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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206307
Supplement #:	000
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Indication(s):	Treatment of Acute Otitis Externa (AOE)
Applicant:	Alcon
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Keywords: fluoroquinolone, acute otitis externa (AOE), superiority

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1 EXECUTIVE SUMMARY

The applicant (Alcon) seeks approval of Finafloxacin Otic Suspension, 0.3% (also known as Finafloxacin throughout this review) for the treatment of acute otitis externa (AOE) in pediatric (age (b) (4) and older), adult, and elderly patients. Finafloxacin is a new molecular entity (NME), a fourth generation fluoroquinolone. In order to support the approval of Finafloxacin otic suspension for AOE, the applicant submitted two pivotal studies: Study C-10-018, and Study C-10-019.

Studies C-10-018 and C-10-019 were two identically designed phase 3 studies. Both were multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies to evaluate the safety and efficacy of Finafloxacin otic suspension, 0.3% versus Vehicle in the treatment of AOE. For both studies, patients aged 6 months and older, with a clinical diagnosis of AOE were enrolled. The primary efficacy endpoint was the percentage of patients with clinical cures at the test-of-cure (TOC) visit (Day 11 + 2); a subject was considered as clinical cure if the subject's sum score of ear tenderness, erythema, and edema was zero (i.e., none). There were two secondary efficacy endpoints for both studies: the percentage of patients with microbiological success at the TOC visit defined as all pre-therapy bacteria being absent in the exit specimen; and time to cessation of ear pain, defined as the first time point that ear pain was absent (morning or evening) and did not return for any/all subsequent diary entries. Cessation of ear pain was reported by the patient or parent/legal guardian via a telephone diary at 1/2 day interval.

The protocol-defined primary analysis set for the evaluation of the primary, secondary efficacy endpoints was the pathogen positive subset of intent-to-treat (ITT) population (referred as ITT pathogen positive subset throughout this review), which included all subjects who received study treatment and had a microbiological specimen in the study ear that contained at least one of the following two organisms (considered by the applicant as etiological agents of AOE) at baseline: *Pseudomonas aeruginosa* and/or *Staphylococcus aureus*. Meanwhile the clinical review team were also interested in study results based on the culture positive subset of ITT population (referred as ITT culture positive subset throughout this review), which included all subjects who received study treatment and were culture positive (not limited to the above two organisms) in the study ear at baseline.

A total of 686 subjects were randomized and treated at 67 centers across U.S., Canada, and Puerto Rico in Study C-10-018; 613 (89.4%) were included in the ITT culture positive subset; 283 (41.2%) were included in the ITT pathogen positive subset. In Study C-10-019, 548 subjects were randomized and treated at 46 centers across U.S., Canada, and Puerto Rico; 480 (87.6%) were included in the ITT culture positive subset; 277 (50.5%) were included in the ITT pathogen positive subset.

Clinical Cure at TOC Visit – Primary Efficacy Endpoint

In Study C-10-018, at the TOC visit, for the ITT pathogen positive subset, 71.7% (104/145) of the patients in the Finafloxacin group had a clinical cure compared with 33.3% (46/138) of the patients in the Vehicle group; the treatment difference (38.4%) was statistically significant

($p<0.001$) with a 95% CI of (27.6%, 49.1%). For the ITT culture positive subset, more patients in the Finafloxacin group had clinical cure compared to the Vehicle group (72.7% [226/311], 51.0% [154/302] respectively); the treatment difference was 21.7% with a 95% confidence interval (CI) of (14.2%, 29.2%).

In Study C-10-019, at the TOC visit, for the ITT pathogen positive subset, 68.7% (101/147) of the patients in the Finafloxacin group had a clinical cure compared with 40.0% (52/130) of the patients in the Vehicle group; the treatment difference (28.7%) was statistically significant ($p<0.001$) with a 95% CI of (17.4%, 40.0%). For the ITT culture positive subset, more patients in the Finafloxacin group had clinical cure compared to the Vehicle group (71.1% [170/239], 46.5% [112/241] respectively); the treatment difference was 24.7% with a 95% CI of (16.1%, 33.2%).

Microbiological Success at TOC Visit – Secondary Efficacy Endpoint #1

In Study C-10-018, at the TOC visit, for the ITT pathogen positive subset, 66.9% (97/145) of the patients in the Finafloxacin group had microbiological success compared with 13.0% (18/138) of the patients in the Vehicle group; the treatment difference (53.9%) was statistically significant ($p<0.001$) with a 95% CI of (44.4%, 63.4%). While for the ITT culture positive subset, more patients in the Finafloxacin group had microbiological success compared to the Vehicle group (60.8% [189/311], 16.6% [50/302] respectively); the treatment difference was 44.2% with a 95% CI of (37.4%, 51.1%).

In Study C-10-019, at the TOC visit, for the ITT pathogen positive subset, 66.0% (97/147) of the patients in the Finafloxacin group had microbiological success compared with 11.5% (15/130) of the patients in the Vehicle group; the treatment difference (54.4%) was statistically significant ($p<0.001$) with a 95% CI of (45.0%, 63.9%). While for the ITT culture positive subset, more patients in the Finafloxacin group had microbiological success compared to the Vehicle group (64.9% [155/239], 17.0% [41/241] respectively); the treatment difference was 47.8% with a 95% CI of (40.2%, 55.5%).

Time to cessation of ear pain – Secondary Efficacy Endpoint #2

In Study C-10-018, for the ITT pathogen positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 4.0 days and 7.0 days respectively; the treatment difference was -3.0 ($p<0.0001$) with a 95% CI of (-5.0, -0.8). For the ITT culture positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 4.0 days and 5.0 days respectively; the treatment difference was -1.0 with a 95% CI of (-2.0, 0.0).

In Study C-10-019, for the ITT pathogen positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 3.0 days and 6.5 days respectively; the treatment difference was -3.6 ($p<0.001$) with a 95% CI of (-5.0, -2.0). For the ITT culture positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 3.0 days and 5.5 days respectively; the treatment difference was -2.3 with a 95% CI of (-3.0, -1.0).

In conclusion, Finafloxacin otic suspension 0.3% demonstrated superiority to Vehicle in terms of:

- The percentage of patients who achieved a clinical cure at the TOC visit;
- The percentage of patients who achieved microbiological success at the TOC visit;
- And the median time to cessation of ear pain as reported by patients (or parents/guardians) in half (1/2) day increments.

Therefore, the statistical reviewer recommends the approval of Finafloxcin otic suspension 0.3% for the treatment of AOE.

Table 1: Summary of the Primary and Secondary Efficacy Results (ITT pathogen positive subset and ITT culture positive subset)

	Study C-10-018			Study C-10-019		
Clinical Cure at TOC						
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**
Pathogen + Subset	104/145 (71.7%)	46/138 (33.3%)	38.4% (27.6%, 49.1%)	101/147 (68.7%)	52/130 (40.0%)	28.7% (17.4%, 40.0%)
Culture + Subset	226/311 (72.7%)	154/302 (51.0%)	21.7% (14.2%, 29.2%)	170/239 (71.1%)	112/241 (46.5%)	24.7% (16.1%, 33.2%)
Microbiological Success at TOC						
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**
Pathogen + Subset	97/145 (66.9%)	18/138 (13.0%)	53.9% (44.4%, 63.4%)	97/147 (66.0%)	15/130 (11.5%)	54.4% (45.0%, 63.9%)
Culture + Subset	189/311 (60.8%)	50/302 (16.6%)	44.2% (37.4%, 51.1%)	155/239 (64.9%)	41/241 (17.0%)	47.8% (40.2%, 55.5%)
Median Time (day) to Cessation of Ear Pain						
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[b]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[b]**
Pathogen + Subset	4.0	7.0	-3.0 (-5.0, -0.8)	3.0	6.5	-3.6 (-5.0, -2.0)
Culture + Subset	4.0	5.0	-1.0 (-2.0, 0.0)	3.0	5.5	-2.3 (-3.0, -1.0)

[a] 95% CI calculated based on normal approximation to binomial data.
[b] Difference and 95% confidence interval estimated using bootstrap procedure with 10,000 bootstrap samples, non-stratified analysis.
Source: Tables 11.4.1.3-2, 11.4.1.2-1, 14.2-24, 14.2-93, and 14.2-94 of Study C-10-018 report; and Tables 11.4.1.3-2, 11.4.1.2-1, 14.2-24, 14.2-89, and 14.2-90 of Study C-10-019 report.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Finafloxacin hydrochloride is a novel fluoroquinolone with antibacterial activity against both Gram-positive and Gram-negative organisms at lower pH (5.8) than normal (7.2); the lower pH is consistent with the more acidic environment of infected tissues. The applicant (Alcon Research, Ltd) studied Finafloxacin for the topical treatment of bacterial otitis in both adults and children while finafloxacin is also being studied for other indications which may require systemic exposure.

