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*APPLICATION NUMBER:*

**207986Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	December 10, 2015
<b>From</b>	Thomas Smith, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA#</b>	207986
<b>Applicant</b>	Otonomy, Inc.
<b>Date of Submission</b>	February 25, 2015
<b>PDUFA Goal Date</b>	December 25, 2015
<b>Proprietary Name / Established (USAN) name</b>	Otiprio®/Ciprofloxacin otic suspension, 6%
<b>Dosage form / Strength</b>	Otic suspension/60 mg/mL
<b>Proposed Indication</b>	Treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube placement
<b>Recommended:</b>	Approval

### 1. Introduction

NDA 207986 was submitted by Otonomy, Inc., on February 25, 2015, for the use of ciprofloxacin 6% otic suspension (Otiprio; OTO-201) for the treatment of pediatric patients with otitis media with effusion undergoing tympanostomy tube placement. The clinical program, conducted under IND 110244, included one phase 1b trial and two phase 3 trials. The phase 3 trials were identical, randomized, double-blind (patient and evaluator), sham-controlled trials in which 532 patients were randomized 2:1 to receive either a single intratympanic dose of OTO-201 or a sham dose. The primary endpoint was treatment failure through day 15 post-administration of study drug.

This review summarizes the findings of the review team and highlights notable issues.

### 2. Background

Otitis media with effusion (OME) is the presence of fluid in the middle ear without evidence of acute infection<sup>1</sup>. It may occur spontaneously or as a consequence of acute otitis media. Approximately 90% of children have OME at some time before school age. OME is generally self-limited, with 75-90% of episodes that follow acute otitis media resolving within three months. However, 5-10% of episodes of OME last one year or longer. Persistent middle ear effusion causes decreased mobility of the tympanic membrane and impairs sound conduction. Tympanostomy tubes are often placed in children with persistent middle ear effusion and hearing impairment who are at risk of speech and language delays or other developmental

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<sup>1</sup> American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, and American Academy of Pediatrics Subcommittee on Otitis Media with Effusion. Otitis media with effusion. Pediatrics 2004; 113:1412-1429.

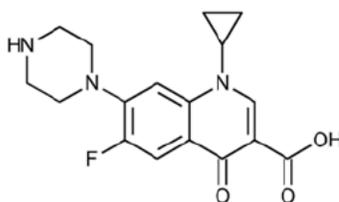
difficulties. Otorrhea commonly follows tympanostomy tube placement; approximately 16% of children develop otorrhea within four weeks of tube placement<sup>2</sup>. The most common pathogens in acute otitis media in children with tympanostomy tubes (AOMT) include the typical pathogens of acute otitis media, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, and those of acute otitis externa (AOE), *Pseudomonas aeruginosa* and *Staphylococcus aureus*<sup>3</sup>. There are no FDA-approved products for the treatment of OME or for the prevention of AOMT. Ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension (Ciprodex) and ofloxacin 0.3% otic solution (Floxin Otic) are approved for the treatment of AOMT and AOE. Ciprofloxacin 0.2% (Cetraxal) and ciprofloxacin 0.2% and hydrocortisone 1% (Cipro HC Otic) are approved for the treatment of AOE only.

Otonomy, Inc., has developed ciprofloxacin 6% otic suspension for the treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube placement. The ciprofloxacin is suspended in a solution containing a thermosensitive mucoadhesive glycol polymer, polaxamer 407, that exists as a liquid at or below room temperature and as a gel when warmed. The drug is administered as a single intratympanic injection of 0.1 mL into each affected ear. This is a 505(b)(2) application that references FDA's prior findings of nonclinical safety for ciprofloxacin tablets (NDA 19-537) to incorporate toxicity information for ciprofloxacin administered by a non-otic route.

### 3. CMC/Device

Chunchun Zhang, Ph.D., was the application technical lead for the quality review team. The team's findings are summarized below.

Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid) is a white (b)(4) powder that is nearly insoluble in water and only slightly soluble in ethanol. It has the molecular formula  $C_{17}H_{18}FN_3O_3$  with a molecular weight of 331.3 and the following structural formula:



There are two suppliers of the drug substance: (b)(4)  
(b)(4) The drug master files were previously reviewed (b)(4) and were found to be adequate to support the submissions. No new CMC updates were noted. Acceptance specifications include tests for description, identification, assay, inorganic impurities, organic impurities, clarity of solution,

<sup>2</sup> Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. *Otolaryngol Head Neck Surg* 2013; 149: S1-S35.

<sup>3</sup> Mandel EM, Casselbrant ML, Kurs-Lasky M. Acute otorrhea: bacteriology of a common complication of tympanostomy tubes. *Ann Otol Rhinol Laryngol* 1994; 103:713.

microbial enumeration, specified microorganisms, loss on drying, bacterial endotoxins, residual solvent, and particle size distribution, and were considered adequate to support this NDA.

The drug product manufacturer is (b) (4), located in (b) (4). The drug product, ciprofloxacin otic suspension, 6%, is supplied as a white, preservative-free, sterile otic suspension of 6% (w/v) ciprofloxacin in a neutral pH, buffered, isotonic solution in a single-patient use glass vial with a rubber stopper containing 1mL. The inactive ingredients are poloxamer 407, sodium chloride, tromethamine, hydrochloric acid, and water for injection. The suspension is thermosensitive, existing as a liquid at room temperature or below and as a gel when warmed. The drug product specifications include tests for appearance, identity, pH, assay, degradants, dose uniformity, dissolution, temperature of gelation, osmolality, poloxamer 407 content, (b) (4) bacterial endotoxins, and sterility, and were considered adequate to support this NDA. The recommended expiry period for the drug product is 30 months when stored from 2°C to 8°C in 2 mL glass vials, in the marketing package, protected from light.

(b) (4)

All facilities reviews and inspections have been completed, and the Office of Pharmaceutical Quality has determined these facilities to be acceptable.

Dr. Zhang and the other members of the product quality review team recommended approval of this NDA. There are no recommended postmarketing commitments.

#### **4. Nonclinical Pharmacology/Toxicology**

James Wild, Ph.D., was the pharmacology/toxicology reviewer for this application. His findings are summarized below.

Several studies evaluated otic and systemic toxicity of OTO-201. In one of three studies that evaluated hearing function, changes in auditory brainstem responses consistent with moderate hearing loss were observed in guinea pigs receiving a single intratympanic dose of 6% OTO-201. In this study, hearing loss was not associated with microscopic evidence of cochlear damage. Hearing loss and cochlear damage were observed with administration of Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) and Cetraxal (ciprofloxacin 0.2%) for 7 days, the approved duration of dosing. In addition, 6% OTO-201 produced ossicle immobility in 4 of 20 ears in one study and 1 of 20 ears in another; these rates are similar to those observed with ciprofloxacin 0.2% in the same studies. Other middle ear findings associated with single-dose administration of 6% OTO-201 included granulomatous inflammation, fibroplasia, foamy macrophages, and foreign material. These changes were considered consistent with a foreign body reaction. There were no consistent toxicologically relevant changes in systemic toxicity endpoints in the single-dose studies.

IND 110244 was placed on full clinical hold on December 13, 2011, because of nonclinical toxicology findings in guinea pigs suggesting that the (b) (4) for the poloxamer 407 vehicle produced (b) (4) that were associated with hearing loss and damage to cochlear hair cells. In response to the clinical hold, Otonomy changed the (b) (4) method which reduced the production of (b) (4). Subsequent animal studies revealed decreased hearing loss with the new (b) (4). The clinical hold was removed on November 30, 2012. Dr. Wild recommended monitoring of (b) (4) levels in batches of the OTO-201 drug product. The drug product specifications include testing for (b) (4).

Studies of otic pharmacokinetics were performed in guinea pigs. Middle ear  $C_{max}$  of ciprofloxacin following a single dose of 50  $\mu$ L of 6% OTO-201 (3 mg) was 91.7  $\mu$ g/mL, the  $AUC_{0-24}$  was 2200  $\mu$ g•h/mL, and the mean residence time was 246 hours. For a pathogen with a minimum inhibitory concentration (MIC) of 2  $\mu$ g/mL, the  $C_{max}$ /MIC ratio was 46, and the  $AUC_{0-24}$ /MIC was 1100 hours. Poloxamer 407 levels decreased by approximately 80% 24 hours after administration and by approximately 99% after 7 days.

