CLINICAL REVIEW

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Reviewer Name(s)	Mark Needles, M.D.
Review Completion Date	02/01/2018
Established Name	Ciprofloxacin otic suspension
Trade Name	OTIPRIO®
Therapeutic Class	Fluoroquinolone Antibacterial
Applicant	Otonomy, Inc.
Formulation(s)	Otic suspension 6% (60 mg/mL) ciprofloxacin
Dosing Regimen	Single external auditory canal administration of 0.2 mL (12 mg) into the affected ear(s)
Indication(s)	Treatment of acute otitis externa due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*
Intended Population(s)	Pediatric patients aged 6 months and older, Adults, and Elderly patients

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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 (ciprofloxacin otic suspension) be approved for the treatment of acute otitis externa (AOE) in pediatric (age 6 months and older), adult, and elderly patients due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Data from one adequate, and well-controlled Phase 3 study support the efficacy of Otiprio for the proposed indication. Treatment with Otiprio was superior to sham (air injection) when given as a single administration of 0.2 mL (12 mg) to the external auditory canal of the affected ear(s). Findings from a smaller Phase 2 study also provide supportive evidence for efficacy and safety.

1.2 Risk Benefit Assessment

Data from a Phase 3 study (201-201609) supports the efficacy of Otiprio for the treatment of AOE in pediatric (age 6 months and older), adult, and elderly patients due to *P. aeruginosa* and *S. aureus*. The primary efficacy endpoint, the proportion of clinical cures at the Day 8 Visit, favored Otiprio treatment over sham and was statistically significant in both the ITT population (randomized patients who did not have Group A streptococci cultured on Day 1) and the Mic-ITT population (ITT patients who had a positive baseline culture for *P. aeruginosa* or S*. aureus*). Statistical significance was maintained when the assessment of otorrhea was incorporated into the primary efficacy endpoint. A beneficial effect favoring Otiprio treatment was noted in the <18 years and ≥18 years age strata. The proportion of clinical cures and no otorrhea at the Day 8 Visit was statistically significant for both age strata in the ITT analysis and the older age stratum in the Mic-ITT analysis. A statistically significant difference favoring Otiprio treatment was also noted in both the ITT and Mic-ITT populations for the proportion of clinical cures at the Day 15 Visit and the proportion of clinical cures and no otorrhea at the Day 15 Visit.

A single Phase 3 study and a smaller Phase 2 study (201-201506) support the safety of Otiprio for the treatment of AOE in pediatric (age 6 months and older), adult, and elderly patients due to *P. aeruginosa* and *S. aureus*. The same dose as selected for marketing was evaluated in both clinical studies, and its use was found to be both safe and well tolerated. Otitis externa was the most frequently reported treatment emergent adverse event (TEAE) in patients treated with Otiprio in either study. Ear pruritus, headache, otitis media, ear discomfort, and nasal congestion were reported in at least 2% of Otiprio patients in Phase 3 study and at an incidence greater than sham. Data from the pediatric, adult, and elderly populations 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

Otiprio (OTO-201) is a sterile, fluoroquinolone antibacterial suspension of 6% (60 mg/mL) ciprofloxacin in a buffered solution containing a mucoadhesive glycol polymer called poloxamer 407. Ciprofloxacin is the single active ingredient and like other fluoroquinolones, the mechanism of action is inhibition of DNA gyrase and topoisomerase IV. The poloxamer 407 vehicle in the 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.

OTO-201 was initially approved in the United States on December 10, 2015 for treatment of pediatric patients ≥6 months of age with bilateral otitis media with effusion (OME) undergoing tympanostomy tube placement. The approved dose for bilateral OME is single intratympanic administration of 0.1 mL (6 mg) into each affected ear during the myringotomy procedure. This supplemental NDA was submitted by the applicant to support a new indication for OTO-201 to treat AOE in pediatric (age 6 months and older), adult, and elderly patients due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The recommended dosage regimen, for all patients, is single otic administration of 0.2 mL (12 mg) OTO-201 to the external ear auditory canal of the affected ear(s). Otic administration for AOE is intended to be performed by a healthcare professional.

Established Name:	Ciprofloxacin otic suspension
Trade Name:	OTIPRIO®
Pharmacological Class:	Topical fluoroquinolone antibacterial
Proposed Indication:	Treatment of acute otitis externa in pediatric (age 6 months and older), adult and elderly patients due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*
Prosed Dosing Regimen:	Single otic administration of 0.2 mL (12 mg) to the affected ear(s)

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.2-1 summarizes the available FDA-approved drugs for the treatment of AOE or superficial infection of the external ear canal.

Table 2.2-1: FDA-Approved Drugs for the Treatment of AOE

Drug Class	Name	Component(s)	Age Group
Fluoroquinolone	CETRAXAL	Ciprofloxacin 0.2% otic solution	≥1 yr
	XTORO	Finafloxacin 0.3% otic suspension	≥1 yr
	OFLOXACIN	Ofloxacin 0.3% otic solution	≥6 mo
Fluoroquinolone + Corticosteroid	CIPRODEX	Ciprofloxacin 0.3%, dexamethasone 0.1% otic suspension	≥6 mo
	CIPRO HC OTIC	Ciprofloxacin 0.2%, hydrocortisone 1% otic suspension	≥1 yr
Am noglycoside + Polypeptide + Corticosteroid	COLY-MYCIN S	Neomycin, colistin, thonzonium, hydrocortisone otic suspension	≥1 yr
	CORTISPORIN; OTICAIR; NEOMYCIN AND POLYMYXIN B SULFATES AND HYDROCORTISONE	Neomycin, polymyxin b, hydrocortisone otic solution or suspension	≥2 yrs
Low pH antiseptic +/- Corticosteroid	ACETIC ACID; VOSOL	Acetic acid 2% otic solution	≥3 yrs
	ACETASOL HC; VOSOL HC; HYDROCORTISONE AND ACETIC ACID	Acetic acid 2%, hydrocortisone 1% otic solution	≥3 yrs

2.3 Availability of Proposed Active Ingredient in the United States

Ciprofloxacin

- Ciprofloxacin otic suspension (OTIPRIO®), indicated for the treatment of pediatric patients (age 6 months and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement
- 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 acute otitis media with tympanostomy tubes (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 0.3% and fluocinolone acetonide 0.025% otic solution (OTOVEL®), indicated for the treatment of AOMT in pediatric patients (aged 6 months and older) due to *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *P. aeruginosa*.
- 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

2.4 Important Safety Issues With Consideration to Related Drugs

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An end-of-Phase-2 meeting was scheduled for April 18, 2016. The meeting was cancelled after the applicant accept the preliminary comments from the Agency on April 14, 2016. The following are the pertinent items included in the Phase 3 protocol that were based on agreements reached at the end-of-Phase 2 meeting:

- Double-blinded study design
- Inclusion of patients age 6 months and older
- Inclusion of patients with bilateral AOE
- Primary endpoint of clinical cure measured at Day 8
- Analysis of clinical outcomes in pathogen-positive patients

The applicant received additional comments related to the Phase 3 protocol design on August 19, 2016. The applicant agreed to the following protocol revisions:

- Otorrhea evaluated as a secondary endpoint
- Collection of post-baseline microbiology cultures from patients with any sign or symptom of AOE (edema, erythema, tenderness, or otorrhea)
- Sample size for the study

Reviewer's Comment:
The Agency suggested that the assessment of otorrhea be incorporated into the primary efficacy endpoint. Otorrhea was not evaluated as part of the primary efficacy endpoint because the applicant referred to the FDA review documents for Xtoro (finafloxacin) in designing the Phase 3 study. The applicant in response to the Agency's comment agreed to evaluate the occurrence otorrhea as a secondary endpoint, but did not incorporate this assessment into the primary endpoint.

2.6 Other Relevant Background Information

Acute otitis externa (AOE) is an infection of the external auditory canal that is commonly seen in children in the ambulatory care setting. In 2007, AOE was diagnosed at approximately 2 million ambulatory care visits in the United States (6.9 visits per 1,000 population) and children between the ages of 5 to 14 years had the highest annual visit rates between 2003 to 2007.[1] More than 90% of the AOE infections in North America are bacterial with the most common pathogens being *Pseudomonas aeruginosa* and *Staphylococcus aureus*. A diagnosis of AOE requires a rapid onset (generally within 48 hours) of signs and symptoms of ear canal inflammation in the past 3 weeks. The typical signs and symptoms include ear canal edema, erythema, tenderness, otorrhea, and otalgia.

