through Day 15	1 (0.6%)	0	1 (0.6%)	0
Through Day 29	1 (0.6%)	0	1 (0.6%)	0
Missed Visits-only				
Through Day 4	4 (2.2%)	2 (2.3%)	1 (0.6%)	2 (2.3%)
Through Day 8	9 (5.0%)	7 (8.0%)	8 (4.5%)	3 (3.4%)
Through Day 15	17 (9.5%)	10 (11.5%)	10 (5.6%)	6 (6.8%)
Through Day 29	21 (11.7%)	13 (14.9%)	14 (7.9%)	7 (8.0%)

Source: Table 11-6, Clinical Study reports

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: After a patient is identified a study treatment failure due to one of the treatment failure components, subsequent events during the study from other treatment failure components are not included in this table

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/s/

MUSHFIQUR M RASHID
11/25/2015

KAREN M HIGGINS
11/30/2015
I concur.

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

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1. EXECUTIVE SUMMARY

Introduction

In this submission, the applicant is seeking approval to market OTIPRIO (OTO-201), a 6% Ciprofloxacin otic suspension (OTO-201) for the treatment of middle ear effusion (MEE) in pediatric patients (aged 6 months to 17 years) with otitis media who are undergoing tympanostomy tube (TT) placement. The applicant has provided findings from two independent and identically-designed Phase 3 studies (Study 201-201302 and Study 201-201303) of OTO-201 to establish the efficacy and safety of a single intratympanic injection for intra-operative treatment of middle ear effusion in pediatric subjects requiring TT placement. Both trials are prospective, randomized, double-blind, sham-controlled, multicenter, phase 3 trials conducted in the United States and Canada. Study 201-201302 was included 179 patients in OTO-201 arm and 87 patients in Sham arm whereas Study 201-201303 included 178 patients in OTO-201 arm and 88 patients in Sham arm.

The primary efficacy endpoint for both studies was the cumulative proportion of study treatment failures through Day 15. The primary endpoint was compared between the OTO-201 and sham groups of the full analysis set using the Cochran-Mantel-Haenszel (CMH) test stratified by age stratum (6 months to 2 years and >2 years). The CMH test was conducted at the 2-tailed 0.05 alpha level using the full analysis set (FAS) which consisted of all randomized patients. Estimates of the treatment difference with associated 95% confidence intervals (CIs) were provided.

Conclusions and Recommendations

Based on the reviewer's analysis of the primary endpoint, cumulative proportion of study treatment failures through Day 15, Study 201-201302 and Study 201-201303 provided adequate evidence supporting the efficacy of OTO-201 for intra-operative treatment of middle ear effusion in pediatric subjects requiring TT placement. The treatment failure rate at day 15 was significantly lower in the OTO-201 treated group than the sham treated group (25% [44/179] versus 45% [39/87]) with a 20% difference (CMH p-value <0.001) in Study 201-201302. Treatment failure rate at day 15 was significantly lower in the OTO-201treated group than the sham treated group (21% [38/178] versus 45% [40/88]) with a 24% difference (CMH p-value<0.001) in Study 201-201303.

The applicant's safety evaluation from these studies indicates that the product was safe and well tolerated. The safety data from Study 201-201302 and Study 201-201303 demonstrated that a single intratympanic injection for intra-operative treatment of middle ear effusion in pediatric subjects requiring TT placement had a similar safety profile to Sham injection. Most of the AEs were mild or moderate in severity. No deaths, life-threatening TEAEs, or TEAEs leading to discontinuation were reported in these studies. Please see the clinical review of safety by Dr. Mark Needles for further details.

2. INTRODUCTION

2.1 Overview

The Applicant's current submission includes two identical pivotal phase 3 trials (Study 201-201302 and Study 201-201303) of OTO-201(6% Ciprofloxacin otic suspension) to establish the efficacy and safety of a single intratympanic injection for intra-operative treatment of middle ear effusion in pediatric subjects (aged 6 months to 17 years) requiring TT placement. The following table provides the description of the two pivotal phase 3 trials:

Table 1: Overview of Clinical Phase 3 Efficacy Program

Study Design	Treatment Groups	Regimen/ Schedule/ Duration	No. of Subjects by study		Median Age (range)		Region (No. of Centers) by study	
			201-201302	201-201303	201-201302	201-201303	201-201302	201-201303
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 middle ear effusion requiring TT placement	OTO-201: 6 mg Sham: Syringe with air	0.1 mL intratymapnic injection into each ear Single dose during myringotomy surgery with TT placement Follow-up to day 29	Randomized: N=266 OTO-201 6 mg: 179 Sham: 87 Treated: N=265 OTO-201 6 mg: 179 Sham: 86	Randomized: N=266 OTO-201 6 mg:178 Sham: 88 Treated: N=265 OTO-201 6 mg: 178 Sham: 87	1.585 years (0.50 to 12.60)	1.535 years (0.51 to 11.63)	US (25), and Canada (4)	US(18) and Canada (1)

The primary objective of these studies was to confirm the effectiveness of OTO-201 in the treatment of pediatric subjects with bilateral middle ear effusion who require TT placement. The secondary objective was to assess the safety and tolerability of OTO-201 when administered intraoperatively to pediatric subjects undergoing myringotomy with TT placement. The primary analysis population was the intent-to-treat (ITT) population which included all randomized patients. Note that ITT population and FAS will be used interchangeably in this review.

2.2 Data Sources

The primary efficacy data (including demographic data) and the baseline characteristics datasets were provided in the file ADEFA.xpt (data for efficacy endpoints: one record per subject per parameter with key PARAMCD) under the network drive:

\\cdsesub1\EVSPROD\NDA207986\0000\m5\datasets\201-201302\analysis\adam\datasets

for study 201-291302

and

\\cdsesub1\EVSPROD\NDA207986\0000\m5\datasets\201-201303\analysis\adam\datasets

for study 201-291303.

The treatment group was denoted by TRTP (planned treatment: Record level identifier of planned treatment at time of assessment). The data for primary efficacy with Success or Failure in column AVAL (Numeric indicator of the specified treatment failure) correspond to AVISITN (analysis visit number) and PARAMCD (code for treatment failure endpoint).