The applicant relied on prior findings of nonclinical safety for ciprofloxacin tablets to incorporate toxicity information for ciprofloxacin administered by a non-otic route. This information is included in labeling in Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility. The potential for genotoxicity and reproductive and developmental toxicity is considered low.

Dr. Wild concluded that OTO-201 is approvable from a pharmacology/toxicology perspective.

## 5. Clinical Pharmacology/Biopharmaceutics

OTO-201 is to be administered as a single intratympanic dose of 0.1 mL (6 mg) to each affected ear following suctioning of the middle ear effusion during tympanostomy tube placement. The dose was selected following a phase 1b dose-escalation study, Study 201-201101, in which OTO-201 was administered in doses of 4 mg or 12 mg in a 0.2 mL volume. Treatment failure rates were similar with both doses, but investigators reported difficulty administering a 0.2 mL volume to all patients; most were able to administer at least 0.1 mL. The applicant therefore chose to proceed with the 6 mg/0.1 mL dose for the phase 3 trials. Additional information is provided about Study 201-201101 in section 7 below.

Dakshina Chilukuri, Ph.D., was the clinical pharmacology reviewer for this application. No new clinical pharmacology information was submitted. The drug is intended for local administration, and plasma concentrations of ciprofloxacin were not measured. Dr. Chilukuri noted that pharmacokinetic studies in animals demonstrated that a single intratympanic injection of OTO-201 produced ciprofloxacin exposure profiles in the middle ear and inner ear comparable to the profiles observed with administration of a similar total doses of Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) and Cetraxal (ciprofloxacin 0.2%), approved otic products administered twice daily for 7 days. Dr. Chilukuri recommended approval of this

application pending acceptable determination of clinical safety and efficacy and agreement on labeling.

## 6. Clinical Microbiology

Jalal Sheikh, Ph.D., was the clinical microbiology reviewer for this application. Dr. Sheikh's findings are summarized below.

Ciprofloxacin is a quinolone antimicrobial that interferes with bacterial DNA gyrase, which is required for the synthesis of bacterial DNA. It has been shown to be active against most isolates of potential otic pathogens in patients with tympanostomy tubes: *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *P. aeruginosa*. Bacterial resistance to fluoroquinolones may be either chromosomally- or plasmid-mediated. Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones, but generally not between ciprofloxacin and other classes of antibacterial agents.

Otonomy provided *in vitro* surveillance data from 2008 to 2010 for ciprofloxacin and levofloxacin. Resistance was rare among *S. pneumoniae* and *H. influenzae*. Few data were available for *M. catarrhalis*, but literature reports suggest high susceptibility rates. Increased resistance was observed for *S. aureus* and *P. aeruginosa*.

Otonomy conducted an *in vitro* study of ciprofloxacin and other antibiotics against isolates of the target pathogens recovered from otic and other respiratory infections from 2010 to 2012. Approximately half of the specimens were collected in the U.S., with most of the remaining specimens collected in Europe and Asia. Ciprofloxacin was highly active against *M. catarrhalis* and most strains of *S. pneumoniae* and *H. influenzae*. It was also highly active against methicillin-susceptible *S. aureus*; the majority of methicillin-resistant *S. aureus* strains were ciprofloxacin nonsusceptible. Approximately 25% of *P. aeruginosa* isolates tested were nonsusceptible.

Otonomy evaluated the time-kill kinetics of ciprofloxacin against three otic or respiratory isolates of each of the target pathogens at concentrations expected to be locally achievable following administration of OTO-201; the three isolates were susceptible, intermediately susceptible, and resistant to fluoroquinolones. Ciprofloxacin was bactericidal at concentrations of 4 to 8 times the MIC for all strains tested, with the exception of the susceptible strain of *P. aeruginosa*, for which bactericidal activity was demonstrated at 64 times the MIC.