Primary AOE is often treated with topical preparations consisting of an antibiotic or steroid alone, an antibiotic and steroid combination, or a low pH antiseptic for 7 to 10 days. Most patients have signs and symptoms improve within 48 to 72 hours after starting appropriate therapy, and there is complete or near-complete resolution by 1 week. In some patients, it may take up to 2 weeks for complete resolution of signs and symptoms to occur.[2]

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 two clinical investigator sites selected for large subject enrollment and high clinical cure rates. Overall the study conduct and applicant's oversight appeared adequate at both sites. All audited study data were adequately verifiable and appeared reliable as reported in the NDA. No significant deficiencies were observed at either of the audited sites; however, minor recordkeeping deficiencies were noted at one site. The amount of data affected by the deficiencies 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 were conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The original protocols and amendments were reviewed and approved by reviewing Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects before any study-related procedures.

3.3 Financial Disclosures

Please see section 9.4 for the Clinical Investigator Financial Disclosure Form.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new chemistry, manufacturing and control (CMC) data was submitted with the current sNDA.

4.2 Clinical Microbiology

The applicant conducted investigations that supported the in vitro activity of ciprofloxacin against the common pathogens related to AOE: *Pseudomonas aeruginosa* and *Staphylococcus aureus*. A single Phase 3 clinical study was performed by the applicant and supported the efficacy of OTO-201 for the treatment of AOE due to *P. aeruginosa* and *S. aureus*. Please refer to Section 6 of this review for the summary of efficacy results in the pathogen positive population (referred to as the Mic-ITT analysis set). 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

No new Pharmacology/Toxicology studies were submitted with the current sNDA.

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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5.3.1-1: Listing of Clinical Trials Relevant to this NDA

Study Identity	Study Objective	Study Design	Treatment Groups/ Regimen	Treatment Duration	No. of Subjects
201-201506 IND 110244 Phase 2	In patients with unilateral otitis externa: *Primary*: Evaluate safety and feasibility of external auditory canal administration of OTO-201 *Secondary*: Assess the clinical activity of OTO-201	Prospective, multicenter, randomized, open-label study Enrolling patients age 6 mo to 80 yrs with unilateral otitis externa	OTO-201 6%: 6 mg = 0.1 mL 12 mg = 0.2 mL 24 mg = 0.4 mL Single administration to the external ear canal of the affected ear	Single Dose Follow-up to Day 29	Randomized 6 mg: 25 12 mg: 25 24 mg: 25 Safety 6 mg: 25 12 mg: 25 24 mg: 25
201-201609 IND 110244 Phase 3	In patients with bilateral or unilateral AOE: *Primary:* Confirm effectiveness of OTO-201 at Day 8 *Secondary:* Assess the safety and tolerability of OTO-201	Prospective, multicenter, randomized, double-blind, sham-controlled study Enrolling patients age 6 mo and older with unilateral or bilateral AOE	OTO-201 6%: 12 mg = 0.2 mL Sham: Syringe with air Single administration to the external ear canal of the affected ear(s)	Single Dose Follow-up to Day 29	Randomized 12 mg: 130 Sham: 132 ITT 12 mg: 130 Sham: 130 Mic-ITT 12 mg: 52 Sham: 56 Safety 12 mg: 127 Sham: 132

Source: Adapted from clinical study reports for 201-201506 and 201-201609.

5.2 Review Strategy

The submitted clinical protocols, study reports, and relevant literature were reviewed. The protocol and efficacy data for the Phase 2 study are summarized in Section 5.3.1. For the Phase 3 study, the protocol is summarized in Section 5.3.2 and the efficacy data summarized in Section 6. All safety data from the Phase 2 and Phase 3 studies are summarized in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 201-201506
A 1-Month, Prospective, Multicenter, Open-Label Study of OTO-201 Given as a Single Administration for Treatment of Otitis Externa

Study 201-201506 was a Phase 2, multicenter, randomized, open-label, dose ranging study of OTO-201 for treatment of otitis externa in patients aged 6 months to 80 years. In this study, single external auditory canal administration of one of three dose levels of OTO-201 (6 mg, 12 mg, or 24 mg) was evaluated. The primary analytic focus was to describe safety and feasibility of external auditory canal administration of OTO-201 among the three OTO-201 doses. Clinical activity endpoints were also evaluated to provide supportive information related to the efficacy of OTO-201 for otitis externa. The clinical activity data from the Phase 2 study was not integrated with data from the pivotal Phase 3 study because of the differences in control groups (none in Phase 2; sham in Phase 3), clinical cure components (4 components in Phase 2; 3 components in Phase 3), and the blinded status of the otoscopic examination (not blinded in Phase 2; blinded in Phase 3).

Seventy-five patients enrolled in the Phase 2 study, including 25 patients each in the 6 mg, 12 mg, and 24 mg OTO-201 dose groups. All patients were males (40 patients, 53%) or females (35 patients, 47%) aged 6 months to 80 years with a clinical diagnosis of unilateral otitis externa. The median age was 37 years (range, 3 to 80 years). All randomized patients received a single external auditory canal administration of either 6 mg (0.1 mL), 12 mg (0.2 mL), or 24 mg (0.4 mL) of OTO-201 to the affected ear. The investigators were able to deliver the entire volume of study drug to 96%, 100%, and 84% of the patients in the 6 mg, 12 mg, and 24 mg OTO-201 groups, respectively.

Patients were treated with OTO-201 at the initial study visit (Day 1) and returned to the study site on Days 4, 8, 15, and 29 for follow-up assessments. Otoscopic examinations were performed at each study visit to assess the signs and symptoms of otitis externa. A scoring scale was used to record edema, erythema, otorrhea, otalgia, and tenderness on the otoscopic exam, with 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Safety assessments included adverse event monitoring (all visits), otoscopic examinations (all visits), and vital signs (Day 1 and 29).

Reviewer's Comment:
Overall, the safety assessments from the Phase 2 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 2 study was proportion of patients designated as clinical cure through Day 15. Clinical cure was defined as complete resolution of 4 signs and symptoms on the otoscopic exam (i.e., scores for edema, erythema, otorrhea, and otalgia equal to zero) and no concomitant antibiotics taken at or prior to the study visit.

Table 5.3.1-1 summarizes the proportion of patients categorized as clinical cures through Days 4, 8, and 15. The 12 mg OTO-201 group had a greater proportion with clinical cure through Day 15 compared to the other OTO-201 groups. The occurrence of clinical cure between Days 8 and 15 were numerically similar in each OTO-201 group.

Table 5.3.1-1: Clinical Cure by Treatment Group & Time point Study 201-201506

	OTO-201 6 mg N = 25	OTO-201 12 mg N = 25	OTO-201 24 mg N = 25	Total N = 25
Clinical Cure by Study Visit – n (%)				
Day 4	9 (36%)	5 (20%)	7 (28%)	21 (28%)
Day 8	15 (60%)	20 (80%)	14 (56%)	49 (65%)
Day 15	14 (56%)	19 (76%)	16 (64%)	49 (65%)

Note: Clinical cure was identified when all four signs and symptoms (edema, erythema, otorrhea, and otalgia) had a score of 0 (complete absence) on the otoscopic exam and no concomitant antibiotics were taken at or prior to the study visit.
Source: Adapted from clinical study report for 201-201506; Clinical reviewer's calculations

5.3.2 Study 201-201609
A 1-Month, Prospective, Randomized, Double-Blind, Sham-controlled, Multicenter, Phase 3 study of OTO-201 Given as a Single Administration for Treatment of Acute Otitis Externa

Study 201-201609 was a Phase 3, multicenter, randomized, double-blind, sham-controlled study of OTO-201 for the treatment of AOE. Single unilateral or bilateral external auditory canal administration of one dose level of OTO-201 (12 mg) to the affected ear(s) was evaluated in relation to sham (empty syringe with air). The Phase 3 study was the pivotal study submitted to support approval of OTO-201 for treatment of AOE in pediatric (age 6 months and older), adult, and elderly patients due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Study Objectives
The primary objective for the Phase 3 study was to evaluate the effectiveness of OTO-201 (12 mg to each affected ear) at Day 8 in the treatment of patients with AOE. A

secondary objective was to assess the safety and tolerability of OTO-201 in patients with AOE.

Trial Design
Enrollment and Randomization
Study 201-201609 was designed as a prospective, randomized, double-blind, sham-controlled, Phase 3 trial of OTO-201 for the treatment of AOE. The study was conducted over an approximate 6 month time period, from June 08, 2016, to December 14, 2016. Enrollment sites were at 37 centers in the United Sates.

Patients, aged 6 months and older, with a clinical diagnosis of unilateral or bilateral AOE confirmed via otoscopic exam were randomized at a 1:1 ratio to receive single, external auditory canal administration of one dose level of OTO-201 (12 mg) or sham (air from empty syringe) to the affected ear(s). The investigators planned to enroll 254 patients and have 127 patients randomized to each treatment group. A total of 262 patients enrolled into the Phase 3 study, including 130 patients randomized to the OTO-201 treatment group and 132 patients randomized to the sham treatment group. Randomization was implemented using a web-based Interactive Web Response System (IWRS).