Acute otitis externa (AOE) is a common condition involving inflammation of the external ear canal. AOE is caused primarily by bacterial infection. Clinically, AOE is characterized by ear pain, swelling of the external auditory canal, and severe tenderness, with or without hearing loss. Left untreated, AOE may evolve into a more serious condition such as malignant (or necrotizing) external otitis, or result in the development of a focal furuncle, or a low-grade infection and inflammation that may require systemic antibiotic treatment. Topical antimicrobials or antibiotics such as acetic acid, aminoglycosides, polymyxin B, and quinolones are the treatment of choice in uncomplicated cases of AOE.

2.1.2 History of Drug Development

Finafloxacin is first developed by MerLion Pharmaceuticals. In 2011, finafloxacin hydrochloride was licensed to the applicant (Alcon) by MerLion Pharmaceuticals in North America for the treatment of ear infections. MerLion Pharmaceuticals is developing finafloxacin for other indications.

The agency accepted the applicant's proposed analyses for the primary and secondary efficacy endpoints for both studies C-10-018 and C-10-019 when their study protocols were submitted for review under IND110576. A Special Protocol Assessment Agreement letter (dated January 13, 2012) was issued to the applicant regarding these two identically-designed studies.

2.1.3 Studies Reviewed

Finafloxacin otic suspension clinical development plan included four clinical studies: two Phase 1 studies (Study C-10-007 and C-10-022), and two pivotal Phase 3 safety and efficacy studies (Studies C-10-018 and C-10-019).

Study C-10-007 was a single-center, multiple dose, randomized, vehicle controlled, fixed sequence phase 1 study to assess the systemic pharmacokinetics of Finafloxacin Otic

Suspension, 0.3% in healthy adult subjects. This study will not be included in the statistical review for this NDA.

Study C-10-022 was a multicenter, open-label, single dose pharmacokinetic, parallel-group study to evaluate systemic pharmacokinetics of Finafloxacin in patients with acute otitis external after a single ototopical administration of Finafloxacin Otic Suspension, 0.3%. This study will not be included in the statistical review for this NDA either.

This statistical review focused on the two pivotal Phase 3 safety and efficacy studies: Studies C-10-018 and C-10-019. Key information of these two studies is presented in the following table.

Table 2: Key Information for Studies C-10-018 and C-10-019

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
C-10-018	*Phase 3 randomized, double-masked, vehicle-controlled study*	*Four drops, twice daily for seven days*	*four days follow-up after the 7-day treatment period*	*Finafloxacin: 347 Vehicle: 346*	*Patients 6 months of age or older with a clinical diagnosis of AOE of less than 4 weeks duration*
C-10-019	*Phase 3 randomized, double-masked, vehicle-controlled study*	*Four drops, twice daily for seven days*	*four days follow-up after the 7-day treatment period*	*Finafloxacin: 274 Vehicle: 275*	*Patients 6 months of age or older with a clinical diagnosis of AOE of less than 4 weeks duration*

Source: Table 2.7.3.1-1 of Summary of Clinical Efficacy.

2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies C-10-018, and C-10-019. The study reports are available at: \\Cdsesub1\evsprod\NDA206307\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-otitis-externa\5351-stud-rep-contr.

The applicant submitted SAS datasets electronically; the datasets for Study C-10-018 are available at: \\Cdsesub1\evsprod\NDA206307\0000\m5\datasets\tdoc0016450; and for Study C-10-019 are available at: \\Cdsesub1\evsprod\NDA206307\0000\m5\datasets\tdoc0016451.

The SAS program codes that were used to generate the results in the study reports are available at: \\Cdsesub1\evsprod\NDA206307\0000\m5\datasets\tdoc0016450\analysis\legacy\programs and \\Cdsesub1\evsprod\NDA206307\0000\m5\datasets\tdoc0016451\analysis\legacy\programs for Study C-10-018 and Study C-10-019 respectively.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were in good quality with definition of each variable. Results of the primary and key secondary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The final statistical analysis plans (SAPs) for the two pivotal studies were submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies C-10-018 and C-10-019 were two identically designed phase 3 pivotal studies. Both studies were multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies to evaluate the safety and efficacy of Finafloxacin Otic Suspension, 0.3% in the treatment of AOE. The objective of these studies was to demonstrate the superiority of Finafloxacin to Vehicle based on clinical cures at TOC visit for the treatment of AOE.

For both studies, patients aged 6 months and older, with a clinical diagnosis of AOE were enrolled. Specifically, the protocol-defined key inclusion criteria were:

- At least 6 months of age
- Had a clinical diagnosis of AOE based on clinical observation and of presumed bacterial origin in at least 1 ear
- Had a combined numerical score of 4 or greater in at least 1 affected ear at the Day 1 examination for tenderness, erythema, and edema
    - For a patient with a bilateral infection, only 1 ear must have met this criterion (e.g., the patient could have been enrolled with a numerical score of 4 in 1 ear and a numerical score of 1 in the other ear; both ears were assessed, cultured, and treated with study medication; and the ear with numerical score of 4 was designated as the study ear)

Patients could not be enrolled if one of the two infected ears required some other form of treatment (other than the study drug). Specifically, the protocol-defined key exclusion criteria were:

- Duration of signs or symptoms of AOE greater than 28 days in the affected ear(s) as reported by patient or parent/legal guardian
- Presence of a tympanostomy tube or perforated tympanic membrane in the affected ear(s); patients with a history of tympanic membrane perforation were not enrolled unless the absence of a current perforation could be confirmed at Visit 1 prior to enrollment
- Clinically diagnosed otic disease other than AOE (e.g., malignant otitis externa) in the affected ear(s)
- Known or suspected ear infection of yeast, fungal, or mycobacterial origin in the affected ear(s)

Enrolled patients were randomized at 1:1 ratio to receive Finafloxacin Otic Suspension, 0.3% or Vehicle administered 4 drops in the affected ear(s) twice daily for 7 days. The randomization was stratified by baseline otowick use. Patients were evaluated for safety and efficacy at Day 1 (Baseline), Day 3 + 2 days (on-therapy), Day 8 + 2 days (end-of-therapy), and Day 11 + 2 days (TOC). Patients also completed a telephone diary twice daily in which they recorded assessments of ear pain, pain medication use, and impact of ear pain on their sleep and other daily activities. Patients were required to continue study treatment for seven days even if his/her signs/symptoms had resolved early.

Table 3: Schedule of Assessment

	Visit 1 Screening/ Baseline	Visit 2 On-Therapy	Visit 3 EOT	Visit 4 TOC/Early Exit
Procedure/ Assessment	Day 1	Day 3 + 2 days	Day 8 + 2 days	Day 11 + 2 days
Patient screening	X			
Informed consent	X			
Demographics	X			
Medical history	X			
Concomitant medications	X	X	X	X
Inclusion/Exclusion	X			
Urine pregnancy test [a]	X			X
Clinical assessment	X	X	X	X
Ear cleansing [b]	X	X	X	X
Ear culture	X			X
Otowick insertion [c]	X	X		
Register in IVRS/IWRS	X			
Patient daily diary [d]	X	X	X	X
Dispense study medication/ acetaminophen	X	X[b]		
Demonstrate dosing technique	X	X[b]		
First dose in office	X			
Study coordinator phone call to patient [e]	X	X		
Treatment Satisfaction Questionnaire [f]			X	X[g]
Adverse events [h]	X	X	X	X
Collect study medication			X	X[i]
Exit from IVRS/IWRS				X

EOT = end-of-therapy; IVRS/IWRS = Interactive Voice/Web Response System; TOC = test-of-cure

[a] Performed for women of childbearing potential, before randomization and at exit.