Otonomy conducted studies in a chinchilla model of otitis media with effusion induced with *S. pneumoniae*. These studies demonstrated that a single intratympanic injection of OTO-201 could reduce middle ear effusion volume and bacterial load.

The clinical microbiology findings in the phase 3 trials are summarized in section 7.

Dr. Sheikh concluded that this application was approvable pending agreement on acceptable labeling.

## 7. Clinical/Statistical- Efficacy

Mark Needles, M.D., was the clinical reviewer, and Mushfiqur Rashid, Ph.D., was the statistical reviewer for this application. The clinical program included a phase 1b dose-escalation safety and tolerability trial that also evaluated clinical activity of OTO-201, and two identical phase 3 trials.

### Study 201-201101

Study 201-201101 was a randomized, double-blind, placebo- and sham-controlled dose escalation trial. Patients 6 months to 12 years of age with bilateral middle ear effusions who were undergoing tympanostomy tube placement were randomized 2:1:1 to receive a single dose of OTO-201, vehicle placebo, or sham intratympanically in each ear at the time of surgery. Two dose cohorts of OTO-201 were studied: 4 mg and 12 mg, administered in a 0.2 mL volume. Cohorts were stratified by age: 6 months to 2 years and >2 years. Study visits were scheduled out to 29 days post-procedure. Safety endpoints included adverse event monitoring, audiometry, tympanometry, and otoscopy. The primary clinical activity assessment was the proportion of treatment failures, with failure defined as development of otorrhea 3 days postprocedure through the day 15 visit or administration of topical or systemic antimicrobial therapy at any time postprocedure through day 15. The primary analysis population was the full analysis set, which included all patients who were randomized and received study drug or a sham injection. This trial was not powered for hypothesis testing.

Eighty-three patients were randomized, 44 in the 4 mg cohort, and 39 in the 12 mg cohort. Forty-two patients were 6 months to 2 years of age, and 41 patients were >2 years; 62.7% were male.

An unplanned interim analysis was performed to analyze clinical activity through the day 15 visit. Although not all patients had completed the study through day 29, the interim day 15 results were considered final. Table 1 shows the proportion of treatment failures through day 15. The proportion of treatment failures was similar in each OTO-201 cohort and lower than in either the placebo or sham groups. The proportion of treatment failures was similar in the placebo and sham groups.

Table 1. Proportion of Treatment Failures through Day 15

<b>Treatment Failure/Cause</b>	<b>OTO-201 4 mg (N=21)</b>	<b>OTO-201 12 mg (N=19)</b>	<b>All OTO-201 (N=40)</b>	<b>Pooled Placebo (N=22)</b>	<b>Pooled Sham (N=21)</b>
Total	3 (14.3)	3 (15.8)	6 (15.0)	10 (45.5)	9 (42.9)
Otorrhea (any ear)	2 (9.5)	2 (10.5)	4 (10.0)	8 (36.4)	5 (23.8)
Rescue medication	1 (4.8)	1 (5.3)	2 (5.0)	2 (9.1)	4 (19.0)

Adapted from Study 201-201101 Study Report, Table 11-4

Following database lock, the treatment failure status of one sham recipient was changed from non-treatment failure to treatment failure. This patient developed bilateral tube obstruction and

was treated with topical rescue medication on day 10. This change did not affect the conclusions drawn from the interim analysis.

As noted in section 5 above, Otonomy decided to proceed with a dose of 6 mg/0.1 mL for the phase 3 trials.

### Studies 201-201302 and 201-201303

Studies 201-201302 and 201-201303 were identical, randomized, double-blind (patient and assessor), sham-controlled phase 3 trials of OTO-201 administered as a single intratympanic injection for the treatment of middle ear effusion in pediatric patients undergoing tympanostomy tube placement. The trials were conducted at sites in the U.S. and Canada from 2013 to 2014. The original protocols were amended once to expand the inclusion criteria out to 17 years of age, to modify the status of patients who missed particular visits, and to clarify study procedures. Following this amendment the statistical analysis plan was amended to reinstate the treatment of missed visits to that of the original protocol, in which missed visits were considered failures.