Blinding
The OTO-201 and sham treatment syringes were prepared by an unblinded qualified medical professional (QMP) or unblinded investigator and the syringes covered to prevent other personnel from visualizing the contents. Physicians administering study drug were not blinded 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 conducted an otoscopic examination to evaluate for signs and symptoms of AOE.

Drug Administration
Enrolled patients with unilateral or bilateral AOE were treated with either OTO-201 (6% ciprofloxacin suspension) or sham (air injection) on the same day as randomization (Day 1). The patients randomized to the OTO-201 group received a 12 mg dose to each affected ear via unilateral or bilateral administration of 0.2 mL to the external auditory canal(s). Patients randomized to the sham group were administered 0.2 mL of air from an empty syringe to the external auditory canal of the affected ear(s). Otorrhea and/or debris in the external auditory canal were irrigated and/or suctioned prior to study drug administration by an unblinded investigator. No subsequent doses of either OTO-201 or sham were administered for the remainder of the study.

Dose selection
The 12 mg dose of OTO-201 in a 0.2 mL dosing volume was selected following the completion of the Phase 2 dose ranging study and agreed to by the Agency. In the Phase 2 study, no safety concerns were identified between the 6 mg, 12 mg, and 24 mg

OTO-201 doses, and the 12 mg dose had the greatest rate of clinical cure across the 3 doses. This dose also represents the same total dose administered in the approved OTO-201 indication: treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement.

Diagnostic criteria
Male and female patients aged 6 months and older with a clinical diagnosis of unilateral or bilateral AOE and at least 1 affected ear with a combined numerical score of ≥4 for edema, erythema, and tenderness.

Noteworthy Inclusion criteria
Patients were eligible for enrollment if they met the following criteria:
1. Male or female aged 6 months or older.
2. Had a clinical diagnosis of unilateral or bilateral AOE as defined by the 2014 AAO-HNS Clinical Practice Guideline: Acute Otitis Externa.[2]
3. Had a combined numerical score of ≥4 in at least 1 affected ear at the screening visit for edema, erythema, and tenderness.
    a. The scoring scale for edema, erythema, and tenderness on the otoscopic exam consisted of 0 = complete absence, 1 = slight presence, 2 = definitely present, and 3 = marked/intense presence.

Noteworthy Exclusion criteria
Patients were not eligible for enrollment if they met the following criteria:
1. Had known tympanic membrane perforation in either ear.
2. Had severe otitis externa that either included auricular cellulitis or chondritis or prevented administration of OTO-201.
3. Had chronic otitis externa, defined as either 1 or more episodes of otitis externa within the last 3 months or more than 3 episodes of otitis externa within the last year.
4. Had eczematoid otitis externa.
5. Had fungal otitis externa, based on clinical signs.
6. Had a history of known immunodeficiency disease.
7. Had diabetes mellitus.
8. Had any infection that required systemic antimicrobial or antifungal agents.
9. Used antimicrobial ear drops to the affected ear within 1 week of screening.
10. Used systemic antimicrobial or antifungal agents within 1 week of screening and within 2 weeks of screening for Zithromax®.
11. Had a history of allergy to ciprofloxacin or any of the components of OTO-201.
12. Had any other clinically significant illness or medical condition that, in the opinion of either the investigator or medical monitor, would prohibit that patient from participating in the study.
13. Pregnant or lactating.

Schedule

Table 5.3.2-1 summarizes the schedule for the noteworthy procedures performed in the Phase 3 study. Patients were randomized and treated with either OTO-201 (12 mg of the 6% ciprofloxacin suspension) or sham (air injection) on Day 1. A swab of the external auditory canal was taken from each affected ear(s) for microbiology culture prior to external auditory canal administration. Patients returned to the study site for follow-up assessments on Day 4, Day 8, Day 15, and Day 29 to evaluate the signs and symptoms of AOE. Patients were encouraged to return to the study site for unscheduled visits if new onset or persistent otitis externa occurred at ≥7 days post study drug administration, experienced an adverse event between scheduled visits, or required follow-up for any adverse event prior to the end of study.

A blinded assessor performed otoscopic examinations at all follow up visits to assess for signs and symptoms of AOE. A scoring scale was used to record erythema, edema, and tenderness on the otoscopic exam, with 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The presence and characterization of otorrhea on the otoscopic exam was documented separately. A microbiology culture specimen was collected at any follow up visit where edema, erythema, tenderness, or otorrhea was observed by the blinded assessor. During Days 1 through 15, patients or their caregivers reported the severity of otalgia in the affected ear(s) in a daily diary. Daily diaries were not completed in patients too young to provide appropriate responses on the Wong-Baker FACES® Pain Rating Scale (typically below 3 years of age).

Table 5.3.2-1: Noteworthy Procedures in Study 201-201609

Procedure	Screening/ Randomization/ 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	Unscheduled
	Day 1	Day 4 (±1 day)	Day 8 (±1 day)	Day 15 (±2 days)	Day 29 (±3 days)	N/A
Informed consent	X					
Eligibility criteria	X					
Medical History	X					
Physical examination	X					
Vital signs	X				X	
Pregnancy test[1]	X				X	
Otoscopic examination	X	X	X	X	X	X
Microbiology culture[2]	X	X	X	X	X	X
Instruct/review Daily Diary requirments[3]	X	X	X	X		
Concomitant medications	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X

[1] Urine pregnancy testing was conducted on all female patients aged 9 years or older at Visits 1 and 5.
[2] On Visit 1, a baseline microbiology culture of the external auditory canal of affected ear(s) was taken prior to administration of OTO-201 or sham. On Visits 2-5, a microbiology culture was only taken if any signs or symptoms of AOE were present, including edema, erythema, tenderness, or otorrhea.
[3] Daily Diary assessments were completed only for patients mature enough to provide appropriate responses to level of otalgia, typically age 3 years and older.
Source: Adapted from clinical study reports for 201-201609.

Concomitant medications
Concomitant medications included all prescription drugs, herbal products, vitamins, minerals, and over the counter medications used by patients 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 may have been given if deemed necessary for the welfare of the patient and if not included in any of the following prohibited list:

- Antibiotics, other than OTO-201, not deemed necessary for the welfare of the patient during the study. The use of topical antibiotics, except for otic antibiotic drops, were allowed during the study.
- Ear drops of any kind (unless the patient meets criteria to be treated per standard of care)
- Over the counter topical agents, such as acetic acid, or devices indicated for the treatment of swimmer's ear
- Other investigational drug(s) or device(s)

Treatment compliance
There were no treatment compliance assessments because the study drug was given by an unblinded investigator as a single administration to the external auditory canal of the affected ear(s). Any deviation in external auditory canal administration was documented.

Rescue medication
Patients were eligible to receive the standard of care treatment for AOE (i.e., otic antibiotic drops) if they showed no improvement in their signs and symptoms by the Day 8 visit or if the patient's daily diary indicated no improvement in otalgia. In addition, patients with baseline microbiology cultures positive for group A streptococci were treated with standard of care, including systemic therapy as needed.

Subjection 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. 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 study, or a patient (or caregiver) requested an early discontinuation.

Clinical cures
The occurrence of clinical cure (CC) following external auditory canal administration of OTO-201 or sham was determined by a blinded assessor at Days 4, 8, 15, and 29. A patient was designated a clinical cure if the blinded assessor noted complete resolution of 3 signs and symptoms on the otoscopic exam (i.e., scores for edema, erythema, and

tenderness equal to zero), and no use of otic antibiotic drops in the study ear or systemic antibiotics at or prior to the study visit.

Reviewer Comment:
For Phase 3 study, the applicant did not incorporate the assessment of otorrhea into the definition of clinical cure. Occurrence of otorrhea was evaluated separately.

Study Endpoints
Primary Efficacy Endpoint

- Occurrence of clinical cure through the Day 8 Visit (CC Day 8)

Reviewer Comment:
The Day 8 timepoint was selected for the primary efficacy endpoint because the pattern of clinical cure in the Phase 2 study indicated there was very little difference between Day 8 and Day 15 timepoints.

Secondary Endpoints

- Occurrence of clinical cure through the Day 15 Visit (CC Day 15)
- Occurrence of clinical cure through the Day 4 Visit (CC Day 4)
- Time-to-cessation of otalgia through the Day 15 Visit

The time-to-cessation of otalgia was the earliest timepoint (study day) on the daily diary where otalgia remained resolved and no concomitant local or systemic analgesic medications were taken for the treatment of pain in the study ear through day 17.