[b] As needed.

[c] Investigators inserted an otowick if the ear canal was compromised by 50% or greater (ie, moderate or severe edema).

[d] Diaries were completed by the patient or parent/legal guardian twice daily throughout the entire study in an electronic diary.

[e] The study coordinator contacted the patient by telephone on Days 2 through 7 (except on the day of Visit 2) to ensure dosing and diary compliance and to evaluate patient progress.

[f] Treatment Satisfaction Questionnaire was completed only by patients > 8 years of age.

[g] Completed only if patient exited prior to Visit 3 (or missed Visit 3).

[h] Monitored for adverse events as described in the study protocol.

[i] Only if the study drug was not collected at Visit 3.

Source: Table 9.1-1 of studies C-10-18 and C-10-19 reports.

For both studies, the applicant defined primary endpoint was:

- Clinical cures in the study ear at TOC visit (Day 11 + 2), defined as the sum of the numerical scores of the 3 clinical signs of AOE (tenderness, erythema, and edema) being equal to '0'. The clinical signs were assessed at each visit by the Investigator using an otoscope.

For both studies, there were two secondary efficacy endpoints which were microbiological success at the TOC visit defined as all pre-therapy bacteria being absent in the ear culture collected, and time to cessation of ear pain, defined as the first time point that ear pain was absent (morning or evening) and did not return for any/all subsequent diary entries. Time to cessation of ear pain was collected via a twice daily telephone diary, and was assessed in half (1/2) day increments.

The sample size estimation of 500 subjects (250 per arm) for both studies was based on the following assumptions proposed by the applicant to support the primary efficacy endpoint:

- Fisher's exact test at the 0.05 two-sided level of significance
- Clinical cure rate of 74% for the finafloxacin treatment group
- A treatment difference of 20% between the finafloxacin group and the vehicle group
- 90% power
- 56% of enrolled subjects who had a positive pathogen at baseline (i.e., a study ear specimen tested positive for two types of pathogen: *Pseudomonas aeruginosa* and/or *Staphylococcus aureus*)

According to the applicant, the above clinical cures rate for the finafloxacin treatment group and pathogen positive rate at baseline were estimated based on previous data.

3.2.2 Statistical Methodologies

Both studies C-10-018 and 019 intended to demonstrate the superiority of finafloxacin to vehicle based on clinical cures in the study ear at TOC visit for the treatment of AOE. The primary efficacy endpoint was clinical cures in the study ear at TOC visit (Day 11 + 2), which was defined as the sum of the numerical scores of the 3 clinical signs of AOE (tenderness, erythema, and edema) being equal to '0'. The clinical signs were assessed at each study visit by the Investigator using an otoscope.

The following table presents the study ear definition; it was noted that one subject could have both ears enrolled but for every enrolled subject only one ear was designated as the study ear based on the criteria listed in this table.

Table 4: Designation of Study Ear

Hierarchical Order for Defining Study Ear	Enrolled Ear(s)	Culture Positive[a] Ear(s)	Pathogen Positive[b] Ear(s)	Study Ear Definition
1	Both[c]	Both	Both	The evaluable ear with the higher value for the sum of the numerical scores of tenderness, erythema and edema at baseline. If both ears were rated equally, the right ear was defined as the study ear.
2	Both[c]	Both	One	The pathogen positive ear
3	Both[c]	One	One	The pathogen positive ear
4	Both[c]	Both	Neither	The evaluable ear with the higher value for the sum of the numerical scores of tenderness, erythema and edema at baseline. If both ears were rated equally, the right ear was defined as the study ear.
5	Both[c]	One	Neither	The culture positive ear
6	Both[c]	Neither	Neither	The evaluable ear with the higher value for the sum of the numerical scores of tenderness, erythema and edema at baseline. If both ears were rated equally, the right ear was defined as the study ear.
7	One	One	One	The enrolled ear
8	One	One	Neither	The enrolled ear
9	One	Neither	Neither	The enrolled ear

Source: Table 9.7.1.1-1 of Study C-10-018 report.

For both studies, there were seven different analysis populations (also known as analysis sets) defined by the applicant:

- **Intent-to-Treat (ITT) analysis set**, which included all patients who received study treatment.
- **Culture positive subset of ITT**, which included all ITT subjects who were culture positive in the study ear at baseline (also referred to as ITT culture positive subset).
- **Pathogen positive subset of ITT**, which included all ITT subjects who had a microbiological specimen that contained at least 1 of the following organisms (considered etiological agents of AOE) at baseline: *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* (also referred to as ITT pathogen positive subset).
- **Per Protocol (PP) analysis set**, which included all subjects who met the inclusion/exclusion criteria, were randomized, received study drug, and had baseline and TOC/exit data or early exit data.
- **Culture positive subset of PP**, which included all PP subjects who were culture positive in the study ear at baseline.
- **Pathogen positive subset of PP**, which included all PP subjects who had a microbiological specimen that contained at least 1 of the following organisms (considered etiological agents of AOE) at baseline: *Pseudomonas aeruginosa* and/or *Staphylococcus aureus*.
- **Safety analysis set**, which included all patients who received exposure to the study drug or potential exposure to the study drug (ie, either returned an opened bottle of study drug or failed to return study drug).

The applicant-defined primary analysis set for the evaluation of the primary, secondary, and supportive efficacy endpoint was the **pathogen positive subset of ITT (aka ITT pathogen positive subset)**. In addition, sensitivity analyses based on the ITT analysis set, the culture

positive subset of ITT **(aka ITT culture positive subset)**, the PP analysis set, the culture positive subset of PP, and the pathogen positive subset of PP were also conducted by the applicant. This statistical review presented the primary and secondary analyses results based on the three ITT-related analysis sets: ITT culture positive subset, ITT pathogen positive subset, and ITT whenever data was available.

For the primary efficacy endpoint of clinical cure at TOC, the number and percent of patients who achieved a clinical cure at TOC were summarized overall and by treatment groups. The treatment groups were compared using a stratified Cochran-Mantel-Haenszel (CMH) test adjusted for the baseline otowick use (the stratification variable).

The secondary endpoint of microbiological success (absence of all pre-therapy bacteria from the exit otic specimen collected) at the TOC visit was analyzed the same way as the primary efficacy endpoint.

The other secondary endpoint of time to cessation of ear pain was reported by the patient or parent/legal guardian via the telephone diary at 1/2 day interval. For all patients who complete the study but their ear pain never ceased, their time to cessation of ear pain was considered right censored at the last diary time point at which they reported having ear pain, regardless of whether they completed all diary entries. For all patients who do not complete the study and their ear pain never ceased, their time to cessation of ear pain was considered right censored at Day 11. For the time to cessation of ear pain, Kaplan-Meier survival curves were generated. A log-rank analysis was conducted to compare the survival distributions of the two treatment groups.