Patients 6 months to 17 years of age with bilateral middle ear effusions who were undergoing tympanostomy tube placement were randomized 2:1 to receive a single 6 mg dose of OTO-201 or a sham injection intratympanically in each ear at the time of surgery. Randomization was stratified by age: 6 months to 2 years and >2 years. Baseline middle ear effusion cultures were obtained at the time of the procedure. Patients were to return for evaluation by a blinded assessor at study visits on days 4, 8, 15, and 29, and caregivers were also instructed to return with the patients for evaluation if otorrhea developed on or after 3 days postprocedure. If otorrhea was present, cultures were to be obtained, and patients were eligible for treatment with Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension), 4 drops bid for 7 days. Safety endpoints included adverse event monitoring, tympanometry, and otoscopy; audiometric evaluations were performed in a subset of patients.

The primary efficacy endpoint was the cumulative proportion of treatment failures through the day 15 visit. Treatment failure included the following events:

- Otic treatment failure: receipt of an otic antimicrobial drop at any time postprocedure through day 15 before confirmation of otorrhea by the blinded assessor
- Systemic antibiotic treatment failure: receipt of a systemic antimicrobial at any time postprocedure through day 15 before confirmation of otorrhea by the blinded assessor
- Otorrhea treatment failure: development of otorrhea with documentation by the blinded assessor at any time from day 4 (3 days postprocedure) through day 15
- Lost-to-follow-up treatment failure: unknown treatment failure status at day 15 because of loss to follow-up
- Missed visit treatment failure: missing treatment failure status at a particular visit because of failure to return for blinded assessment but not lost to follow-up

The primary efficacy analysis was performed in the full analysis set, which was the intent-to-treat population of all randomized patients. Additional efficacy analyses were performed in the per protocol set, which was the subset of patients without major protocol deviations and who

had evaluations by the blinded assessor at days 4, 8, and 15, and the microbiologically evaluable set, which was the subset with positive cultures (*P. aeruginosa*, *S. aureus*, *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*) of baseline middle ear effusions.

Otonomy determined the sample size for the phase 3 trials using estimates from Study 201-201101, adjusting the anticipated treatment failure rates to account for sampling variability in Study 201-201101, expected losses to follow-up and missed visits, and a relatively greater proportion of younger children (ages 6 months to 2 years) expected to be enrolled in the phase 3 trials. The treatment failure rates for the phase 3 trials were hypothesized to be 0.25 and 0.46 for the OTO-201 and sham groups, respectively. With 2:1 (OTO-201: sham) randomization and assuming a common odds ratio (OR) of 0.37 favoring OTO-201, a sample size of 264 patients had approximately 95% power to reject the null hypothesis of an OR = 1 (i.e., no association between treatment and treatment failure) using a Cochran-Mantel-Haenszel test at a two-tailed type 1 error rate of 0.05 adjusted for age.

Otonomy reported that, after breaking the study blind and locking the database, they discovered that the identification of otic or systemic antibiotics used to define treatment failure was based on designation by the study site rather than by the blinded medical reviewer, as was prespecified in the statistical analysis plan. They repeated the affected analyses following review of concomitant medications by an independent medical reviewer blinded to treatment allocation, treatment received, and individual patient data. They also reported that the analyses of components of treatment failure were not mutually exclusive, so that patients might be counted as failures twice if they had two events that constituted failure (e.g., receipt of an otic antimicrobial followed by receipt of a systemic antimicrobial). They repeated the affected analyses and identified them in table, listing, and figure numbers. The results presented below have been reviewed and verified by the FDA clinical and statistical reviewers.

Total enrollment in the trials was 532 patients, with 266 patients in each trial. All patients were from the U.S. or Canada. The patients ranged in age from 0.5 years to 12.6 years, with a median age of 1.5 years. Three hundred twenty-six patients (61%) were 6 months to 2 years of age, and 206 patients (39%) were greater than 2 years of age. Three hundred four patients (57%) were male; 429 (81%) were white, 66 (12%) were black, and 7% were other. Baseline cultures grew potential otic pathogens from at least one ear in 119 patients (22%); isolates were: *H. influenzae*, 66 (12%); *S. pneumoniae*, 32 (6%); *M. catarrhalis*, 22 (4%); *S. aureus*, 10 (2%); and *P. aeruginosa*, 3 (1%); a patient could have more than one isolate. Cultures were negative or grew nonpathogens in 406 patients (76%), and results were unknown (not recorded or missing) for 7 patients (1%).