- Occurrence of microbiological eradication through the Day 8 Visit

Microbial eradication in patients with positive pathogen(s) at baseline for *Pseudomonas aeruginosa* or *Staphylococcus aureus* was defined as either:

  - Microbial eradication without presumption – patients who had a post-baseline microbiological culture that confirmed eradication of the baseline bacterial pathogen (i.e., negative culture with respect to the *P. aeruginosa* and/or *S. aureus* pathogens), and did not receive otic antibiotic drops in the study ear or systemic antibiotics at or prior to the study visit.
  - Microbial eradication with presumption – patients who did not have a post-baseline microbiological culture, but had presumed eradication of the baseline bacterial pathogen(s) because they were identified as clinical cures and did not receive otic antibiotic drops in the study ear or systemic antibiotics at or prior to the study visit.

- Otorrhea through the Day 4, Day 8, Day 15, and Day 29 Visits

Cessation of otorrhea, using otoscopic exam by the blinded assessor, was defined as the resolution of otorrhea and no use of otic antibiotic drops in the study ear or systemic antibiotics at or prior to the study visit.

Safety Endpoints

- Adverse Events (AEs)

- Otoscopic examinations
- Vital sign measurements
- Physical examination

Statistical Analysis Plan
Determination of Sample Size
The investigators made assumptions based on literature comparisons and the Phase 2 study results to estimate the sample size for the Phase 3 study. A sample size of 127 per treatment group would achieve 91% power to detect a 21% difference in the proportion of patients with CC Day 8 in OTO-201 and sham. After assuming 48% of patients would be pathogen positive, the investigators estimated the pathogen positive sub-population would achieve 90% power to detect a 30% difference between the treatment groups. The Fisher's exact test conducted at the two-tailed 0.05 alpha level was used to estimate power and sample size.

Analysis Sets
The unit of analysis for the efficacy analyses was patient; thus, a "study ear" was identified for each patient. Patient with unilateral AOE had their affected ear identified as the "study ear." For patients with bilateral AOE, the "study ear" was the affected ear with the higher combined clinical score for edema, erythema, and tenderness. The safety analyses did not utilize "study ear." Instead, treated and affected ears were summarized separately. The analysis sets used in the key efficacy or safety analyses are defined below.

- **Intent-to-Treat Analysis Set (ITT):** The ITT population included all patients who were randomized and did not have a positive baseline culture for Group A streptococci. Patients were analyzed as randomized. The ITT analysis set was used for the efficacy analyses unless otherwise noted.
- **Micro Intent-to-Treat Analysis Set (Mic-ITT):** The Mic-ITT or pathogen-positive population included all ITT patients who had a positive baseline culture for either *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Patients were analyzed as randomized. The Mic-ITT analysis set was used for specified endpoints in the efficacy analysis.
- **Safety Analysis Set:** The safety population included all patients who received study drug. Patients were analyzed as treated. The safety analysis set was used for the safety analyses unless otherwise noted.

Primary Efficacy Analysis
The primary efficacy endpoint, cumulative proportion of patients with CC Day 8, was compared between the treatment groups using Fisher's Exact test. The primary objective of the study was met if there was a statistically significant difference (i.e., 0.05 level of significance) in favor of OTO-201.

Secondary Efficacy Analysis

Once the primary objective was met, the secondary efficacy endpoints were compared between the treatment groups. A gate keeping strategy (sequential closed testing procedure) was used to control the familywise type I error rate. The evaluations were conducted in the following order:

1. Cumulative proportion with CC Day 15
2. Cumulative proportion with CC Day 8 using Mic-ITT analysis set
3. Cumulative proportion with CC Day 15 using Mic-ITT analysis set
4. Cumulative proportion with CC Day 4 using Mic-ITT analysis set
5. Cumulative proportion with CC Day 4
6. Time-to-cessation of otalgia using Kaplan-Meir method

The clinical cure endpoints in the gate keeping strategy were analyzed in the same manner as the primary efficacy endpoint. The time-to-cessation of otalgia endpoint was compared between the treatment groups using Kaplan-Meier estimates and log-rank test. If at any step one of the comparisons between the treatment groups was not statistically significant, the remaining comparisons in the gate keeping strategy would be considered exploratory.

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) Version 19.0, and summarized by system organ class and preferred term. Changes from baseline with respect to otoscopic examinations (i.e., the appearance of the tympanic membrane and middle ear, and the presence of cerumen) and vital sign measurements were tabulated. Physical examination data at baseline was presented as individual subject line listings.

6 Review of Efficacy

Efficacy Summary

A Phase 3 study demonstrated the efficacy of Otiprio for the treatment of AOE in pediatric, adult, and elderly patients due to *P. aeruginosa* and *S. aureus*. Clinical cure at Day 8 was the primary efficacy endpoint, and defined as the complete absence of signs and symptoms of AOE (i.e., edema, erythema, and tenderness as determined by the blinded assessor), and no concomitant systemic or local (given in the study ear) antibiotic was taken at or prior to the Day 8 visit. A statistically significant difference favoring Otiprio treatment was achieved for the primary efficacy endpoint in the ITT population and in the subset of patients with a positive baseline culture for *P. aeruginosa* or *S. aureus* (Mic-ITT population). Statistical significance was maintained after incorporating the assessment of otorrhea into the primary efficacy endpoint. Though there was some variability related to the degree of treatment effect in different

age groups (pediatric, adult, and elderly), an overall beneficial effect was observed with Otiprio treatment compared to sham in the Phase 3 study.

6.1 Indication for Study 201-201609

Treatment of unilateral or bilateral AOE in patients aged 6 months and older.

6.1.1 Methods

The review of efficacy relied on the data from one prospective, randomized, double blind, sham-controlled Phase 3 study: Study 201-201609. Please see Section 5.3 for description of the clinical study design for the Phase 3 study. Supportive efficacy data from the Phase 2 study (Study 201-201506) 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 for all patients who were randomized and did not have positive cultures for Group A Streptococci at baseline (ITT population). The ITT population consisted of 260 patients who were equally distributed across the OTO-201 and sham treatment groups (130 patients, each). The OTO-201 and sham groups each consisted of 55 males (42%) and 75 females (58%). The mean ages were 36.7 years (range 5.0 to 83.8 years) and 34.8 years (range 3.3 to 77.1 years) for the OTO-201 and sham groups, respectively. Pediatric patients <18 years of age accounted for 22% of patients in the OTO-201 group and 29% of patients in the sham group. Elderly patients, age ≥65 years, accounted for 7% and 10% of patients in the OTO-201 and sham groups, respectively.

Table 6.1.2-1: Demographics (ITT Analysis Set)

	OTO-201 12 mg N=130	**Sham N=130**	**Total N=260**
Sex – n (%)			
Male	55 (42)	55 (42)	110 (42)
Female	75 (58)	75 (58)	150 (58)
Age (years)[1]			
Mean (SD)	36.7 (19.3)	34.8 (20.6)	35.8 (19.9)
Median	36.9	32.9	34.4
Min, Max	5.0, 83.8	3.3, 77.1	3.3, 83.8
Age Groups[2] – n (%)			
≤17 years	29 (22)	38 (29)	67 (26)
18 to 64 years	92 (71)	79 (61)	171 (66)
≥65 years	9 (7)	13 (10)	22 (8)
Race – n (%)			
Wh te	111 (85)	109 (84)	220 (85)
Black or African American	14 (11)	15 (12)	29 (11)

Asian	0	3 (2)	3 (1)
Not Reported	2 (2)	2 (2)	4 (2)
Other	3 (2)	1 (1)	4 (2)
Ethnicity – n (%)			
Hispanic or Latino	41 (32)	43 (33)	84 (32)
Not Hispanic or Latino	87 (67)	86 (66)	173 (67)
Not Reported or Unknown	2 (2)	1 (1)	3 (1)

[1] Age in years was calculated by (date of screening – date of birth)/365.25.
[2] Age groups are based on the patient's chronological age in years at the initial study visit.
Source: Adapted from clinical study report for 201-201609, Table 4; Clinical reviewer's calculations.

Reviewer's Comment:
The demographic characteristics were well-balanced across the treatment groups.

Baseline AOE Characteristics
Table 6.1.2-2 summarizes the baseline AOE characteristics for the patients in the ITT analysis set. The percentages in the OTO-201 and sham groups with bilateral AOE were 12% and 8%, respectively. Both treatment groups had a mean combined score of 6 (range, 4 to 9) in the study ear. Otorrhea (any amount) from the study ear was observed in 60% and 58% of the patients in the OTO-201 and sham groups, respectively. A positive baseline microbiological status was defined as a positive baseline culture for either *Pseudomonas aeruginosa* or *Staphylococcus aureus*. The percentage of patients with a positive microbiological culture in the study ear was 40% in the OTO-201 group and 43% in the sham group. The most common pathogen cultured in both treatment groups was *P. aeruginosa*.