For the primary efficacy analysis, missing data were imputed as "failures" for patients who did not complete the study or who had missing scores for 1 or more of the components of clinical cure (i.e., missing scores for tenderness, erythema, and/or edema). Sensitivity analysis using last observation carried forward (LOCF) to impute missing data was performed. In addition, sensitivity analyses were also conducted by the applicant based on observed data only, based on three different PP analysis sets (pathogen positive subset of PP, culture positive subset of PP, and PP), and each component of the clinical cure (i.e. tenderness, erythema, and edema)

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study C-10-018

Six hundred and ninety-three patients were randomized into the study, including 347 in the Finafloxacin group and 346 in the Vehicle group. Among these 693 subjects, six patients were randomized in error and did not receive study drug; one patient that exited at Visit 2 but did not dose with study medication. Of the enrolled patients, 547 (78.9%) completed the study. Among the 140 patients who discontinued early, more patients in the Vehicle group discontinued the study early compared to patients in the Finafloxacin group (27.7% [96/346] versus 14.4% [50/347], respectively); the most commonly reported reason for discontinuation was treatment failure (Finafloxacin: 33 [9.5%]; Vehicle: 66 [19.1%]), followed by adverse events (AE) (Finafloxacin: 6 [1.7%]; Vehicle: 15 [4.3%]).

Table 5: Study C-10-018 Subjects' Disposition

	Finafloxacin (N=347) n %	Vehicle (N=346) n %	Total (N=693) n (%)
Number of Subjects Randomized	347 (100.0%)	346 (100.0%)	693 (100.0%)
Number of Subjects Completed Study	297 (85.6%)	250 (72.3%)	547 (78.9%)
Number of Subjects Discontinued Study	48 (13.8%)	92 (26.6%)	140 (20.2%)
Adverse Event	6 (1.7%)	15 (4.3%)	21 (3.0%)
Lost to Follow-up	3 (0.9%)	4 (1.2%)	7 (1.0%)
Subject Decision Unrelated to an AE	4 (1.2%)	3 (0.9%)	7 (1.0%)
Treatment Failure	33 (9.5%)	66 (19.1%)	99 (14.3%)
Baseline Culture Positive for Group A Strep	0 (0.0%)	1 (0.3%)	1 (0.1%)
Baseline Culture Positive for Yeast / Fungi	0 (0.0%)	1 (0.3%)	1 (0.1%)
Other[a]	2 (0.6%)	2 (0.6%)	4 (0.6%)
Randomized in Error[a]	2 (0.6%)	4 (1.2%)	6 (0.9%)

[a] Six patients were randomized in error and did not receive study drug; and one exited at Visit 2 but did not dose with any study medication.
Source: Tables 10.1-1 and 10.1-2 of Study C-10-018 report.

Thus, of the 693 enrolled patients, 686 patients who received at least one dose of study treatment were included in the safety analysis dataset; all these 686 patients were also included in the ITT analysis dataset. Among the ITT patients, 613 (89.4%) were culture positive and were included in the culture positive subset of the ITT analysis set; 283 (41.2%) were pathogen positive at baseline and were included in the primary efficacy analysis dataset (i.e., the pathogen positive subset of the ITT analysis dataset).

Table 6: Study C-10-018 Analysis Population

	Finafloxacin (N=347) n %	Vehicle (N=346) n %	Total (N=693) n (%)
Safety Population	344	342	686
Intent-to-Treat	344 (100%)	342 (100%)	686 (100%)
ITT culture positive subset	311 (90.4%)	302 (88.3%)	613 (89.4%)
ITT pathogen positive subset	145 (42.2%)	138 (40.4%)	283 (41.2%)

Source: Figure 10.1-1 of Study C-10-018 Report.

As presented in the following tables (for ITT, ITT culture positive subset, and ITT pathogen positive subset), there were no noted differences in demographic and baseline characteristics between the treatment groups for all the three populations.

Table 7: Study C-10-018 Demographic and Baseline Characteristics (ITT)

Characteristics	Finafloxacin (N=344)	Vehicle (N=342)	Total (N=686)
	n (%)	n (%)	n (%)
Gender			
Male	142 (41.3)	159 (46.5)	301 (43.9)
Female	202 (58.7)	183 (53.5)	385 (56.1)

Characteristics	Finafloxacin (N=344)	Vehicle (N=342)	Total (N=686)
	n (%)	n (%)	n (%)
Age			
Mean (Std)	31.3 (20.2)	31.9 (21.7)	31.6 (21.0)
Min, Max	0.8, 85.0	0.9, 84.0	0.8, 85.0
6 to 23 Months	3 (0.9)	2 (0.6)	5 (0.7)
2 to 11 Years	61 (17.7)	83 (24.3)	144 (21.0)
12 to 17 Years	64 (18.6)	42 (12.3)	106 (15.5)
18 to 64 Years	195 (56.7)	186 (54.4)	381 (55.5)
≥ 65 Years	21 (6.1)	29 (8.5)	50 (7.3)
Race			
White/Caucasian	298 (86.6)	283 (82.7)	581 (84.7)
Black/African American	18 (5.2)	20 (5.8)	38 (5.5)
Asian	3 (0.9)	13 (3.8)	16 (2.3)
American Indian	4 (1.2)	1 (0.3)	5 (0.7)
Other	5 (1.5)	6 (1.8)	11 (1.6)
Multi-Racial	16 (4.7)	19 (5.6)	35 (5.1)
Ethnicity			
Hispanic, Latino, or Spanish	119 (34.6)	118 (34.5)	237 (34.5)
Not Hispanic, Latino, or Spanish	225 (65.4)	224 (65.5)	449 (65.5)
Baseline Otowick Use Status			
No	248 (72.1)	250 (73.1)	498 (72.6)
Yes	96 (27.9)	92 (26.9)	188 (27.4)
Duration of Current Episode			
Up to 7 Days	260 (75.6)	259 (75.7)	519 (75.7)
8 to 14 Days	59 (17.2)	56 (16.4)	115 (16.8)
15 to 21 Days	17 (4.9)	23 (6.7)	40 (5.8)
22 to 28 Days	8 (2.3)	4 (1.2)	12 (1.7)

Source: Tables 14.1.1-4 and 14.1.2-7 of Study C-10-018 report.

Table 8: Study C-10-018 Demographic and Baseline Characteristics (ITT culture positive subset)

Characteristics	Finafloxacin (N=311)	Vehicle (N=302)	Total (N=613)
	n (%)	n (%)	n (%)
Gender			
Male	135 (43.4)	139 (46.0)	274 (44.7)
Female	176 (56.6)	163 (54.0)	339 (55.3)
Age			
Median			
Min, Max	0.8, 85.0	0.9, 84.0	0.8, 85.0
6 to 23 Months	3 (1.0)	2 (0.7)	5 (0.8)
2 to 11 Years	55 (17.7)	70 (23.2)	125 (20.4)
12 to 17 Years	57 (18.3)	40 (13.2)	97 (15.8)
18 to 64 Years	177 (56.9)	165 (54.6)	342 (55.8)
≥ 65 Years	19 (6.1)	25 (8.3)	44 (7.2)

Characteristics	Finafloxacin (N=311)	Vehicle (N=302)	Total (N=613)
	n (%)	n (%)	n (%)
Race			
White/Caucasian	270 (86.8)	249 (82.5)	519 (84.7)
Black/African American	17 (5.5)	17 (5.6)	34 (5.5)
Asian	2 (0.6)	10 (3.3)	12 (2.0)
American Indian	4 (1.3)	1 (0.3)	5 (0.8)
Other	4 (1.3)	6 (2.0)	10 (1.6)
Multi-Racial	14 (4.5)	19 (6.3)	33 (5.4)
Ethnicity			
Hispanic, Latino, or Spanish	106 (34.1)	105 (34.8)	211 (34.4)
Not Hispanic, Latino, or Spanish	205 (65.9)	197 (65.2)	402 (65.6)
Baseline Otowick Use Status			
No	223 (71.7)	215 (71.2)	438 (71.5)
Yes	88 (28.3)	87 (28.8)	175 (28.5)
Duration of Current Episode			
Up to 7 Days	234 (75.2)	228 (75.5)	462 (75.4)
8 to 14 Days	55 (17.7)	50 (16.6)	105 (17.1)
15 to 21 Days	16 (5.1)	20 (6.6)	36 (5.9)
22 to 28 Days	6 (1.9)	4 (1.3)	10 (1.6)

Source: Tables 14.1.1-7 and 14.1.2-16 of Study C-10-018 report.