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant has stated that the data for Study 201-201302 and Study 201-201303 were collected using eCRF. The applicant stated the following:

> Site staff entered subject data directly into the clinical database using eCRFs. Discrepancies were automatically generated within the electronic data capture (EDC) system for the site staff to resolve immediately. In addition, as a result of data review by the sponsor or designee, manual queries could be issued electronically in the EDC system. Queries could also be issued as a result of source data verification by the clinical monitor. The investigator or other authorized study site personnel made all corrections within the EDC system. The clinical monitor and data management teams ensured appropriate resolution of queries. The investigator was required to authorize changes to the recorded safety and efficacy data.
>
> Steps taken to assure the accuracy and reliability of data included the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel prior to study initiation, and periodic monitoring visits by the sponsor or its representatives. The sponsor or its representatives performed on-site monitoring visits as frequently as necessary, based on study center activity, to review protocol compliance, compare eCRFs with individual subject medical records and clinic charts, and ensure that the study was being conducted according to pertinent regulatory requirements. The review of medical records was performed in a manner that ensured subject confidentiality was maintained. During and after on-site monitoring visits, the sponsor or its representatives reviewed eCRFs in the EDC system database for accuracy and completeness. Any discrepancies were resolved with the investigator or designees, as appropriate, and documented in the EDC system.

The quality and integrity of the submission are acceptable. The submission uses the electronic common technical document (eCTD) format. The submission is well organized and easy to navigate. Submitted Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets meet the Clinical Data Interchange Standards Consortium (CDISC) standards. It is possible to reproduce the primary endpoint and the secondary endpoints from both the SDTM and ADAM datasets that the applicant provided.

3.2. Evaluation of Efficacy

3.2.1 Trial Design and Endpoints

Studies 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 pediatric otolaryngologist became unblinded at the time of treatment administration. This person continued to assess the patient at subsequent visits. The otoscopic exams were not blinded. Only the external assessment of otorrhea was blinded.

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 total of 29 and 19 centers were used for Studies 201-201302 and 201-201303, respectively.

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 with 176 assigned to OTO-201 and 88 assigned to sham. Each Phase 3 study enrolled 266 patients and the patients were randomized to either OTO-201 or sham using a 2:1 allocation ratio stratified by age: 6 months to 2 years or >2 years. Only patients with bilateral effusion confirmed on the day of surgery were randomized prior to the surgery. 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.

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.

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 used an investigational drug or device in the month prior to screening.
16. Patient had been previously exposed to OTO-201.
17. Patient was a menarcheal or post-menarcheal female.
18. Patients 4 years and older were not able to complete all baseline assessments; patients younger than 4 years were not able to complete all baseline assessments, not including audiometry.
19. Patient is a sibling or resides in the same household as another participating subject.

Schedule of Assessments

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), if the patients experienced an adverse event between scheduled visits, or if the patients required follow-up on any adverse event prior to the end of study visit (Day 29 Visit). See Table below for the schedule of assessments.

Table 2: Schedule of events 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						
Physical 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	

Source: Applicant's Table 9-1, Clinical Study Report

[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

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 did not 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 requires withdrawal from the study, if a patient developed a condition that made it unwise to continue with the trial, or if a patient (or caregiver) requests an early discontinuation. Patients were discontinued from the Phase 3 studies for the following reasons:

- Withdrawal of consent
- Did not follow-up
- Early termination in error after the Day 15 Visit

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 post-surgery (on or after Day 4) through the Day 15 Visit.
- Otic treatment failure – patient given an otic antibiotic any time post-surgery 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 post-surgery 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.

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 post baseline bacteriology sample collected that confirmed eradication of the baseline bacterial pathogen.
  - Microbiological response with presumption – patients who did not have a post baseline 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 Pseudomonas aeruginosa, Staphylococcus aureus, Strepotoccus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis in at least one ear.

Safety Endpoints

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

3.2.2 Statistical Methodologies

Determination of Sample Size

The Cochran-Mantel-Haenszel (CMH) test was 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) and with failure rates of 25% in the OTO-201 group and 46% in the Sham group 46%, the studies would have the power of 93% to reject the null hypothesis of no difference.

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 *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Strepotoccus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* 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. Overall risk differences for each age stratum were presented with their associated 95% confidence intervals (CI).

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 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. See the clinical microbiologist's review for details.

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.

Handling of missing data

Subjects were defined as a study treatment failure from the earliest time point at which a qualifying event occurred and were considered a study treatment failure for the remainder of the study. Subjects whose study treatment failure status was unknown at the scheduled Day 15 Visit because they were lost-to-follow-up were classified as a study treatment failure for the primary analysis (i.e., a lost-to-follow-up treatment failure) at the date of discontinuation, or date of last contact, if date of discontinuation is unknown. Subjects not lost-to-follow-up with a missing treatment failure status at a particular visit were classified as a study treatment failure (a missed visit treatment failure) at the target study day of the first missed visit if they had not yet been identified as a study treatment failure.

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 for 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.

Subgroup Analyses

The primary endpoint was analyzed for the following subgroups of patients:

1) Demographic subgroups, including:
    a) Age (< 2years, 2 to < 17 years);
    b) Gender (males and females);
    c) Race (White, Black or African American, and Other);
2) Investigative sites

Note that the above subgroup analyses were pre-specified. However, the protocols did not mention whether the above subgroup analyses would be subject to meeting the primary hypothesis.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition

Patient disposition for Study 201-201302 and Study 201-201303 are provided below.

Table 3:Patient 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%)

Source: Sponsor's Table 10.1, Clinical Study reports

[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.

Note that in study 201-201302, one patient was randomized to sham but received OTO-201 while in study 201-201303, two patients were randomized to sham but received OTO-201 and one patient was randomized to OTO-201 but received sham.

For the primary efficacy analysis using the ITT population, all premature discontinuations were considered study treatment failures. There were a total of 2 patients in Study 201-201302 (1 for OTO-201 and 1 for sham) and 2 patients in Study 201-201303 (2 for OTO-201) who did not complete the study through the Day 15 Visit. Two of these patients (1 in Study 201-201302 and 1 in Study 201-201303) were randomized to OTO-201 and then discontinued from the study prior to study drug administration. The other 2 patients (1 sham patient in Study 201-201302 and 1 OTO-201 patient in Study 201-201303) did not follow-up at any time after the Day 15 Visit.

Protocol Deviations in Study 201-201302

Forty eight 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), or 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, or 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 patient
  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

Thirty three 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), or 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, or 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.

Demographic Characteristics by Study (Full Analysis Set)

Demographic characteristics were well-balanced across the two Phase 3 studies and across the two treatment groups. See Table below.