Table 6.1.2-2: Baseline AOE Characteristics (ITT Analysis Set)

	OTO-201 12 mg N=130	**Sham N=130**	**Total N=260**
Baseline Clinical Diagnosis – n (%)			
Uni ateral AOE	115 (88)	119 (92)	234 (90)
Bilateral AOE	15 (12)	11 (8)	26 (10)
Baseline Signs and Symptoms in Study Ear – n (%)			
Edema			
None	3 (2)	1 (1)	4 (2)
Mild or Moderate	118 (91)	120 (92)	238 (92)
Severe	9 (7)	9 (7)	18 (7)
Erythema			
None	3 (2)	3 (2)	6 (2)
Mild or Moderate	112 (86)	105 (81)	217 (83)
Severe	15 (12)	22 (17)	37 (14)
Tenderness			
None	0	2 (2)	2 (1)
Mild or Moderate	112 (86)	105 (81)	217 (83)

Severe	18 (14)	23 (18)	41 (16)
Otorrhea			
None	52 (40)	54 (42)	106 (41)
Trace or Moderate	69 (53)	68 (52)	137 (53)
Copious	9 (7)	8 (6)	17 (7)
Baseline Microbiology Culture Result of Study Ear – n (%)			
Positive[1]	52 (40)	56 (43)	108 (42)
Pseudomonas aeruginosa	39 (30)	38 (29)	77 (30)
Staphylococcus aureus	20 (15)	24 (18)	44 (17)
Negative[2]	73 (56)	74 (57)	147 (57)
Unknown[3]	5 (4)	0	5 (2)

[1] "Positive" indicates that the baseline microbiology culture from the study ear was positive for *Pseudomonas aeruginosa* and/or *Staphylococcus aureus*.
[2] "Negative" indicates that the baseline microbiology culture from the study ear grew either no organism or grew organism(s) that were not *Pseudomonas aeruginosa* or *Staphylococcus aureus*.
[3] "Unknown" indicates that the baseline microbiology culture result from the study ear was not recorded (or missing).
Source: Adapted from clinical study report for 201-201609, Table 5; Clinical reviewer's calculations.

Reviewer's Comment:
No meaningful differences were observed in the baseline AOE characteristics between treatment groups.

6.1.3 Subject Disposition

Table 6.1.3-1 summarizes the proportion of patients in each analysis population and the subject disposition. Three patients from the ITT analysis set were randomized to the OTO-201 group and excluded from the safety analysis set because they never received the study drug. Two patients from the safety analysis set were treated with sham and excluded from the ITT analysis set because they had a positive baseline microbiology culture for Group A streptococci.

Table 6.1.3-1: Subject Disposition

	OTO-201 N=130	**Sham N=132**	**Total N=262**
Analysis populations – n (%)[1]			
ITT Analysis Set[2]	130 (100)	130 (98)	260 (99)
Mic-ITT Analysis Set[3]	52 (40)	56 (42)	108 (41)
Safety Analysis Set[4]	127 (98)	132 (100)	259 (99)
Study Drug Administration – n (%)[1]			
None	3 (2)	0	3 (1)
One Ear	117 (90)	122 (92)	239 (91)
Both Ears	10 (8)	10 (8)	20 (8)
Study Completion through Visit 5/ Day 29 – n (%)[1]			
Completed	123 (95)	132 (100)	255 (97)
Discontinued	7 (5)	0	7 (3)
Reason for Premature Discontinuation – n (%)[1]			

Lost to Follow-Up	4 (3)	0	4 (2)
Exclusion Criteria	3 (2)	0	3 (1)

[1] Percentages were calculated using the number of patients randomized.
[2] The ITT Analysis Set included all randomized patients who did not have Group A Streptococci cultured on Day 1.
[3] The Mic-ITT Analysis Set included all ITT patients who had a positive baseline culture for *P. aeruginosa* and/or *S. aureus*.
[4] The Safety Analysis Set included all randomized patients who received study drug.
Source: Adapted from clinical study report for 201-201609, Table 3; Clinical reviewer's calculations.

Seven patients randomized to the OTO-201 group were discontinued prematurely from the Phase 3 study. Three patients exited the study before any treatment was administered because an exclusion criterion, diabetes mellitus or tympanic membrane perforation, was found post-randomization. Four patients were given OTO-201 treatment and lost to follow up because they either did not attend any follow up visit (1 patient), did not attend the Day 15 and 29 Visits (2 patients), or briefly attended the Day 29 Visit and left before any procedures were performed (1 patient).

6.1.4 Analysis of Primary Endpoint(s)

CC Day 8

Table 6.1.4-1 summarizes the results from the applicant's efficacy analysis of CC Day 8 using the ITT and Mic-ITT analysis sets. The ITT analysis set included all randomized patients who did not have a positive baseline culture for Group A streptococci. The Mic-ITT analysis set included all ITT patients who had a positive baseline culture for *P. aeruginosa* and/or *S. aureus*. The applicant's analysis was verified by this reviewer and the Statistics Reviewer, Edward Bein, Ph.D. The Statistics Reviewer discovered that 1 patient randomized to OTO-201 and in the ITT analysis set was incorrectly categorized by the applicant as a treatment failure at Day 8. The patient should have been considered a CC Day 8 because no signs or symptoms of AOE were identified on the otoscopic exam, and their use of a concomitant antibiotic (ceftriaxone for "Strep Throat") did not occur until Day 15. This observation was confirmed by the applicant and the analysis of CC Day 8 used the correct categorization.

Table 6.1.4-1: Primary Efficacy – CC Day 8 (ITT and Mic-ITT Analysis Sets)

	ITT analysis set		**Mic-ITT analysis set**	
	OTO-201 N=130	**Sham N=130**	**OTO-201 N=52**	**Sham N=56**
CC Day 8				
n (%)	92 (71)	63 (48)	33 (63)	20 (36)
% Difference (95% CI)	22.3 (10.4, 34.2)		27.7 (8.7, 45.3)	
p-value[1]	<0.001		0.007	

Note: Clinical cure (CC) was defined as the complete absence of 3 signs and symptoms on the otoscopic exam (edema, erythema, and tenderness), and no use of otic antibiotic drops in the study ear or systemic antibiotics at or prior to the analyzed visit
[1] The p-values were calculated from a Fisher's exact test.
Source: Adapted from clinical study report for 201-201609, Clinical reviewer's calculations

Reviewer's Comment:
A statistically significant difference favoring OTO-201 treatment was observed in both the ITT and Mic-ITT analysis sets.

Clinical cures and no otorrhea
The applicant's definition of CC did not incorporate the assessment of otorrhea, and only edema, erythema, and tenderness were the necessary assessments to determine CC. This reviewer and the Statistics Reviewer, Edward Bein, Ph.D., performed additional analyses of the primary efficacy endpoint to assess whether incorporating the assessment of otorrhea impacted the interpretation of the results. The analyses were performed because otorrhea alone could be the only sign of ongoing AOE and the resolution of otorrhea is an important outcome for patients. Tables 6.1.4-2 summarizes the proportion of patients with CC and no otorrhea at Day 8 using the ITT and Mic-ITT analysis sets.

Table 6.1.4-2: CC and No Otorrhea at Day 8 (ITT and Mic-ITT Analysis Sets)

	ITT analysis set		Mic-ITT analysis set	
	OTO-201 N=130	**Sham N=130**	**OTO-201 N=52**	**Sham N=56**
CC and No Otorrhea at Day 8				
n (%)	90 (69)	60 (46)	31 (60)	19 (34)
% Difference (95% CI)	23.1 (10.7, 34.6)		25.7 (6.6, 43.3)	
p-value[1]	<0.001		0.012	

Note: CC and no otorrhea was defined as the complete absence of 4 signs and symptoms on the otoscopic exam (edema, erythema, tenderness, and otorrhea), and no use of otic antibiotic drops in the study ear or systemic antibiotics at or prior to the analyzed visit.
[1] The p-values were calculated from a Fisher's exact test.
Source: Adapted from clinical study report for 201-201609; Clinical reviewer's calculations

Reviewer's Comment:
The differences in the proportion of patients with CC were not meaningfully affected if the assessment of otorrhea was incorporated into the endpoint. A statistically significant difference favoring OTO-201 treatment was achieved in both the ITT and Mic-ITT analysis sets.

Age Group Analysis
Table 6.1.4-3 summarizes the results for CC and no otorrhea at Day 8 in two relevant age groups, pediatric (<18 years old) and adult/elderly (≥18 years old). Age groups in this analysis were based on the patient's chronological age at the initial study visit. The age in decimal form was not rounded up to the nearest whole number.