Table 9: Study C-10-018 Demographic and Baseline Characteristics (ITT pathogen positive subset)

Characteristics	Finafloxacin (N=145)	Vehicle (N=138)	Total (N=283)
	n (%)	n (%)	n (%)
Gender			
Male	63 (43.4)	63 (45.7)	126 (44.5)
Female	82 (56.6)	75 (54.3)	157 (55.5)
Age			
Mean (Std)	28.6 (19.3)	30.3 (21.7)	29.4 (20.4)
Min, Max	3.0, 84.0	4.0, 84.0	3.0, 80.0
6 to 23 Months[a]	0 (0.0)	0 (0.0)	0 (0.0)
2 to 11 Years	30 (20.7)	41 (29.7)	71 (25.1)
12 to 17 Years	32 (22.1)	18 (13.0)	50 (17.7)
18 to 64 Years	77 (53.1)	70 (50.7)	147 (51.9)
≥ 65 Years	6 (4.1)	9 (6.5)	15 (5.3)
Race			
White/Caucasian	131 (90.3)	120 (87.0)	251 (88.7)
Black/African American	7 (4.8)	5 (3.6)	12 (4.2)
Asian	0 (0.0)	1 (0.7)	1 (0.4)
American Indian	2 (1.4)	0 (0.0)	2 (0.7)
Other	3 (2.1)	4 (2.9)	7 (2.5)
Multi-Racial	2 (1.4)	8 (5.8)	10 (3.5)

Characteristics	Finafloxacin (N=145)	Vehicle (N=138)	Total (N=283)
	n (%)	n (%)	n (%)
Ethnicity			
Hispanic, Latino, or Spanish	47 (32.4)	44 (31.9)	91 (32.2)
Not Hispanic, Latino, or Spanish	98 (67.6)	94 (68.1)	192 (67.8)
Baseline Otowick Use Status			
No	99 (68.3)	84 (60.9)	183 (64.7)
Yes	46 (31.7)	54 (39.1)	100 (35.3)
Duration of Current Episode			
Up to 7 Days	113 (77.9)	113 (81.9)	226 (79.9)
8 to 14 Days	27 (18.6)	17 (12.3)	44 (15.5)
15 to 21 Days	4 (2.8)	5 (3.6)	9 (3.2)
22 to 28 Days	1 (0.7)	3 (2.2)	4 (1.4)

[a] The youngest patient evaluable for Finafloxacin Otic Suspension 0.3% was 4 years old and for Vehicle was 3 years old.
Source: Tables 11.2.1-1 and 11.2.2-3 of Study C-10-018 report.

3.2.3.2 Study C-10-019

Five hundred and forty-nine patients were randomized into the study, including 274 in the Finafloxacin group and 275 in the Vehicle group. Among these patients, one patient was randomized in error and did not receive study drug. Of the remaining 548 enrolled patients, 416 (75.8%) completed the study. Among the 132 (24.0%) patients who discontinued early, more patients in the Vehicle group discontinued the study early compared to patients in the Finafloxacin group (34.9% [96/275] versus 13.5% [37/274], respectively); the most commonly reported reason for discontinuation was treatment failure (Finafloxacin: 21 [7.7%]; Vehicle: 83 [30.2%]), followed by AE (Finafloxacin: 12 [4.4%]; Vehicle: 7 [2.5%]).

Table 10: Study C-10-019 Subjects' Disposition

	Finafloxacin (N=274) n %	Vehicle (N=275) n %	Total (N=549) n (%)
Number of Subjects Randomized	274 (100.0%)	275 (100.0%)	549 (100.0%)
Number of Subjects Completed Study	237 (86.5%)	179 (65.1%)	416 (75.8%)
Number of Subjects Discontinued Study	37 (13.5%)	95 (34.5%)	132 (24.0%)
Adverse Event	12 (4.4%)	7 (2.5%)	19 (3.5%)
Lost to Follow-up	1 (0.4%)	3 (1.1%)	4 (0.7%)
Subject Decision Unrelated to an AE	3 (1.1%)	1 (0.4%)	4 (0.7%)
Treatment Failure	21 (7.7%)	83 (30.2%)	104 (18.9%)
Other	0 (0.0%)	1 (0.4%)	1 (0.2%)
Randomized in Error[a]	0 (0.0%)	1 (0.4%)	1 (0.2%)

[a] One patient was randomized in error and did not receive study drug.
Source: Tables 10.1-1 and 10.1-2 of Study C-10-019 report.

Thus, of the 549 enrolled patients, 548 who received at least one dose of study treatment were included in the safety analysis dataset; and all these 548 patients were also included in the ITT analysis dataset. Among the ITT patients, 480 (87.6%) were culture positive and were included in the culture positive subset of the ITT analysis set; 277 (50.5%) were pathogen positive at Baseline and were included in the primary efficacy analysis dataset (i.e., the pathogen positive subset of the ITT analysis dataset).

Table 11: Study C-10-019 Analysis Population

	Finafloxacin (N=274) n %	**Vehicle (N=275) n %**	**Total (N=549) n (%)**
Safety Population	274	274	548
Intent-to-Treat	274 (100%)	274 (100%)	548 (100%)
ITT culture positive subset	239 (87.2%)	241 (88.0%)	480 (87.6%)
ITT pathogen positive subset	147 (53.6%)	130 (47.4%)	277 (50.5%)

Source: Figure 10.1-1 of Study C-10-019 Report.

As presented in the following tables (for ITT, ITT culture positive subset, and ITT pathogen positive subset), there were no noted differences in demographic and baseline characteristics between the treatment groups for all the three population.

Table 12: Study C-10-019 Demographic and Baseline Characteristics (ITT)

Characteristics	**Finafloxacin (N=274)**	**Vehicle (N=274)**	**Total (N=548)**
	n (%)	**n (%)**	**n (%)**
Gender			
Male	126 (46.0)	104 (38.0)	230 (42.0)
Female	148 (54.0)	170 (62.0)	318 (58.0)
Age			
Mean (Std)	18.5 (15.9)	19.3 (15.5)	18.9 (15.7)
Min, Max	2.0, 82.0	0.9, 74.0	0.9, 82.0
28 Days to 23 Months	0 (0.0)	1 (0.4)	1 (0.2)
2 to 11 Years	130 (47.4)	120 (43.8)	250 (45.6)
12 to 17 Years	56 (20.4)	62 (22.6)	118 (21.5)
18 to 64 Years	80 (29.2)	87 (31.8)	167 (30.5)
≥ 65 Years	8 (2.9)	4 (1.5)	12 (2.2)
Race			
White/Caucasian	235 (85.8)	223 (81.4)	458 (83.6)
Black/African American	26 (9.5)	34 (12.4)	60 (10.9)
Asian	2 (0.7)	3 (1.1)	5 (0.9)
Native Hawaiian	1 (0.4)	1 (0.4)	2 (0.4)
American Indian	6 (2.2)	2 (0.7)	8 (1.5)
Other	2 (0.7)	7 (2.6)	9 (1.6)
Multi-Racial	2 (0.7)	4 (1.5)	6 (1.1)
Ethnicity			
Hispanic, Latino, or Spanish	77 (28.1)	69 (25.2)	146 (26.6)
Not Hispanic, Latino, or Spanish	197 (71.9)	205 (74.8)	402 (73.4)

Characteristics	Finafloxacin (N=274)	Vehicle (N=274)	Total (N=548)
	n (%)	n (%)	n (%)
Baseline Otowick Use Status			
No	232 (84.7)	234 (85.4)	466 (85.0)
Yes	42 (15.3)	40 (14.6)	82 (15.0)
Duration of Current Episode			
Up to 7 Days	237 (86.5)	231 (84.3)	468 (85.4)
8 to 14 Days	25 (9.1)	30 (10.9)	55 (10.0)
15 to 21 Days	10 (3.6)	11 (4.0)	21 (3.8)
22 to 28 Days	2 (0.7)	2 (0.7)	4 (0.7)

Source: Tables 14.1.1-4 and 14.1.2-7 of Study C-10-019 report.