Table 4: Demographic Characteristics by Study (Full Analysis Set)

Demographic Parameters	Study 201-201302		Study 201-201303	
	OTO-201 6 mg N=179	Sham N=87	OTO-201 6 mg N=178	Sham N= 88
Sex n (%)				
Male	104 (58.1%)	56 (64.4%)	96 (53.9%)	48 (54.5%)
Female	75 (41.9%)	31 (35.6%)	82 (46.1%)	40 (40.5%)
Age (years)				
Median (years)	1.510	1.610	1.500	1.585
Age stratum – n (%)				
6 months to 2 years	109 (60.9%)	53 (60.9%)	111 (62.4%)	53 (60.2%)
> 2 years	70 (39.1%)	34 (39.1%)	67 (37.6%)	35 (39.8%)
Race				
White	148 (82.7%)	69 (79.3%)	140 (78.7%)	72 (81.8%)
Black	20 (11.2%)	13 (14.9%)	23 (12.9%)	10 (11.4%)
Asian	2 (1.1%)	0	2 (1.1%)	2 (2.3%)
Native American/Canadian	1 (0.6%)	0	1 (0.6%)	1 (1.1%)
Native Hawaiian or Other Pacific Islander	0	0	2 (1.1%)	0
Not Applicable	1 (0.6%)	1 (1.1%)	1 (0.6%)	2 (2.3%)
Other	7 (3.9%)	4 (4.6%)	9 (5.1%)	1 (1.1%)

Source: Applicant's Table 11-1, Clinical Study report

Baseline Microbiology Results by Study and Treatment Group (Full Analysis Set)

Baseline microbiology results by were well-balanced across the two Phase 3 studies and across the two treatment groups. See Table 5.

Table 5: Baseline Microbiology Results by Study and Treatment Group (Full Analysis Set)

Characteristics	Study 201-201302		Study 201-201303	
	OTO-201 6 mg N=179	Sham N=87	OTO-201 6 mg N=178	Sham N= 88
Baseline microbiology results – n (%)[1]				
Positive[2]				
Both Ears	17 (9.5%)	11 (12.6%)	7 (3.9%)	6 (6.8%)
At Least One Ear[3]	41 (22.9%)	22 (25.3%)	29 (16.3%)	27 (30.7%)
S. pneumoniae – positive				
Both Ears	2 (1.1%)	2 (2.3%)	6 (3.4%)	1 (1.1%)
At Least One Ear	10 (5.6%)	6 (6.9%)	10 (5.6%)	6 (6.8%)
H. influenzae – positive				
Both Ears	10 (5.6%)	9 (10.3%)	1 (0.6%)	4 (4.5%)
At Least One Ear	26 (14.5%)	15 (17.2%)	13 (7.3%)	12 (13.6%)
M. catarrhalis – positive				
Both Ears	0	0	0	1 (1.1%)
At Least One Ear	8 (4.5%)	3 (3.4%)	6 (3.4%)	5 (5.7%)
S. aureus – positive				
Both Ears	4 (2.2%)	1 (1.1%)	0	0
At Least One Ear	5 (2.8%)	1 (1.1%)	1 (0.6%)	3 (3.4%)
P. aeruginosa – positive				
Both Ears	0	0	0	0
At Least One Ear	1 (0.6%)	0	0	2 (2.3%)
Unknown[4]				
Both Ears	3 (1.7%)	2 (2.3%)	2 (1.1%)	0
At Least One Ear	7 (3.9%)	3 (3.4%)	4 (2.2%)	2 (2.3%)

Source: Sponsor's Table 11-2, Clinical Study Reports

[1] Baseline was defined as the last measurement taken on or prior to the day of study drug administration.

[2] This category represents subjects for which the baseline microbiology culture was positive for a 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] Microbiology culture unknown indicates that the microbiology culture results were not recorded (or missing).

3.2.4 Results and Conclusions

Primary Analysis

The primary evaluation of the efficacy of OTO-201 is based on data from 2 identically designed, randomized, double-blind, sham-controlled studies for the treatment of middle ear effusion in pediatric subjects with otitis media requiring tympanostomy tube (TT) placement. The

reviewer's primary analysis was consistent with the applicant's analysis. The primary efficacy analysis is summarized in the following table.

Table 6: Primary Efficacy - Study Treatment Failures through Day 15 by Treatment Group (Full Analysis Set)

Overall				
	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[a] through Day 15				
n (%)	44(25%)	39(45%)	38(21%)	40(45%)
% Difference: Sham - OTO-201 (95% CI) [b]	20% (8%, 32%)		24% (12%, 36%)	
CMH p-value [c]	<0.001		<0.001	
Age Group: 6 months through 2 years				
	Study 201-201302		Study 201-201303	
	OTO-201 6mg N = 109	Sham N = 53	OTO-201 6mg N = 111	Sham N = 53
Cumulative proportion of Study Treatment Failures[a] through Day 15				
n (%)	33 (30.3%)	28 (52.8%)	28 (25.2%)	33 (62.3%)
% Difference: Sham- OTO-201 (95% CI)[b]	23% (7%, 39%)		37% (22%, 53%)	
p-value[b]	0.005		<0.001	
Age Group: >2 years				
	Study 201-201302		Study 201-201303	
	OTO-201 6mg N = 70	Sham N = 34	OTO-201 6mg N = 67	Sham N = 35
Cumulative proportion of Study Treatment Failures[a] through Day 15				
n (%)	11 (15.7%)	11 (32.4%)	10 (14.9%)	7 (20.0%)
% Difference: Sham - OTO-201 (95% CI) [b]	17% (1%, 35%)		5% (11%, 21%)	
p-value[b]	0.051		0.514	

[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] All % differences and the corresponding 95% CIs were not adjusted for age strata. % differences were estimated by the proportion of patients with treatment failure in the sham group - the proportion of patients with treatment failure in the OTO-201 6 mg group and the CI was computed using normal approximation to the binomial

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

Based on the reviewer's analysis of the primary endpoint, the cumulative proportion of study treatment failures through Day 15, Study 201-201302 and Study 201-201303 provided adequate evidence supporting the efficacy of OTO-201 for intra-operative treatment of middle ear effusion in pediatric subjects requiring TT placement. Treatment failure rate at day 15 was significantly lower in OTO-201 treated group than sham treated group (25% [44/179] vs. 45% [39/87]) with a 20% difference (CMH p-value <0.001) in Study 201-201302. Treatment failure rate at day 15 was significantly lower in OTO-201 treated group than sham treated group (21% [38/178] vs.45% [40/88]) with a 24%% difference (CMH p-value<0.001) in Study 201-201303. The results by strata also show numerically higher failure rates in the Sham group compared to the treated group. The effect in the younger age group was stronger than in the older age group and reached statistical significance in both studies, despite the study not being powered to detect differences within age strata. The treatment effect in the older age group was fairly small in Study 201-201303, but close to significant in Study 201-201302. A detailed subgroup analysis by age-group will be provided in Section 4.1.