Table 6.1.4-3: CC and No Otorrhea at Day 8 by Age Group (ITT and Mic-ITT Analysis Sets)

Pediatric patients: <18 years				
	ITT analysis set		**Mic-ITT analysis set**	
	OTO-201 N=29	**Sham N=38**	**OTO-201 N=13**	**Sham N=21**
CC and No Otorrhea at Day 8				
n (%)	20 (69)	14 (37)	7 (54)	7 (33)
% Difference (95% CI)	32.1 (7.8, 53.4)		20.5 (-14.6, 52.5)	
p-value[1]	0.014		0.296	
Adult/Elderly patients: ≥18 years				
	ITT analysis set		**Mic-ITT analysis set**	
	OTO-201 N=101	**Sham N=92**	**OTO-201 N=39**	**Sham N=35**
CC and No Otorrhea at Day 8				
n (%)	70 (69)	46 (50)	24 (62)	12 (34)
% Difference (95% CI)	19.3 (5.3, 32.9)		27.3 (4.2, 48.3)	
p-value[1]	0.008		0.022	

Source: Adapted from clinical study report for 201-201609; Clinical reviewer's calculations

Reviewer's Comment:
Across both age groups, the OTO-201 group had a greater proportion of patients with CC and no otorrhea at Day 8. Both age groups from the ITT analysis set had a statistically significant difference favoring OTO-201 treatment. A statistically significant difference was not apparent in the pediatric age group from the Mic-ITT analysis set.

There were only 22 and 10 elderly patients ≥65 years of age in the ITT and Mic-ITT analysis sets, respectively. The proportion of elderly patients in the ITT analysis set who achieved CC and no otorrhea at Day 8 were 33% in the OTO-201 group (n/nn = 3/9) and 31% in the sham group (n/nn = 4/13). None of the elderly patients in the Mic-ITT analysis set achieved CC and no otorrhea at Day 8.

6.1.5 Analysis of Secondary Endpoints(s)

CC Day 4 and CC Day 15

Table 6.1.5-1 summarizes the results from the applicant's efficacy analyses of CC Day 4 and CC Day 15 using the ITT and Mic-ITT analysis sets. The applicant's analyses were verified by this reviewer and the Statistics Reviewer, Edward Bein, Ph.D.

Table 6.1.5-1: Secondary Efficacy – CC Days 4 and 15 (ITT and Mic-ITT Analysis Sets)

	ITT analysis set	**Mic-ITT analysis set**

	OTO-201 N=130	Sham N=130	OTO-201 N=52	Sham N=56
CC Day 4				
n (%)	59 (45)	40 (31)	18 (35)	15 (27)
% Difference (95% CI)	14.6 (2.3, 26.6)		7.8 (-10.9, 26.6)	
p-value[1]	0.021		0.409	
CC Day 15				
n (%)	97 (75)	69 (53)	36 (69)	21 (38)
% Difference (95% CI)	21.5 (9.1, 33.5)		31.7 (13.0, 49.0)	
p-value	<0.001		0.001	

Note: Clinical cure (CC) was defined as the complete absence of 3 signs and symptoms on the otoscopic exam (edema, erythema, and tenderness), and no use of otic antibiotic drops in the study ear or systemic antibiotics at or prior to the analyzed visit.

[1] The p-values were calculated from a Fisher's exact test.

Source: Adapted from clinical study report for 201-201609; Clinical reviewer's calculations

Reviewer's Comment:

The OTO-201 group in the ITT and Mic-ITT analysis sets had a greater proportion of patients with CC at Days 4 and 15 compared to the sham group. Statistical significance was achieved for CC Day 15 using the ITT and Mic-ITT analysis sets. The applicant considered the statistical comparisons for CC Day 4 using the ITT and Mic-ITT analysis sets as exploratory because statistical significance was not achieved for CC Day 4 using the Mic-ITT analysis set.

Clinical cures and no otorrhea at Days 4 and 15

As mentioned earlier, the applicant's definition of CC did not incorporate the assessment of otorrhea. This reviewer and the Statistics Reviewer, Edward Bein, Ph.D., performed additional analyses of the secondary efficacy endpoints to assess whether incorporating the assessment of otorrhea impacted the interpretation of the results. The analyses were performed because otorrhea alone could be the only sign of ongoing AOE and the resolution of otorrhea is an important outcome for patients. Tables 6.1.5-2 summarizes the proportion of patients with CC and no otorrhea at Days 4 and 15 using the ITT and Mic-ITT analysis sets.

Table 6.1.5-2: CC and No Otorrhea at Days 4 and 15 (ITT and Mic-ITT Analysis Sets)

	ITT analysis set		Mic-ITT analysis set	
	OTO-201 N=130	Sham N=130	OTO-201 N=52	Sham N=56
CC and No Otorrhea at Day 4				
n (%)	56 (43)	38 (29)	17 (33)	13 (23)
% Difference (95% CI)	13.8 (1.6, 26.1)		9.5 (-9.4, 28.2)	
p-value[1]	0.028		0.291	
CC and No Otorrhea at Day 15				
n (%)	96 (74)	66 (51)	35 (67)	18 (32)

% Difference (95% CI)	23.1 (11.4, 35.0)	35.2 (16.4, 52.1)
p-value	<0.001	<0.001

Note: CC and no otorrhea was defined as the complete absence of 4 signs and symptoms on the otoscopic exam (edema, erythema, tenderness, and otorrhea), and no use of otic antibiotic drops in the study ear or systemic antibiotics at or prior to the analyzed visit.

[1] The p-values were calculated from a Fisher's exact test.

Source: Adapted from clinical study report for 201-201609; Clinical reviewer's calculations

Reviewer's Comment:

The differences in the proportion of patients with CC were not meaningfully affected if the assessment of otorrhea was incorporated into the endpoint. A statistically significant difference favoring OTO-201 treatment was achieved at Day 15 in both analysis sets. Statistical significance was not achieved for CC and no otorrhea at Day 4 using the Mic-ITT analysis set.

6.1.6 Other Endpoints

The applicant performed a sequential closed testing procedure to evaluate the secondary endpoints. If at any step a statistically significant difference was not achieved between the treatment groups, this and the remaining comparisons would be considered exploratory. Statistical significance was not achieved for CC Day 4 using the Mic-ITT analysis set; thus, analyses of CC Day 4 using the ITT and Mic-ITT analysis sets and time-to-cessation of otalgia using the ITT analysis set were considered exploratory. Please see the review by the Statistics Reviewer, Edward Bein, Ph.D., for further details on time-to-cessation of otalgia and other exploratory analyses.

6.1.7 Subpopulations

Subgroup analyses of the efficacy endpoints were conducted by age group, sex, race, and baseline microbiology status/pathogen type. Overall, the results from the Phase 3 study indicated a treatment effect favoring OTO-201 in all age groups (pediatric, adult, and elderly), sex groups (male and female), and race groups (white, nonwhite). Differences in the magnitude of treatment effect were observed, particularly groups with a small sample size (i.e., elderly patients).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dose of OTO-201 is 12 mg (0.2 mL dosing volume) administered to each affected ear. The 12 mg (0.2 mL) dose is recommended in the label because of the efficacy results demonstrated in the Phase 3 study and supported in a smaller Phase 2 study. In the Phase 2 study, the 12 mg OTO-201 group had greater proportions of patients with complete resolution of signs and symptoms at Days 8 and 15 compared to the other OTO-201 dose groups. Based on these findings, the 12 mg (0.2 mL) dose was selected for the Phase 3 study and this dose was confirmed as efficacious.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The overall treatment effect of OTO-201, as demonstrated by CC and no otorrhea, was persistent to Day 29. In the ITT analysis set, the proportion of patients with persistence

of efficacy from Day 8 to 29 was 92%. The reasons persistence of efficacy was not observed in the OTO-201 group were lost to follow up (3 patients), use of otic or systemic antibiotics (2 patients), or a mild sign or symptom observed by the blinded assessor (2 patients).

6.1.10 Additional Efficacy Issues/Analyses

No other analyses were performed.

7 Review of Safety

Safety Summary

A Phase 2 and Phase 3 study each demonstrated the safety of Otiprio for the treatment of pediatric, adult, and elderly patients with AOE. Three OTO-201 doses (6 mg, 12 mg, and 24 mg) were evaluated in the Phase 2 study, while a 12 mg dose was evaluated in the Phase 3 study (same as selected for marketing). The majority of TEAEs associated with Otiprio were minor, mild or moderate in severity, and self-limited. There were no deaths, SAEs, or TEAEs leading to study discontinuation in any of the clinical studies. There were no meaningful differences in the safety of Otiprio between the pediatric and adult/elderly patients.