Table 2 shows the results for each trial for the intent to treat and per protocol populations. In each trial, there were significantly fewer treatment failures in patients who received OTO-201 compared with those receiving sham. The most common reason for exclusion from the per protocol population was a study visit outside the designated window.

Table 2. Cumulative Proportion of Treatment Failures through Day 15 in Phase 3 Trials

Population	Study 201-201302 (N=266)			Study 201-201303 (N=266)		
	OTO-201	Sham	% Difference (Sham – OTO-201) (95% confidence interval)	OTO-201	Sham	% Difference (Sham – OTO-201) (95% confidence interval)
Intent to Treat	25% (44/179)	45% (39/87)	20% (8%, 32%) <sup>1</sup>	21% (38/178)	45% (40/88)	24% (12%, 36%) <sup>1</sup>
Per Protocol	12% (18/148)	39% (27/70)	27% (14%, 39%) <sup>1</sup>	17% (27/159)	39% (29/74)	22% (10%, 35%) <sup>1</sup>

<sup>1</sup> p-value <0.001 for Cochran-Mantel-Haenszel test (adjusted for age group)  
Adapted from FDA statistical review, Tables 6 and 7

The effect of OTO-201 compared with sham was greater in children in the 6 months to 2 years group than in the >2 years group. In the pooled trials, in children 6 months to 2 years of age, treatment failure rates were 61/220 (28%) for OTO-201 and 61/106 (58%) for sham; in children >2 years of age, failure rates were 21/137 (15%) for OTO-201 and 18/69 (26%) for sham. In both treatment groups, children in the 6 months to 2 years group had greater failure rates than children >2 years of age.

Table 3 shows the components of treatment failure through the day 15 visit. Patients were considered treatment failures from the time of the first-occurring component, and they remained failures for that reason for the rest of the trial. The most common reasons for treatment failure overall were otorrhea, missed visits, and prescription of otic antibiotic drops before confirmation by the blinded assessor. Among sham recipients, the most common reasons for failure were otorrhea and prescription of otic antibiotic drops. Among OTO-201 recipients, the most common reasons for failure were missed visits and otorrhea. In each study, the proportions of missed visits and lost to follow-up were similar between treatment groups.

Table 3. Components of Treatment Failure through Day 15 (Intent to Treat Population)

Treatment failure	Study 201-201302		Study 201-201303		Pooled	
	OTO-201 N=179 n (%)	Sham N=87 n (%)	OTO-201 N=178 n (%)	Sham N=88 n (%)	OTO-201 N=357 n (%)	Sham N=175 n (%)
Overall	44 (25)	39 (45)	38 (21)	40 (45)	82 (23)	79 (45)
By component						
Otic antibiotic drops	10 (6)	15 (17)	9 (5)	7 (8)	19 (5)	22 (13)
Systemic antibiotics	3 (2)	4 (5)	6 (3)	3 (3)	9 (3)	7 (4)
Otorrhea	13 (7)	10 (11)	12 (7)	24 (27)	25 (7)	34 (19)
Lost to follow-up	1 (1)	0	1 (1)	0	2 (1)	0
Missed visit	17 (9)	10 (11)	10 (6)	6 (7)	27 (8)	16 (9)

Adapted from FDA clinical review, Table 6.1.5-3

Otonomy performed sensitivity analyses to evaluate the effects of various components of the treatment failure definition on the overall trial outcomes. For each trial, three analyses were performed excluding use of systemic antibiotics, lost to follow-up, and missed visits from the definition of treatment failure. In each case, a treatment difference similar to that observed in the primary analysis favoring OTO-201 remained.