Per Protocol Analysis:

This reviewer conducted sensitivity analysis using the Per-Protocol analysis set which included all randomized patients from the ITT population who did not have major protocol deviations and had external ear examinations for otorrhea conducted by the blinded assessor at the Day 4, Day 8, and Day 15 Visits. It is to be noted here that this is a subset analysis based on the post-randomization exclusions.

Table 7: Primary Efficacy - Study Treatment Failures[a] through Day 15 by Treatment Group (Per-Protocol Analysis Set)

	Study 201-201302		Study 201-201303	
	OTO-201 6mg N = 148	Sham N = 70	OTO-201 6mg N = 159	Sham N = 74
n (%)	18 (12.2%)	27 (38.6%)	27 (17.0%)	29 (39.2%)
% Difference: Sham - OTO-201 (95% CI)[b]	27% (14%, 39%)		22% (10%, 35%)	
CMH p-value[c]	<0.001		<0.001	

Source: Reviewer's Table

[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

[b] All % differences and the corresponding 95% CIs were not adjusted for age strata. % 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 and the CI was computed using normal approximation to the binomial.

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

Based on the reviewer's analysis of the primary endpoint for the per protocol population, the cumulative proportion of study treatment failures through Day 15, Study 201-201302 and Study 201-201303 provided adequate evidence supporting the efficacy of OTO-201 for intra-operative

treatment of middle ear effusion in pediatric subjects requiring TT placement. Treatment failure rate at day 15 was significantly lower in OTO-201treated group than sham treated group (12% [18/148] vs. 39% [27/70]), with a 27% difference (CMH p-value <0.001) in Study 201-201302. Treatment failure rate at day 15 was significantly lower in OTO-201 treated group than sham treated group (17% [27/159] vs. 39% [29/74]) with a 22% difference (CMH p-value<0.001) in Study 201-201303. The per protocol analysis of the primary endpoint is consistent with the ITT analysis of the primary endpoint.

Note that forty eight 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), or Visit 5 (Day 15) in study 201-201302. Thirty three 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), or Visit 5 (Day 15) in study 201-2013023.

Sensitivity Analyses

Treatment failures due to otorrhea only through Day 15:

It is of interest to examine the treatment failures due to otorrhea only through Day 15 since a treatment failure due to otorrhea only is a major component of the primary endpoint. Treatment failures due to otorrhea only through Day 15 are summarized in Table 8.

Table 8: Secondary Efficacy - Study Treatment Failures due to Otorrhea only through Day 15 by Treatment Group (Full Analysis Set)

	Study 201-201302			Study 201-201303		
	OTO-201 6 mg (N = 179)	Sham (N = 87)	% Difference : Sham-OTO-201	OTO-201 6 mg (N = 178)	Sham (N = 88)	% Difference : Sham-OTO-201
n (%)	13 (7.3%)	10 (11.5%)	4%	12 (6.7%)	24 (27.3%)	20%
CMH p-value	0.250			<0.001		

Source: Sponsor's study reports, Table 11-5, page 64

It can be seen from the above table that 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. However, the CMH test suggested that there was no significant difference in treatment failures through day 15 between the treatment groups in Study 201-201302. Note that the study was not powered for testing the difference in treatment failures due to otorrhea only through day 15 between the treatment groups.

Components of Study Treatment Failure:
The analysis of the components of study treatment failure includes only the earliest occurring treatment failure event, and patients remained a study treatment failure due to that component for the remainder of the study (at the time point of observation and for the subsequent endpoint time points). Other treatment failure components occurring after a patient is identified a study treatment failure were not included in this analysis. Components of Study Treatment Failure by Study, Treatment Group and Time point (Full Analysis Set) by Study, Treatment Group and Time point are provided in the following table:

Table 9: Components of Study Treatment Failure by Study, Treatment Group and Time point (Full Analysis Set)

	Study 201-201302		Study 201-201303	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88
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%)
Through Day 8	11 (6.1%)	8 (9.2%)	9 (5.1%)	21 (23.9%)
Through Day 15	44 (24.6%)	39 (44.8%)	38 (21.3%)	40 (45.5%)
Through Day 29	15 (8.4%)	12 (13.8%)	22 (12.4%)	29 (33.0%)
Otic Antibiotics-only				
Through Day 4	2 (1.1%)	12 (13.8%)	1 (0.6%)	5 (5.7%)
Through Day 8	4 (2.2%)	15 (17.2%)	4 (2.2%)	5 (5.7%)
Through Day 15	10 (5.6%)	15 (17.2%)	9 (5.1%)	7 (8.0%)
Through Day 29	15 (8.4%)	17 (19.5%)	12 (6.7%)	9 (10.2%)
Systemic Antibiotics-only				
Through Day 4	1 (0.6%)	0	0	1 (1.1%)
Through Day 8	2 (1.1%)	1 (1.1%)	3 (1.7%)	3 (3.4%)
Through Day 15	3 (1.7%)	4 (4.6%)	6 (3.4%)	3 (3.4%)
Through Day 29	6 (3.4%)	6 (6.9%)	9 (5.1%)	6 (6.8%)
Lost-to-follow-up-only				
Through Day 4	1 (0.6%)	0	1 (0.6%)	0
Through Day 8	1 (0.6%)	0	1 (0.6%)	0
Through Day 15	1 (0.6%)	0	1 (0.6%)	0
Through Day 29	1 (0.6%)	0	1 (0.6%)	0
Missed Visits-only				
Through Day 4	4 (2.2%)	2 (2.3%)	1 (0.6%)	2 (2.3%)
Through Day 8	9 (5.0%)	7 (8.0%)	8 (4.5%)	3 (3.4%)
Through Day 15	17 (9.5%)	10 (11.5%)	10 (5.6%)	6 (6.8%)
Through Day 29	21 (11.7%)	13 (14.9%)	14 (7.9%)	7 (8.0%)

Source: Table 11-6, Clinical Study reports

[1] 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

Note: % Difference: (Sham - OTO-201)

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: After a patient is identified a study treatment failure due to one of the treatment failure components, subsequent events during the study from other treatment failure components are not included in this table

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. Note that the

study was not powered for testing the difference in treatment failures (at any visit) by components between the treatment groups.