7.1 Methods

Pediatric and adult patients with otitis externa or AOE were enrolled into the Phase 2 and Phase 3 studies. Patients in the Phase 2 study had unilateral otitis externa and received one of three dose levels of OTO-201 (6 mg, 12 mg, or 24 mg); while, patients in the Phase 3 study had unilateral or bilateral AOE and one dose level of OTO-201 (12 mg) was evaluated relative to sham (empty syringe). The study treatment in both studies was given as a single administration to the external auditory canal of the affected ear. After treatment on Day 1, patients in the Phase 2 and Phase 3 studies returned to the study site for safety assessments on Day 4, 8, 15, and 29. The following safety assessments were performed in both clinical studies: adverse events, otoscopic examinations, vital signs, and physical examinations. Additional information related to the study designs for the Phase 2 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 Clinical Safety Program

Study Identifier	Study Design	Study Population	Regimen/Schedule/Duration	Treatment (N)	Safety assessments
201-201506 **IND 110244** **Phase 2**	Prospective, multicenter, randomized, open-label study	Male and female patients age 6 months to 80 year with unilateral otitis externa	OTO-201 6%: 6 mg = 0.1 mL 12 mg = 0.2 mL 24 mg = 0.4 mL Single unilateral administration to the external ear canal of the affected ear Follow-up to day 29	• OTO-201 4 mg (N=25) 12 mg (N=25) 24 mg (N=25)	• Adverse Events • Otoscopic exams • Vital signs • Physical exam
201-201609 **IND 110244** **Phase 3**	Prospective, multicenter, randomized, double-blind, sham-controlled study	Male and female patients age 6 months and older with unilateral or bilateral AOE	OTO-201 6%: 12 mg = 0.2 mL Sham: Syringe with air Single unilateral or bilateral administration to the external ear canal of the affected ear(s) Follow-up to day 29	• OTO-201 12 mg (N=127) • Sham (N=132)	• Adverse Events • Otoscopic exams • Vital signs • Physical exam

Source: Adapted from clinical study reports for 201-201506 and 201-201609.

7.1.2 Categorization of Adverse Events

The routine clinical testing required to establish the safety of external auditory canal administration of OTO-201 was adequately addressed in the design and conduct of the Phase 2 and Phase 3 studies. All adverse events were coded using a MedDRA dictionary and received causality assessment from the Investigator.

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

The safety data from the Phase 2 study were not pooled with the data from the Phase 3 study because of the small number of enrolled patients and the different design of the study.

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 patient exposure to OTO-201 or sham across the Phase 2 and Phase 3 studies. A total of 75 patients were treated with OTO-201 during the Phase 2 study. This population consisted of 29% pediatric patients (<18 years of age), 59% adult patients (18 to <65 years of age), and 12% elderly patients (≥65 years of age). There were 259 patients treated with OTO-201 or sham during Phase 3 study. The composition of pediatric, adult, and elderly patients in this population was 27%, 66%, and 8%, respectively. Twenty patients from the Phase 3 study (8% for each treatment group) had the study drug administered bilaterally to both affected ears. The other patients treated in either study had the study drug administered unilaterally to one affected ear.

Table 7.2.1-1: Patient Exposure to OTO-201 or Sham Across Studies 201-201506 and 201-201609 (Safety Analysis Set)

Treatment	Study 201-201506 N = 75 n (%)	Study 201-201609 N=259 n (%)	Total N = 334 n (%)
6 mg OTO-201	25 (33)	-	25 (7)
12 mg OTO-201	25 (33)	127 (49)	152 (46)
24 mg OTO-201	25 (33)	-	25 (7)
Sham	-	132 (51)	132 (40)

Source: Adapted from summary of clinical safety, Table 5.

7.2.2 Explorations for Dose Response

Three dose levels of OTO-201, 6 mg, 12 mg, and 24 mg, were evaluated in the Phase 2 study. The clinical activity results demonstrated that all 3 doses were effective, but the 12 mg dose was more effective than either the 6 mg or the 24 mg dose. No meaningful differences in safety findings were observed between the three doses.

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

7.2.3 Special Animal and/or In Vitro Testing

No additional animal or *in vitro* testing was conducted for this submission. Nonclinical investigations of ototoxicity, systemic toxicity, local toxicity (dermal toxicity or delayed-hypersensitivity), and antigenicity were submitted in the original NDA submission.

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 2 and Phase 3 studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

Minimal systemic exposure is expected from this low-dose topical product administered to the external ear canal.

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

The adverse events reported in the Phase 2 and Phase 3 studies are consistent with those reported with other topical otic fluoroquinolones. The assessment of these adverse events within the clinical studies was adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the Phase 2 or the Phase 3 studies.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) reported during the Phase 2 or Phase 3 studies.

7.3.3 Dropouts and/or Discontinuations

All 75 patients who participated in the Phase 2 study completed the study through Day 29.

Seven patients in the OTO-201 group were prematurely discontinued from the Phase 3 study: 4 patients were lost to follow up and 3 patients were found to meet an exclusion criteria post-randomization and therefore did not receive study drug. Please see Section 6.1.3 for additional information regarding dropouts in the Phase 3 study.

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

No specific primary safety concerns were identified for the submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 7.4.1-1 summarizes the common TEAEs reported during the Phase 2 study, and defined as TEAEs experienced by at least 2 patients in any treatment group. Otitis externa was the most frequently reported event. Recurrent cases involving the affected ear and emergent cases involving the unaffected ear were reported as adverse events. There were 2 patients (8%) in 6 mg OTO-201 group, 2 patients (8%) in the 12 mg OTO-201 group, and 3 patients (12%) in the 24 mg OTO-201 group who had recurrent otitis externa reported. Another 2 patients (1 each in the 12 mg and 24 mg OTO-201 groups) developed otitis externa in the unaffected ear alone. Most of the TEAEs in the Phase 2 study were reported as mild or moderate. A single patient in the 12 mg OTO-201 group had severe otitis externa in the affected ear that resolved with Ciprodex treatment. The investigator did not believe the event was related to the study treatment.

Table 7.4.1-1: Summary of TEAEs Experienced by at least 2 Subjects in Any Treatment Group Study 201-201101

	OTO-201			
Preferred term	**6 mg N=25 n (%)**	**12 mg N=25 n (%)**	**24 mg N=25 n (%)**	**Total N=75 n (%)**
Otitis externa	2 (8)	3 (12)	4 (16)	9 (12)
Ear pain	0	1 (4)	3 (12)	4 (5)
Hypoacusis	0	1 (4)	3 (12)	4 (5)
Otorrhea	0	2 (8)	1 (4)	3 (4)
Fungal infection[1]	3 (12)	0	0	3 (4)
Ear Eczema	1 (4)	0	2 (8)	3 (4)
Ear Erythema	0	0	2 (8)	2 (3)

[1] Includes: recurrent otitis externa in the affected ear or development in the unaffected ear.
[2] Includes: worsening/persistent ear pain in the affected ear.
[3] Includes: fungal otitis externa or fungal infection in the affected ear.
MedDRA Version 18.0
Source: Adapted from clinical study report for 201-201506, Table 12-3; Clinical reviewer's calculations.

Reviewer's Comment:
Otorrhea was the only TEAE reported by 2 or more patients in any treatment group and more frequently in the 12 mg OTO-201 group. This reviewer agrees with the investigator's assessment that the single severe TEAE reported in the Phase 3 study was not related to study treatment.

Table 7.4.2-2 summarizes the common TEAEs reported during the Phase 3 study, and defined as TEAEs experienced by at least 2% of patients in the OTO-201 group. Otitis externa was the most frequently reported event. Recurrent otitis externa in the affected ear at study entry was reported in 1 patient (1%) in the OTO-201 group and 6 patients (5%) in the sham group. Another 5 patients (2 in the OTO-201 group and 3 in the sham

group) developed otitis externa in the unaffected ear alone. Most of the common TEAEs in the Phase 3 study were reported as mild or moderate. A single patient in the OTO-201 group had severe ear pain in the affected ear that resolved with Ciprodex treatment. The investigator did not believe the event was related to the study treatment.

Table 7.4.1-2: Summary of TEAEs Experienced at rates ≥2% in the OTO-201 patients Study 201-201609 (Safety Analysis Set)

Preferred term	OTO-201 12 mg N=127 n (%)	Sham N=132 n (%)	Total N=259 n (%)
Otitis externa[1]	3 (2)	9 (7)	12 (5)
Ear pain[2]	3 (2)	3 (2)	6 (2)
Ear pruritus	3 (2)	2 (2)	5 (2)
Headache	3 (2)	1 (1)	4 (2)
Otitis media	2 (2)	1 (1)	3 (1)
Ear discomfort	2 (2)	0	2 (1)
Nasal congestion	2 (2)	0	2 (1)

[1] Includes: recurrent otitis externa in the affected ear or development in the unaffected ear.
[2] Includes: worsening/persistent ear pain in the affected ear or development in the unaffected ear.
MedDRA Version 19.0
Source: Adapted from clinical study report for 201-201609, Table 11; Clinical reviewer's calculations.