Table 13: Study C-10-019 Demographic and Baseline Characteristics (ITT culture positive subset)

Characteristics	Finafloxacin (N=239)	Vehicle (N=241)	Total (N=480)
	n (%)	n (%)	n (%)
Gender			
Male	108 (45.2)	89 (36.9)	197 (41.0)
Female	131 (54.8)	152 (63.1)	283 (59.0)
Age			
Mean (Std)	19.0 (15.6)	19.7 (15.7)	19.3 (15.6)
Min, Max	2.0, 76.0	0.9, 73.0	0.9, 76.0
28 Days to 23 Months	0 (0.0)	1 (0.4)	1 (0.2)
2 to 11 Years	106 (44.4)	102 (42.3)	208 (43.3)
12 to 17 Years	52 (21.8)	55 (22.8)	107 (22.3)
18 to 64 Years	75 (31.4)	80 (33.2)	155 (32.3)
≥ 65 Years	6 (2.5)	3 (1.2)	9 (1.9)
Race			
White/Caucasian	205 (85.8)	195 (80.9)	400 (83.3)
Black/African American	22 (9.2)	32 (13.3)	54 (11.3)
Asian	2 (0.8)	3 (1.2)	5 (1.0)
Native Hawaiian	1 (0.4)	1 (0.4)	2 (0.4)
American Indian	5 (2.1)	1 (0.4)	6 (1.3)
Other	2 (0.8)	5 (2.1)	7 (1.5)
Multi-Racial	2 (0.8)	4 (1.7)	6 (1.3)
Ethnicity			
Hispanic, Latino, or Spanish	66 (27.6)	60 (24.9)	126 (26.3)
Not Hispanic, Latino, or Spanish	173 (72.4)	181 (75.1)	354 (73.8)
Baseline Otowick Use Status			
No	202 (84.5)	202 (83.8)	404 (84.2)
Yes	37 (15.5)	39 (16.2)	76 (15.8)
Duration of Current Episode			
Up to 7 Days	206 (86.2)	203 (84.2)	409 (85.2)
8 to 14 Days	22 (9.2)	25 (10.4)	47 (9.8)

Characteristics	Finafloxacin (N=239)	Vehicle (N=241)	Total (N=480)
	n (%)	n (%)	n (%)
15 to 21 Days	9 (3.8)	11 (4.6)	20 (4.2)
22 to 28 Days	2 (0.8)	2 (0.8)	4 (0.8)

Source: Tables 14.1.1-7 and 14.1.2-16 of Study C-10-019 report.

Table 14: Study C-10-019 Demographic and Baseline Characteristics (ITT pathogen positive subset)

Characteristics	Finafloxacin (N=147)	Vehicle (N=130)	Total (N=277)
	n (%)	n (%)	n (%)
Gender			
Male	76 (51.7)	55 (42.3)	131 (47.3)
Female	71 (48.3)	75 (57.7)	146 (52.7)
Age			
Mean (Std)	15.5 (13.4)	17.3 (14.6)	16.4 (14.0)
Min, Max	2.0, 76.0	2.0, 69.0	2.0, 76.0
28 Days to 23 Months[a]			
2 to 11 Years	76 (51.7)	65 (50.0)	141 (50.9)
12 to 17 Years	39 (26.5)	32 (24.6)	71 (25.6)
18 to 64 Years	28 (19.0)	31 (23.8)	59 (21.3)
≥ 65 Years	4 (2.7)	2 (1.5)	6 (2.2)
Race			
White/Caucasian	132 (89.8)	106 (81.5)	238 (85.9)
Black/African American	12 (8.2)	15 (11.5)	27 (9.7)
Asian	1 (0.7)	2 (1.5)	3 (1.1)
Native Hawaiian	0 (0.0)	1 (0.8)	1 (0.4)
American Indian	1 (0.7)	1 (0.8)	2 (0.7)
Other	1 (0.7)	3 (2.3)	4 (1.4)
Multi-Racial	0 (0.0)	2 (1.5)	2 (0.7)
Ethnicity			
Hispanic, Latino, or Spanish	29 (19.7)	23 (17.7)	52 (18.8)
Not Hispanic, Latino, or Spanish	118 (80.3)	107 (82.3)	225 (81.2)
Baseline Otowick Use Status			
No	117 (79.6)	99 (76.2)	216 (78.0)
Yes	30 (20.4)	31 (23.8)	61 (22.0)
Duration of Current Episode			
Up to 7 Days	133 (90.5)	115 (88.5)	248 (89.5)
8 to 14 Days	9 (6.1)	9 (6.9)	18 (6.5)
15 to 21 Days	4 (2.7)	4 (3.1)	8 (2.9)
22 to 28 Days	1 (0.7)	2 (1.5)	3 (1.1)

[a] The youngest patient evaluable for Finafloxacin Otic Suspension 0.3% was 2 years old and for Vehicle was 2 years old.
Source: Tables 11.2.1-1 and 11.2.2-3 of Study C-10-019 report.

3.2.4 Results and Conclusions

3.2.4.1 Clinical Cure Rate

The primary efficacy endpoint was the percentage of patients with clinical cures at the TOC visit (Day 11 + 2); a subject was considered as clinical cure if the subject's sum score of tenderness, erythema, and edema was zero (i.e., none) at the TOC visit. The assessment of the signs and symptoms of AOE (i.e., tenderness, erythema, and edema) was conducted by the Investigator using an otoscope during the Baseline/Sceening Visit (Day 1) before the administration of the study drug, and during Day 3 (+2 days), 8 (+2 days), and 11 (+ 2 days or early exit) visits. The primary efficacy analysis set was the ITT pathogen positive subset.

For Study C-10-018, at Day 3 visit, the clinical cure rate was similar between the Finafloxacin group and the Vehicle group. By Day 8 visit, there were more subjects in Finafloxacin group had clinical cure compared to Vehicle group. At the TOC visit, for the ITT pathogen positive subset, 71.7% (104/145) of the patients in the Finafloxacin group had a clinical cure compared with 33.3% (46/138) of the patients in the Vehicle group; the treatment difference (38.4%) was statistically significant ($p<0.001$) with a 95% CI of (27.6%, 49.1%). For both the culture positive subset of the ITT analysis set and the ITT analysis set, the treatment difference was also statistically significant favoring Finafloxacin group.

For Study C-10-019, similar trends in clinical cure rate for Day 3 and Day 8 visits as in Study C-10-18 were observed. At the TOC visit, for the ITT pathogen positive subset, 68.7% (101/147) of the patients in the Finafloxacin group had a clinical cure compared with 40.0% (52/130) of the patients in the Vehicle group; the treatment difference (28.7%) was statistically significant ($p<0.001$) with a 95% CI of (17.4%, 40.0%). For both the culture positive subset of the ITT analysis set and the ITT analysis set, the treatment difference was also statistically significant favoring Finafloxacin group.

Moreover, clinical cure rates of Finafloxacin and Vehicle and the treatment differences for all the three different analysis sets were consistent between Study C-10-018 and C-10-019.