Dr. Needles examined the missed visit treatment failures and found that most of them had the missed visit rescheduled, and the planned assessments were performed 1 to 2 days (range -1 to 6 days) outside the visit window. Only 1 patient in Study 201-201302 and 3 patients in Study 201-201303 lacked an assessment in this broader time frame. The conclusions from the primary efficacy analysis are unchanged if the patients who had assessments in the broader time frame were not considered treatment failures until the occurrence of another failure component.

The development of otorrhea is the most unequivocal manifestation of treatment failure in this indication. In Study 201-201302, otorrhea-only treatment failure observed by the blinded assessor was reported in 13/179 (7%) OTO-201 recipients and in 10/87 (11%) sham recipients; in Study 201-201303, otorrhea-only treatment failure was reported in 12/178 (7%) OTO-201 recipients and in 24/88 (27%) sham recipients. Only the latter difference is statistically significant. In Study 201-201302, through the day 15 visit, 15/87 (17%) sham recipients and 10/179 (6%) OTO-201 recipients were designated as treatment failures because of prescription of otic antibiotic drops before evaluation by the blinded assessor.

Patients who received otic or systemic antibiotics before confirmation of otorrhea by the blinded assessor may or may not have had otorrhea. Otonomy performed an analysis in which failures due to observed otorrhea were combined with failures due to presumed otorrhea, which was considered to be failure due to antibiotic treatment (otic or systemic) if the treatment was prescribed for otorrhea, defined as otorrhea, ear drainage, ear infection, effusion, otitis externa, or otitis media. This analysis did not include patients who may have had observed or presumed otorrhea after having failed because of another reason. Dr. Needles performed a similar analysis which attempted to identify patients who failed and had any occurrence of observed or presumed otorrhea (as defined above). Each analysis is consistent with the primary analysis favoring treatment with OTO-201.

The primary efficacy endpoint was the cumulative proportion of treatment failures through the day 15 visit. Significant differences in failure rates favoring OTO-201 were also observed at the day 4, day 8, and day 29 visits. The primary benefit of treatment occurred by the day 8 visit. In both trials, after day 8, treatment failure rates increased by approximately 10% for both groups by the day 15 visit and by another 10% by the day 29 visit.

Table 4 shows clinical failure rates through day 15 by baseline culture result in the pooled trials. Patients with positive baseline cultures in at least one ear were more likely to have treatment failure than patients with negative cultures in both ears regardless of treatment. Patients who received OTO-201 had lower failure rates than patients who received sham, whether cultures were positive or negative. The beneficial effect of OTO-201 for patients with positive baseline cultures was observed in those with *H. influenzae* or *S. pneumoniae*.

Table 4. Clinical Failure Rate through Day 15 by Baseline Culture Result (Pooled Trials)

<b>Baseline Culture</b>	<b>OTO-201 n/N (%)</b>	<b>Sham n/N (%)</b>
<b>Positive<sup>1</sup></b>	21/70 (30)	30/49 (61)
<i>Haemophilus influenzae</i>	8/39 (21)	16/27 (59)
<i>Streptococcus pneumoniae</i>	9/20 (45)	10/12 (83)
<i>Moraxella catarrhalis</i>	6/14 (43)	4/8 (50)
<i>Staphylococcus aureus</i>	2/6 (33)	2/4 (50)
<i>Pseudomonas aeruginosa</i>	1/1 (100)	0/2 (0)
<b>Negative<sup>2</sup></b>	46/232 (20)	40/98 (41)

<sup>1</sup> Positive: culture positive for a potential pathogen in at least one ear; a patient could have more than one isolate.

<sup>2</sup> Negative: culture negative in both ears; excludes cultures that grew nonpathogens.

Adapted from FDA clinical review, Table 6.1.10-1

If the negative culture category is expanded to include patients with cultures that grew nonpathogens at baseline, pooled treatment failure rates were 59/282 (21%) for patients receiving OTO-201 and 49/124 (40%) for patients receiving sham.

### Conclusion

Drs. Needles and Rashid concluded that these phase 3 trials demonstrated the efficacy of OTO-201 for the treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube placement. I concur with their conclusion.