Analyses not categorizing as study treatment failures if identified as systemic antibiotic treatment failures, lost-to-follow-up treatment failures, or missed visit treatment failures

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. Table below summarizes the comparison of three sensitivity analyses of the primary efficacy endpoint between the OTO-201 and sham group.

Table 10: 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%)
% Difference (95% CI)	17% (5%, 29%)		24% (12%, 36%)	
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%)
% Difference (95% CI)	21% (9%, 33%)		25% (13%,37%)	
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%)
% Difference (95% CI)	18% (7%, 30%)		25% (12%, 35%)	
p-value	<0.001		<0.001	

Source: Sponsor's Tables 14.2.2, 14.2.3, and 14.2.4 respectively
Note: % Difference: (Sham - OTO-201)

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: All treatment 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.

It can be seen from the above table that both phase 3 studies had statistically significant differences favoring OTO-201 treatment when

a) assuming patients prescribed systemic antibiotics were non-treatment failures
b) assuming patients with missing observations due to being lost-to-follow-up or missed visits were non-treatment failures.

Secondary Efficacy Endpoints Analyses

The reviewer's secondary efficacy endpoints analyses are provided below.

Study Treatment Failures through Days 4, 8, and 29:

Study Treatment Failures through Days 4, 8, and 29 by the Treatment Group (Full Analysis Set) are summarized in the following table:

Table 11: Secondary Efficacy - Study Treatment Failures[a] through Days 4, 8, and 29 by Treatment Group (Full Analysis Set)

	Study 201-201302		Study 201-201303	
	OTO-201 6 mg N = 179	Sham N = 87	OTO-201 6 mg N = 178	Sham N = 88
Day 4				
n %)	16 (8.9%)	21 (24.1%)	9 (5.1%)	25 (28.4%)
% Difference: Sham- OTO-201 (95% CI)[b]	15% (5%, 25%)		23% (13%, 33%)	
CMH p-value[c]	<0.001		<0.001	
Day 8				
n %)	27 (15.1%)	31 (35.6%)	25 (14.0%)	32 (36.4%)
% Difference: Sham- OTO-201 95% CI)[b]	20% (9%, 32%)		22% (11%, 34%)	
CMH p-value[c]	<0.001		<0.001	
Day 29				
n %)	58 (32.4%)	48 (55.2%)	58 (32.6%)	51 (58.0%)
% Difference: Sham- OTO-201 (95% CI)[b]	23% (10%, 35%)		25% (13%, 38%)	
CMH p-value[c]	<0.001		<0.001	

Source: Reviewer's Table

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

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

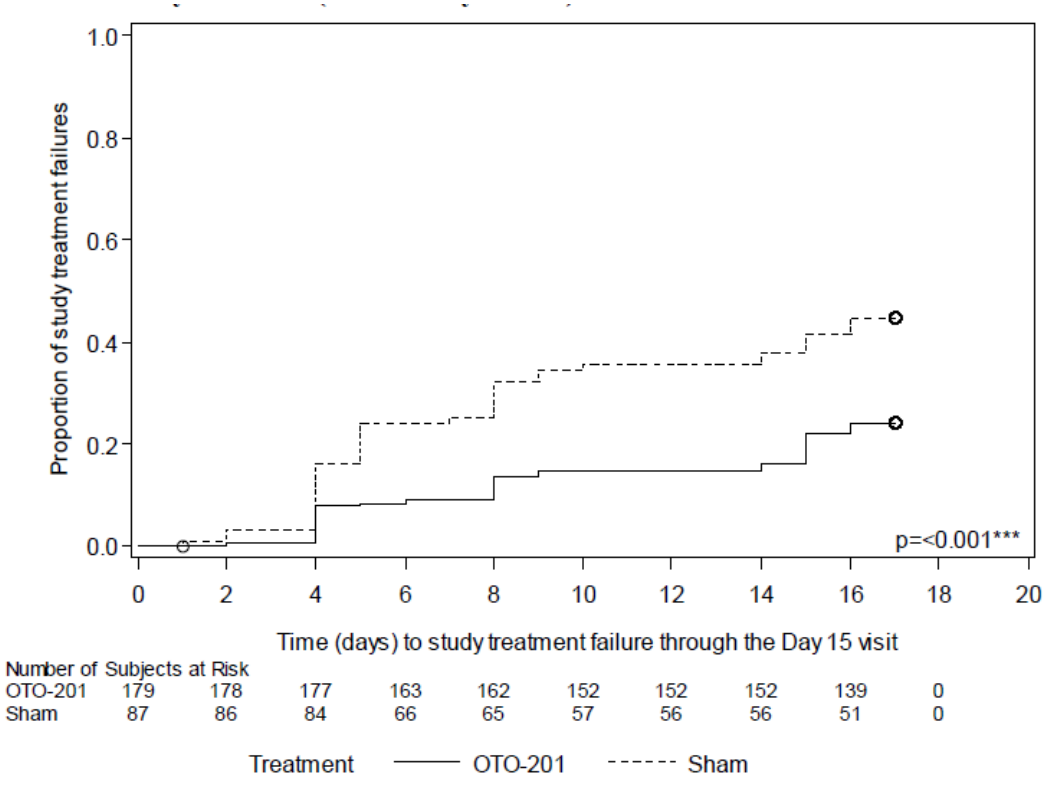
Table 11 shows that study treatment failures rates through Days 4, 8, and 29 were lower in OTO-201 6 mg treated than Sham treated group in both trials. Note that the reviewer's analyses were consistent with the applicant's analyses.

Time-to-Study Treatment Failure through the Day 15 Visit

This reviewer has conducted analyses of Time-to-Study Treatment Failure through the Day 15 Visit for both studies. This reviewer's analyses were consistent with the applicant analyses. The results are summarized below.

Figure 1 shows a Kaplan-Meier plot of the time to study treatment failure through the Day 15 Visit with censoring of lost-to-follow-up treatment failures for Study 201-201302.