Table 15: Clinical Cure Rate over Time for Studies C-10-018 and C-10-019 (ITT pathogen positive subset, ITT culture positive subset, and ITT)

	ITT pathogen positive subset					
	Study C-10-018			**Study C-10-019**		
Visit	**Finafloxacin (N=145)**	**Vehicle (N=138)**	**Fina vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin (N=147)**	**Vehicle (N=130)**	**Fina vs. Vehicle Difference (95% CI)[a]**
Day 3*	11 (7.6%)	7 (5.1%)	2.5% (-3.1%, 8.2%)	15 (10.2%)	6 (4.6%)	5.6% (-0.5%, 11.7%)
Day 8*	78 (53.8%)	32 (23.2%)	30.6% (19.9%, 41.3%)	72 (49.0%)	25 (19.2%)	29.7% (19.2%, 40.3%)
Day 11	104 (71.7%)	46 (33.3%)	38.4% (27.6%, 49.1%)	101 (68.7%)	52 (40.0%)	28.7% (17.4%, 40.0%)
	ITT culture positive subset					
	Study C-10-018			**Study C-10-019**		
	Finafloxacin (N=311)	**Vehicle (N=302)**	**Fina vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin (N=239)**	**Vehicle (N=241)**	**Fina vs. Vehicle Difference (95% CI)[a]**
Day 3*	28 (9.0%)	19 (6.3%)	2.7% (-1.5%, 6.9%)	20 (8.4%)	16 (6.6%)	1.7% (-3.0%, 6.4%)

Day 8*	177 (56.9%)	107 (35.4%)	21.5% (13.8%, 29.2%)	113 (47.3%)	59 (24.5%)	22.8% (14.5%, 31.1%)
Day 11	226 (72.7%)	154 (51.0%)	21.7% (14.2%, 29.2%)	170 (71.1%)	112 (46.5%)	24.7% (16.1%, 33.2%)
	ITT					
	Study C-10-018			**Study C-10-019**		
	Finafloxacin (N=344)	**Vehicle (N=342)**	**Fina vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin (N=274)**	**Vehicle (N=274)**	**Fina vs. Vehicle Difference (95% CI)[a]**
Day 3*	30 (8.7%)	20 (5.9%)	2.8% (-1.0%, 6.8%)	24 (8.8%)	18 (6.6%)	2.2% (-2.3%, 6.6%)
Day 8*	194 (56.4%)	122 (35.7%)	20.7% (13.4%, 28.0%)	131 (47.8%)	74 (27.0%)	20.8% (12.9%, 28.7%)
Day 11	245 (71.2%)	173 (50.6%)	20.6% (13.5%, 27.8%)	194 (70.8%)	134 (48.9%)	21.9% (13.9%, 29.9%)

***** Cures at Days 3 and 8 are sustained cures. A sustained clinical cure was attained at the indicated visit if the sum of tenderness, erythema, and edema was zero (ie, none) at the indicated visit and remained zero throughout the study.
[a] 95% CI calculated based on normal approximation to binomial data.
Source: Table 11.4.1.3-2 of Study C-10-018 report and Table 11.4.1.3-2 of Study C-10-019 report.

For the analysis of the primary efficacy endpoint, the outcome of clinical cure at Day 11 was imputed as a "failure" for any patient who did not complete the study or who had missing scores for 1 or more of the components of clinical cure. In Study C-10-018, for the ITT culture positive subset, 13.5% (42/311) subjects in the Finafloxacin group had their clinical cure scores missing at TOC visit; and 26.5% (80/302) subjects in the Vehicle group had their clinical cure scores missing at TOC visit. In Study C-10-019, the rates of subjects who had clinical cure scores missing at TOC visit were 13.0% (31/239) and 36.1 (87/241) for Finaflaxacin and Vehicle respectively (Table 16).

For majority of these patients, the reason for them not completing the study and therefore having missing clinical cure scores was treatment failure. In Study C-10-018, the percentages of subjects who had clinical cure rates missing due to treatment failure were 71.4% (30/42) for the Finafloxacin group and 71.3% (57/80) in the Vehicle group; in Study C-10-019, these percentages were 58.1% (18/31) and 86.2% (75/87) for Finaflaxacin and Vehicle respectively (Table 16). Therefore imputing "failure" for clinical cure for these treatment failure patients with missing data was considered by the statistical reviewer as appropriate.

For the remaining subjects who had missing scores of clinical cure for reasons other than treatment failure (adverse events, lost to follow-up, etc.), additional sensitivity analyses were performed by the statistical reviewer where Finafloxacin-treated patients with missing data had their clinical cure outcomes imputed as failures at TOC and Vehicle-treated patients with missing data in the Vehicle group had their clinical cure outcomes imputed as successes at TOC (this could be considered as a worst case scenario analysis). The results of this analysis were consistent with the primary analysis results (Table 17).

Table 16: Reasons for Having Missing Clinical Cure Scores (ITT pathogen positive subset, ITT culture positive subset, and ITT)

	ITT pathogen positive subset			
	Study C-10-018		**Study C-10-019**	
	Finafloxacin (N=145)	**Vehicle (N=138)**	**Finafloxacin (N=147)**	**Vehicle (N=130)**
Number of Subjects Who Had Missing Scores	17 (11.7%)	49 (35.5%)	24 (16.3%)	55 (42.3%)
Treatment Failure	15 (10.2%)	35 (25.4%)	14 (9.5%)	48 (36.9%)

Adverse Event	0 (0.0%)	11 (8.0%)	8 (5.4%)	4 (3.1%)
Other	2 (1.4%)	3 (2.2%)	2 (1.4%)	3 (2.3%)
	ITT culture positive subset			
	Study C-10-018		**Study C-10-019**	
	Finafloxacin (N=311)	**Vehicle (N=302)**	**Finafloxacin (N=239)**	**Vehicle (N=241)**
Number of Subjects Who Had Missing Scores	42 (13.5%)	80 (26.5%)	31 (13.0%)	87 (36.1%)
Treatment Failure	30 (9.6%)	57 (18.9%)	18 (7.5%)	75 (31.1%)
Adverse Event	4 (1.3%)	14 (4.6%)	11 (4.6%)	7 (2.9%)
Other	8 (2.6%)	9 (3.0%)	2 (0.8%)	5 (2.1%)
	ITT			
	Study C-10-018		**Study C-10-019**	
	Finafloxacin (N=344)	**Vehicle (N=342)**	**Finafloxacin (N=274)**	**Vehicle (N=274)**
Number of Subjects Who Had Missing Scores	46 (13.4%)	92 (26.9%)	36 (13.1%)	94 (34.3%)
Treatment Failure	32 (9.3%)	66 (19.3%)	21 (7.7%)	82 (29.9%)
Adverse Event	6 (1.7%)	15 (4.4%)	11 (4.0%)	7 (2.6%)
Other	8 (2.3%)	11 (3.2%)	4 (1.5%)	5 (1.8%)

Source: Statistical reviewer's calculation.

Table 17: Clinical Cure Based on Worst Case Scenario at TOC for Studies C-10-018 and C-10-019 (ITT pathogen positive subset, ITT culture positive subset, and ITT)

	Study C-10-018			**Study C-10-019**		
	Finafloxacin	**Vehicle**	**Fina vs. Vehicle Difference (95% CI)***	**Finafloxacin**	**Vehicle**	**Fina vs. Vehicle Difference (95% CI)***
Pathogen + Subset	104/145 (71.7%)	60/138 (43.5%)	28.3% (17.2%, 39.3%)	101/147 (68.7%)	59/130 (45.4%)	23.3% (12.0%, 34.7%)
Culture + Subset	226/311 (72.7%)	177/302 (58.6%)	14.1% (6.6%, 21.5%)	170/239 (71.1%)	124/241 (51.5%)	19.7% (11.4%, 28.2%)
ITT	245/344 (71.2%)	199/342 (58.2%)	13.0% (6.0%, 20.1%)	194/274 (70.8%)	146/274 (53.3%)	17.5% (9.5%, 25.5%)

* 95% CI calculated based on normal approximation to binomial data.
Source: Statistical reviewer's calculation.

Additional sensitivity analyses conducted by the applicant based on observed data only, based on three different PP analysis sets (pathogen positive subset of PP, culture positive subset of PP, and PP), and each component of the clinical cure (i.e. tenderness, erythema, and edema) were also supportive of the primary efficacy results.

In conclusion, Finafloxacin otic suspension 0.3% was superior to Vehicle in regard to the percentage of patients who achieved clinical cure at the TOC visit.

3.2.4.2 Microbiological Cure

Microbiological success was defined as the absence of all pre-therapy bacteria from the otic specimen obtained at TOC visit. Microbiological success at TOC visit was evaluated for two analysis sets: ITT pathogen positive subset, and ITT culture positive subset.