## **8. Safety**

Mark Needles, M.D., reviewed the safety data for this submission. The trials summarized in the Clinical/Statistical – Efficacy section above included 40 patients who received single doses of OTO-201 to each ear in the phase 1b study and 357 patients who received single doses to each ear in the phase 3 trials.

There were no deaths and four serious adverse events reported. In the phase 1b study, one patient who received OTO-201 had chemical poisoning from ingesting a dishwashing detergent tablet. In the phase 3 trials, three patients in the OTO-201 group had serious adverse events: two with bronchiolitis and one with gastroenteritis. These events were not related to trial therapy. There were no dropouts or discontinuations from the studies due to adverse events.

In the phase 3 trials, adverse events that were reported at least 1.5 times more frequently in patients treated with OTO-201 than in sham recipients included teething, nasopharyngitis, irritability, and rhinorrhea.

Otoscopic examinations in the phase 3 studies showed similar rates of tympanostomy tube obstruction or extrusion by day 29 in the OTO-201 and sham groups. At day 29, at least one tube was obstructed in 18/354 (5%) OTO-201 recipients and 7/171 (4%) sham recipients; at least one tube had extruded in 3/354 (1%) OTO-201 recipients and 1/171 (1%) sham

recipients. Tympanometry assessments in both groups were similar, demonstrating type B patterns with large canal volume in most patients. Audiometry assessments were completed in approximately 95% of patients  $\geq 4$  years of age and approximately 50% of patients  $< 4$  years of age and showed that 85% of tested ears in the OTO-201 group and 82% of the tested ears in the sham group had normal hearing by day 29.

The 120-day safety update report summarized safety information from two additional studies that enrolled 72 patients. The adverse event profile from these studies is similar to that described above.

Dr. Needles concluded that the adverse events associated with OTO-201 were generally minor and self-limited and that there were no significant effects of the drug on otoscopic examinations, tympanometry, and audiometry. I concur with his conclusion.

## **9. Advisory Committee Meeting**

Not applicable.

## **10. Pediatrics**

The applicant requested a partial waiver of pediatric studies in children less than 6 months of age because studies are impossible or highly impracticable. Tympanostomy tube placement is rarely performed in this age group. The Division of Anti-Infective Products (DAIP) presented the partial waiver request and the pediatric assessment to the Pediatric Review Committee (PeRC) on November 18, 2015, and PeRC concurred with DAIP's plan to grant the partial waiver.

## **11. Other Relevant Regulatory Issues**

The Office of Scientific Investigations conducted inspections of 4 clinical investigator sites from the phase 3 trials and concluded that the data from the trials may be considered reliable. Otonomy stated there were no clinical investigators who had disclosable financial interests or arrangements.

## **12. Labeling**

The Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Surveillance and Epidemiology determined that the proprietary name, Otiprio, was acceptable. DMEPA and the Office of Prescription Drug Promotion provided recommendations that were incorporated into final labeling.

## **13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

I concur with the recommendation of the review team to approve ciprofloxacin otic suspension, 6%, for the treatment of pediatric patients with otitis media with middle ear effusion undergoing tympanostomy tube placement.

- Risk Benefit Assessment

Two identical, randomized, double-blind (patient and evaluator), sham-controlled, phase 3 trials were conducted in which 532 pediatric patients with bilateral otitis media with middle ear effusion undergoing tympanostomy tube placement were randomized 2:1 to receive either a single intratympanic dose of OTO-201 or a sham dose at the time of surgery. The primary endpoint was treatment failure through day 15 post-administration of study drug. In each trial, there were significantly fewer treatment failures in patients who received OTO-201 compared with those receiving sham; the observed differences in treatment failure rate were 20% and 24%. Various sensitivity analyses support the primary analysis. The adverse events associated with OTO-201 were generally minor and self-limited, and there were no significant effects of the drug on otoscopic examinations, tympanometry, and audiometry.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Routine postmarketing safety monitoring is sufficient.

- Recommendation for other Postmarketing Requirements and Commitments

There are no recommended postmarketing requirements or commitments.

- Recommended Comments to Applicant

There are no recommended comments to the applicant.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS D SMITH  
12/10/2015