Figure 1: Kaplan-Meier plot of the time to study treatment failure through the Day 15 Visit with censoring of lost-to-follow-up treatment failures (Study. 201-201302)



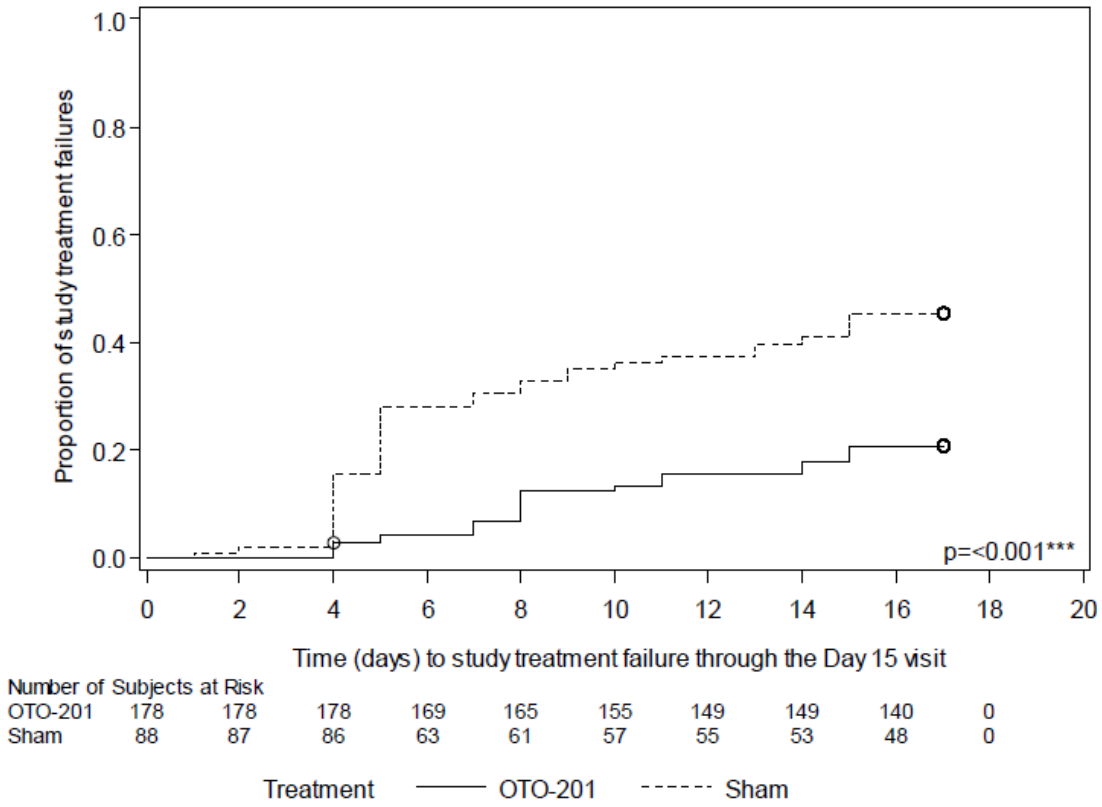
Source: Sponsor's Figure 11-1, page 62, Clinical Study Report

The time-to-treatment failure curves were significantly different between OTO-201 and sham groups using a log-rank test adjusted for age (log-rank test p-value <0.001). Although the median time to study treatment failure was not estimable in either treatment group, because of

too few events, the results suggest that sham subjects were more likely to fail earlier starting at Day 4 when compared with OTO-201 subjects.

Figure 2 shows a Kaplan-Meier plot of the time to study treatment failure through the Day 15 Visit with censoring of lost-to-follow-up treatment failures in Study 201-201303.

Figure 2: Kaplan-Meier plot of the time to study treatment failure through the Day 15 Visit with censoring of lost-to-follow-up treatment failures (Study. 201-201303).



Source: Sponsor's Figure 11-1, page 62, Clinical Study Report

The time-to-treatment failure curves were significantly different between OTO-201 and sham groups using a log-rank test adjusted for age (log-rank test: p-value <0.001). Although the median time to study treatment failure was not estimable in either treatment group, because of not enough events, the results suggest that sham subjects were more likely to fail earlier starting at Day 4 when compared to OTO-201 subjects.

3.3 Evaluation of Safety

Two randomized, multicenter, controlled clinical trials in 532 pediatric patients with bilateral otitis media with effusion undergoing myringotomy with tympanostomy tube placement

evaluated the safety and efficacy of OTIPRIO when administered intraoperatively as a single dose. Because the two studies were identical, the applicant poled the two studies for the safety assessment.

The safety profile of OTO-201 was assessed by the analysis of adverse events (AEs), vital signs, otoscopy, tympanometry, audiometry, and concomitant medication use. A total of 8.7% of subjects reported a treatment-emergent adverse event (TEAEs). The applicant has reported that the majority of TEAEs associated with intratympanic administration of OTO-201 were mild or moderate in severity, with only 3 being reported as severe (2 in the Otiprio group, and 1 in the sham group). See clinical review of Dr. Mark Needles for further details.

The applicant's summary of adverse reactions that occurred in at least 3% of OTIPRIO patients and at an incidence greater than sham are presented in Table 12.

Table 12: Adverse Reactions in Pooled Phase 3 Studies

	OTIPRIO (N=357)	Sham (N=173)
Nasopharyngitis	5%	4%
Irritability	5%	3%
Rhinorrhea	3%	2%

Source: Sponsor's Table 8, Module 2, Section 2.7.4 Summary of Clinical Safety, Page 34

The applicant has reported that no deaths, life-threatening TEAEs, or TEAEs leading to discontinuation were reported in these studies. The Sponsor has also reported that the safety evaluation from these studies indicates that the product was safe and well tolerated.

3.4 Benefit-Risk Assessment

The primary evaluation of the efficacy of OTO-201 (6 mg [0.1 mL of a 6.0% ciprofloxacin suspension] administered to each ear) is based on data from 2 identically designed, randomized, double-blind, sham-controlled studies for treatment of middle ear effusion in pediatric subjects with otitis media requiring tympanostomy tube (TT) placement. Overall, 532 subjects were enrolled in the pivotal Phase 3 studies (201-201302 and 201-201303 combined).

The results from studies 201-201302 and 201-201303 demonstrated superiority of OTO-201 over sham in the primary endpoint and the secondary endpoints (failure rates at day 4, day 8, day29 and time to failure through day 15). The results from studies 201-201302 and 201-201303 also demonstrated superiority of OTO-201 over sham with respect to the primary endpoint in the per protocol population.

The applicant reported that treatment with OTO-201 in the pediatric population was overall safe and well-tolerated through 28 days post-treatment in both adequate and well-controlled Phase 3 studies.

4 FINDINGS IN SPECIAL/SUBGROUP POPLATIONS

The applicant's subgroup analyses included the following factors: demographics and baseline characteristics (age, sex, and race) and sites.