Reviewer's Comment:
The TEAEs reported by at least 2% of patients in the OTO-201 group and more frequently in the OTO-201 group were ear pruritus, headache, otitis media, ear discomfort, and nasal congestion. This reviewer agrees with the investigator's assessment that the single severe TEAE reported in the Phase 3 study was not related to study treatment.

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 2 and Phase 3 studies underwent temperature, systolic blood pressure, diastolic blood pressure, and pulse rate measurements at baseline and the Day 29 Visits. No overall clinically relevant differences in vital sign changes were observed between the OTO-201 and sham treatment groups.

7.4.4 Electrocardiograms (ECGs)
Electrocardiograms were not performed in Phase 2 or Phase 3 studies.

7.4.5 Special Safety Studies/Clinical Trials
No special safety studies were submitted in this submission.

7.4.6 Immunogenicity
Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
OTO-201 in the Phase 2 study was administered as either a single 6 mg (0.1 mL), 12 mg (0.2 mL), or 24 mg (0.4 mL) dose into the affected ear. No safety concerns resulting from either dose were noted from the safety assessments.

OTO-201 in the Phase 3 study was administered to patients as a single 12 mg (0.2 mL) dose into each affected ear(s) and dose dependency for adverse events was not applicable in this study.

7.5.2 Time Dependency for Adverse Events
An exploration of time dependency for adverse events was not conducted.

7.5.3 Drug-Demographic Interactions
No drug-drug interaction studies were submitted with this application.

7.5.4 Drug-Disease Interactions
Not applicable.

7.5.5 Drug-Drug Interactions
No drug-drug interaction studies were submitted with this application. Drug interactions are unlikely to occur because of the limited systemic exposure to OTO-201 following administration.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity
Not applicable.

7.6.2 Human Reproduction and Pregnancy Data
Pregnant or lactating 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
The safety analysis set for the Phase 2 study consisted of 22 pediatric patients <18 years of age. The minimum and maximum ages for the pediatric patients were 3 years and 16 years, respectively. A review of adverse events did not reveal any notable differences in the TEAEs reported between the pediatric and adult/elderly patients. No single TEAE was reported in 2 or more pediatric patients in any treatment group.

The safety analysis set for the Phase 3 study consisted of 69 pediatric patients <18 years of age. The minimum and maximum ages for the pediatric patients were 3 years and 17 years, respectively. A review of adverse events did not reveal any notable differences in the TEAEs reported between the pediatric and adult/elderly patients. Among the pediatric patients, otitis externa was reported in 2 patients in each treatment group and more frequently in the OTO-201 group compared to the sham group (7% and 5%, respectively). None of the other TEAEs were reported in 2 or more pediatric patients in the OTO-201 group.

The applicant did not conduct a formal assessment on the effect of OTO-201 on growth and development. Assessments of effects on growth were unnecessary in the case of limited, low-dose exposure to a topical fluoroquinolone product such as this.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential for overdose, drug abuse, withdrawal, or rebound are not expected concerns because OTO-201 administered as a single dose by a trained clinician.

7.7 Additional Submissions / Safety Issues

A safety update report was not submitted to this sNDA. There were no ongoing studies at the time of submission.

8 Postmarket Experience

DAIP and OSE monitor post-marketing AEs continuously and specific events are reviewed as needed.

9 Appendices

9.1 Literature Review/References

An independent literature review did not produce any additional significant information regarding OTO-201.

References

1. CDC. Estimated burden of acute otitis externa--United States, 2003-2007. *MMWR Morb Mortal Wkly Rep*. 2011;60(19):605-609.

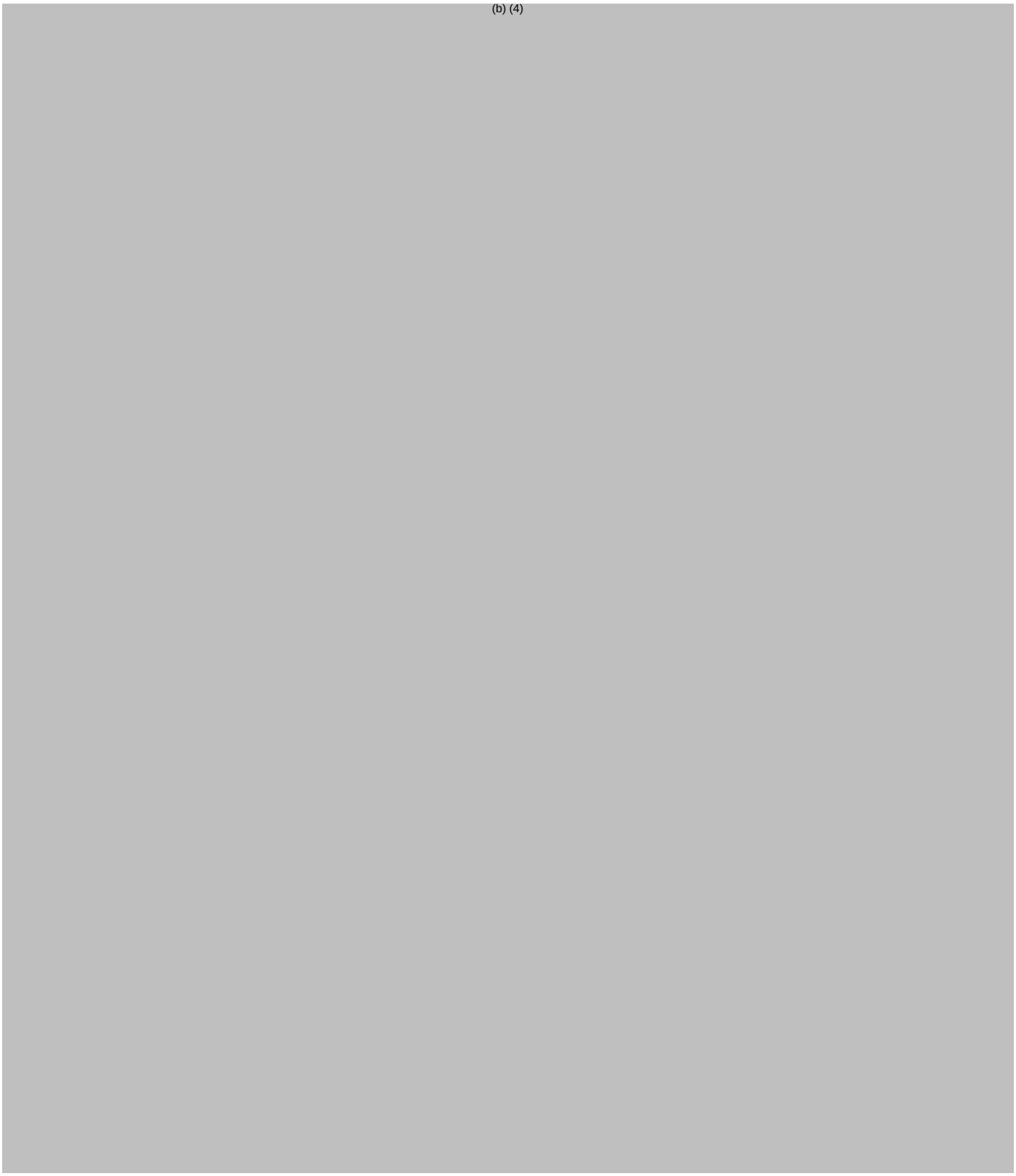
2. American Academy of Otolaryngology--Head and Neck Surgery. Clinical Practice Guideline: Acute Otitis Externa. *Otolaryngology—Head and Neck Surgery*. 2014; 150(1S): S1-S24.

9.2 Labeling Recommendations

Labeling negotiations were ongoing at the time this review was finalized. Below are some of the preliminary proposed modifications to the clinically-relevant sections of the label.

(b) (4)

(b) (4)



(b) (4)

9.3 Advisory Committee Meeting

Not applicable.

9.4 Clinical Investigator Financial Disclosure

Application Number: 207986/S-2

Submission Date(s): May 02, 2017

Applicant: Otonomy, Inc.

Product: Otiprio (ciprofloxacin otic suspension)

Reviewer: Mark Needles, M.D.

Date of Review: 02/01/2018

Covered Clinical Study (Name and/or Number): 201-201506 and 201-201609

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Study 201-201506: 9 investigators Study 201-201609: 36 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: N/A		

Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from applicant)

The applicant determined there were no financial interests or arrangements to disclose from the investigators in Studies 201-201506 and 201-201609.

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
02/01/2018

THOMAS D SMITH
02/01/2018