It is to be noted that subgroup analyses were limited by a high degree of variability resulting from the small number of subjects included in each subgroup. Both trials were not powered to test the effectiveness of the drug for the subgroups. In addition, there was a problem (inflation of type I error) of multiple hypotheses testing related to subgroup analyses. For these reasons, confidence intervals for treatment differences in subgroups were not considered to be informative. Therefore, the subgroup analyses have to be interpreted very cautiously.

A few of these subgroup analyses are provided below using Breslow-Day test (unadjusted for age-group) for the homogeneity of odd ratios.

4.1Gender, Race, Age, and Geographic Region

Analysis by gender

The following table provides treatment failure rates at day 15 by gender for both 201-201302 and 201-201303 trials.

Table 13: Study Treatment Failures through Day 15 by Gender and Treatment Group (Full Analysis Set)

	Study 201-201302			Study 201-201303		
Gender	OTO-201 6 mg n/N (%)	Sham n/N (%)	% Difference (Sham – Otiprio)	OTO-201 6 mg n N (%)	Sham n/N (%)	% Difference (Sham – Otiprio)
Male	19/104 (18.3%)	27/56 (48.2%)	29.9%	18/96 (18.8%)	24/48 (50.0%)	31.2%
Female	25/75 (33.3%)	12/31 (38.7%)	5.4%	20/82 (24.4%)	16/ 40 (40.0%)	15.6%

Source: Reviewer's Table

Table 13 shows that failure rates at day 15 in each trial were lower in OTO-201 6 mg than Sham group. Breslow-Day test (p-value 0.03) suggested that there was a treatment by gender interaction in Study 201-201302. Thus the treatment benefits across male and female patients were not consistent. There was a substantial treatment benefit in male patients while only a small treatment difference was seen in female patients. However, Breslow-Day test (p-value 0.19) suggested that there was no treatment by gender interaction in Study 201-201303.

Though the treatment effect was also smaller in females in this study, there did appear to be a numerical advantage with treatment. Thus, the lack of an effect seen in females in Study 201-201302 was not repeated in Study 201-201303.

Analysis by race

The following table provides treatment failure rates at day 15 by race for both 201-201302 and 201-201303 trials.

Table 14: Study Treatment Failures through Day 15 by Race and Treatment Group (Full Analysis Set)

	Study 201-201302			Study 201-201303		
	OTO-201 6 mg n/N (%)	Sham n/N (%)	% Difference (Sham – Otiprio)	OTO-201 6 mg n/N (%)	Sham n/N (%)	% Difference (Sham – Otiprio)
White	38/148 (25.7%)	28/69 (40.6%)	14.9%	32/140 (22.9%)	33/72 (45.8%)	22.9%
African American	4/20 (20.0%)	4/23 (17.4%)	-2.3%	4/23 (17.4%)	5/10 (50%)	32.6%
Other	2/11 (18.2%)	4/5 (80.0%)	61.8%	2/15 (13.3%)	2/6 (33.3%)	20.0%

Source: Reviewer's Table

In both trials, lower treatment failure rates at day 15 were observed in the OTO-201 6 mg treated group compared to the sham treated group except African American race in study 201-201302. However, because of the small sample sizes, it is difficult to interpret the lack of a treatment effect in this subgroup. Breslow-Day test did not suggest any interaction between race and treatment groups (p-value 0.24 in study 201-201302 and p-value 0.48 in study 201-201303) in either trial and the results of study 201-201-303 did show a numerical advantage of OTO-201 over sham.

Analysis by age-group

The following table provides treatment failure rates at day 15 by age-group for both 201-201302 and 201-201303 trials.

Table 15: Study Treatment Failures through Day 15 by Race and Treatment Group (Full Analysis Set)

	Study 201-201302			Study 201-201303		
Age-Group	OTO-201 6 mg n/N (%)	Sham n/N (%)	% Difference (Sham – Otiprio)	OTO-201 6 mg n/N (%)	Sham n/N (%)	% Difference (Sham – Otiprio)
Age Group: 6 months through 2 years	33/109 (30.3%)	28/53 (52.8%)	22.5%	28/111 (25.2)	33/53 (62.3)	37.1%
Age Group: >2 years	11/70 (15.7%)	11/34 (32.4%)	16.7%	10/67 (14.9)	7/ 35 (20.0)	5.1%

Source: Reviewer's Table

In both trials, lower treatment failure rates at day 15 were observed in the OTO-201 6 mg treated group compared to the sham treated group. The Breslow-Day test (p-value 0.99) did not suggest any interaction between age-group and treatment groups in study 201-201302. Thus the treatment benefit was consistent in both age groups in Study 201-201302. However, the Breslow-Day test (p-value 0.06) suggesting there was interaction between age and treatment groups in Study 201-201303. Note that the presence of interaction does not invalidate the overall conclusion of the study. It only says that the treatment benefit is not consistent in both age groups. In study 201-201303, there was a larger treatment effect seen in the younger patients compared to the older patients.

Analysis by geographic region

This reviewer conducted subgroup analyses of sites corresponding to the primary endpoint for both trials. The Breslow-day test did not point to an inconsistent treatment benefit across the center in both studies (p-value 0.37 in Study 201-201302 and 0.17 in 201-201303).

4.2 Other Special/Subgroup Analyses

There were no other subgroups considered for this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues that impacted the overall conclusions. However, this reviewer has identified the following minor issues which have not impacted the overall conclusions.

Treatment by gender interaction:
Breslow-Day test (p-value 0.03) suggested that there was a treatment by gender interaction in Study 201-201302 with a substantial treatment benefit in male patients and little to no treatment effect in females. However, in Study 201-201303 though the treatment effect was still smaller in female patients, there appeared to be a larger numerical advantage in females compared to Study 201-201-302.

Treatment by age-group interaction:
Breslow-Day test (p-value 0.06) suggested there was interaction between age and treatment groups in study 201-201303. There was a substantial treatment failure in Age Group: 6 months through 2 years with a low treatment failure seen in the older age group. In Study 201-201302 an interaction was not seen.

5.2 Collective Evidence

The reviewer's summary of the collective evidence of effectiveness and/or safety is a compilation of the main findings from two phase 3 trials which is provided below.

The superiority of OTO-201 when used for treatment of middle ear effusion in pediatric subjects with otitis media requiring TT placement has been confirmed by individual study results from:

- Two pivotal prospective, randomized, double-blind, sham-controlled, multicenter, Phase 3 studies conducted in 532 subjects (530 subjects treated) in the U.S. and Canada (201-201302 and 201-201303).

Each of the pivotal Phase 3 efficacy studies met its primary endpoint. The prespecified primary efficacy endpoint and age-adjusted analysis showed a statistically significant association between treatment group and study treatment failure in favor of OTO-201 $p < 0.001$. The per protocol and secondary efficacy analyses provided supportive evidence for

OTO-201, when administered at the recommended dose of 6 mg (0.1 mL of a 6.0% ciprofloxacin suspension).

The results of these studies support that the administration of OTO-201 will be effective for the treatment of middle ear effusion in pediatric subjects with otitis media requiring TT placement.

5.3 Conclusions and Recommendations

The applicant completed two randomized, prospective, double-blind, sham-controlled Phase 3 clinical trials with identical protocols among pediatric subjects male or female aged from 6 months to 17 years at approximately 55 centers in the United States and Canada. Both trials enrolled a total of 532 randomized subjects, comprising 357 randomized to Otiprio 6 mg group and 175 randomized to the sham group. The primary efficacy endpoint for both studies was the cumulative proportion of subjects designated as study treatment failures through the Day 15 Visit. The data from these 2 independent Phase 3 studies support the efficacy of OTO-201 in the treatment of middle ear effusion in pediatric subjects with otitis media requiring TT placement.

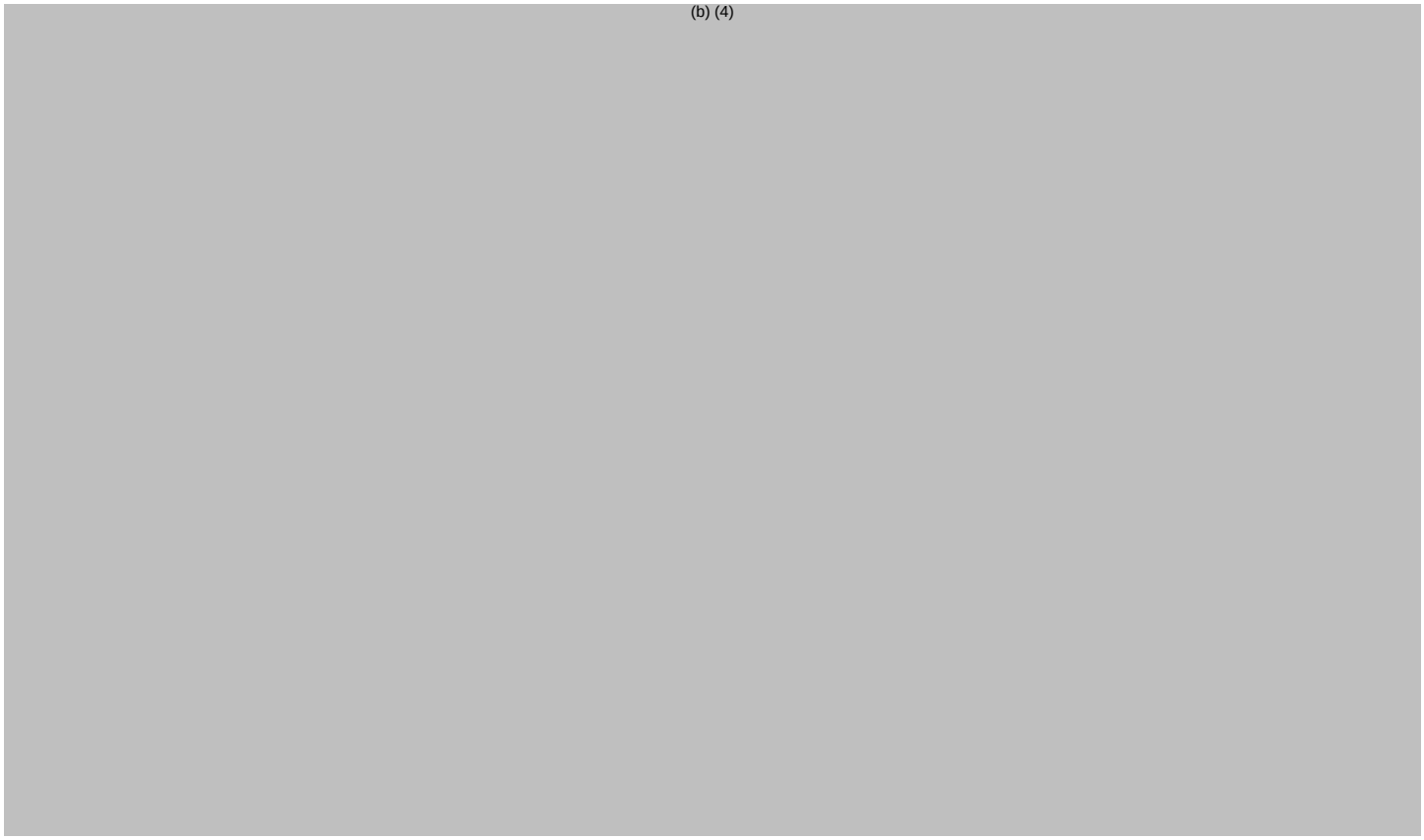
The safety data from Study 201-201302 and Study 201-201303 demonstrated that a single intratympanic injection for intra-operative treatment of middle ear effusion in pediatric subjects requiring TT placement had a similar safety profile to Sham injection. Most of the AEs were mild or moderate in severity. No deaths, life-threatening TEAEs, or TEAEs leading to discontinuation were reported in these studies. The safety evaluation from these studies indicates that the product was safe and well tolerated.

5.4 Labeling Recommendations (Section 14 Clinical Studies)

The division's labeling meetings (internal) are still ongoing. However, the following paragraph has been tentatively finalized and will be sent to the Sponsor for their response.

Two randomized, multicenter, controlled clinical trials in 532 pediatric patients with bilateral otitis media with effusion undergoing myringotomy with tympanostomy tube placement evaluated the safety and efficacy of OTIPRIO when administered intraoperatively as a single dose. The median age of patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age. The efficacy endpoint for both trials was the cumulative proportion of study treatment failures through Day 15, defined as the occurrence of any of the following events: otorrhea as determined by a blinded assessor, otic or systemic antibacterial drug use for any reason, as well as patients who missed visits or were lost-to-follow-up.

(b) (4)



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/s/

MUSHFIQUR M RASHID
11/20/2015

KAREN M HIGGINS
11/20/2015
I concur.