For Study C-10-018, at the TOC visit, for the ITT pathogen positive subset, 66.9% (97/145) of the patients in the Finafloxacin group had microbiological success compared with 13.0% (18/138) of the patients in the Vehicle group; the treatment difference (53.9%) was statistically significant (p<0.001) with a 95% CI of (44.4%, 63.4%). For the ITT culture positive subset, more patients in the Finafloxacin group had microbiological success compared to the Vehicle group (60.8% [189/311], 16.6% [50/302] respectively); the treatment difference was 44.2% with a 95% CI of (37.4%, 51.1%).

For Study C-10-019, at the TOC visit, for the ITT pathogen positive subset, 66.0% (97/147) of the patients in the Finafloxacin group had microbiological success compared with 11.5% (15/130) of the patients in the Vehicle group; the treatment difference (54.4%) was statistically significant (p<0.001) with a 95% CI of (45.0%, 63.9%). For the ITT culture positive subset, more patients in the Finafloxacin group had microbiological success compared to the Vehicle group (64.9% [155/239], 17.0% [41/241] respectively); the treatment difference was 47.8% with a 95% CI of (40.2%, 55.5%).

In addition, microbiological success rates of Finafloxacin and Vehicle and the treatment differences for the two analyses sets were consistent between Study C-10-018 and C-10-019.

Table 18: Microbiological Cure at TOC Visit for Studies C-10-018 and C-10-019 (ITT pathogen positive subset, and ITT culture positive subset)

	Study C-10-018			Study C-10-019		
	Finafloxacin	**Vehicle**	**Fina vs. Vehicle Difference (95% CI)***	**Finafloxacin**	**Vehicle**	**Fina vs. Vehicle Difference (95% CI)***
Pathogen + Subset	97/145 (66.9%)	18/138 (13.0%)	53.9% (44.4%, 63.4%)	97/147 (66.0%)	15/130 (11.5%)	54.4% (45.0%, 63.9%)
Culture + Subset	189/311 (60.8%)	50/302 (16.6%)	44.2% (37.4%, 51.1%)	155/239 (64.9%)	41/241 (17.0%)	47.8% (40.2%, 55.5%)

* 95% CI calculated based on normal approximation to binomial data.
Source: Tables 11.4.1.2-1 and 14.2-24 of Study C-10-018 report and Tables 11.4.1.2-1 and 14.2-24 of Study C-10-019 report.

Similar as for the primary efficacy analysis, for majority of patients with missing microbiological success data, the reason for them not completing the study was treatment failure; therefore imputing "failure" for microbiological success for these treatment failure patients with missing data was considered by the statistical reviewer as appropriate. For the subjects who had missing scores of microbiological success for reasons other than treatment failure (adverse events, lost to follow-up, etc.), additional sensitivity analyses were performed by the statistical reviewer using the same worst case scenario analysis as the primary efficacy endpoint; the results of this analysis were consistent with the applicant's analysis results presented in the above table.

Additional sensitivity analyses conducted by the applicant based on observed data only, based on the two difference PP analysis sets (pathogen positive subset of PP, and culture positive subset of PP) were also supportive of the results presented in the above table.

In conclusion, Finafloxacin otic suspension 0.3% was superior to Vehicle in regard to the percentage of patients who achieved microbiological success at the TOC visit.

3.2.4.3 Time to Cessation of Ear Pain

Time to cessation of ear pain was defined as the first time point for which ear pain was absent (morning or evening) and did not subsequently return. Cessation of ear pain was reported by the patient or parent/legal guardian via the telephone diary at 1/2 day interval starting at Day 1. For all patients who complete the study but their ear pain never ceased, their time to cessation of ear pain was considered right censored at the last diary time point at which they reported having ear pain, regardless of whether they completed all diary entries or not. For all patients who do not complete the study and their ear pain never ceased, their time to cessation of ear pain was considered right censored at Day 11.

In Study C-10-018, for the ITT pathogen positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 4.0 days and 7.0 days respectively; the treatment difference was -3.0 with a 95% CI of (-5.0, -0.8). For the ITT culture positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 4.0 days and 5.0 days respectively; the treatment difference was -1.0 with a 95% CI of (-2.0, 0.0).

In Study C-10-019, for the ITT pathogen positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 3.0 days and 6.5 days respectively; the treatment difference was -3.6 with a 95% CI of (-5.0, -2.0). For the ITT culture positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 3.0 days and 5.5 days respectively; the treatment difference was -2.3 with a 95% CI of (-3.0, -1.0).

Kaplan-Meier survival curves of time of cessation of ear pain also indicated the treatment effect of Finafloxacin over Vehicle.

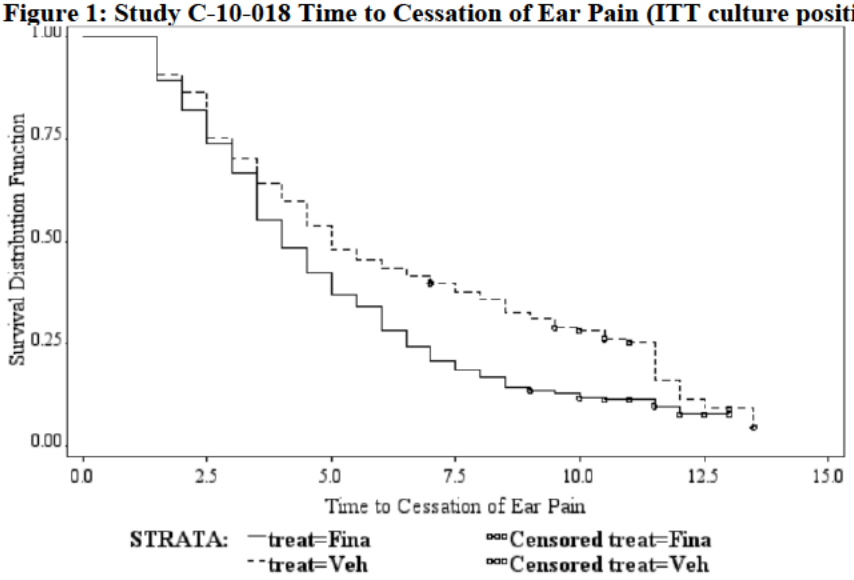
Table 19: Time (in Days) to Cessation of Ear Pain for Studies C-10-018 and C-10-019 (ITT pathogen positive subset, and ITT culture positive subset)

	ITT pathogen positive subset					
	Study C-10-018			Study C-10-019		
Visit	Finafloxacin (N=138)	Vehicle (N=128)	Difference (95% CI)[b]	Finafloxacin (N=138)	Vehicle (N=125)	Difference (95% CI)[b]
Events	123 (89.1%)	88 (68.8%)		122 (88.4%)	86 (68.8%)	
Median	4.0	7.0	-3.0 (-5.0, -0.8)	3.0	6.5	-3.6 (-5.0, -2.0)
p-value for log-rank test		<0.001			<0.001	
	ITT culture positive subset					
	Study C-10-018			Study C-10-019		
Visit	Finafloxacin (N=286)	Vehicle (N=271)	Difference (95% CI)[b]	Finafloxacin (N=222)	Vehicle (N=230)	Difference (95% CI)[b]
Events	255 (89.2%)	209 (77.1%)		198 (89.2%)	167 (72.6%)	
Median	4.0	5.0	-1.0 (-2.0, 0.0)	3.0	5.5	-2.3 (-3.0, -1.0)
p-value for log-rank test		<0.001			<0.001	
	ITT					
Visit	Study C-10-018			Study C-10-019		

	Finafloxacin (N=317)	Vehicle (N=309)	Difference (95% CI)[b]	Finafloxacin (N=256)	Vehicle (N=258)	Difference (95% CI)[b]
Events	282 (89.0%)	235 (76.1%)		226 (88.3%)	190 (73.6%)	
Median	4.0	5.0	-1.0 (-2.0, -0.5)	3.0	5.5	-2.2 (-3.0, -1.0)
p-value for log-rank test		<0.001			<0.001	

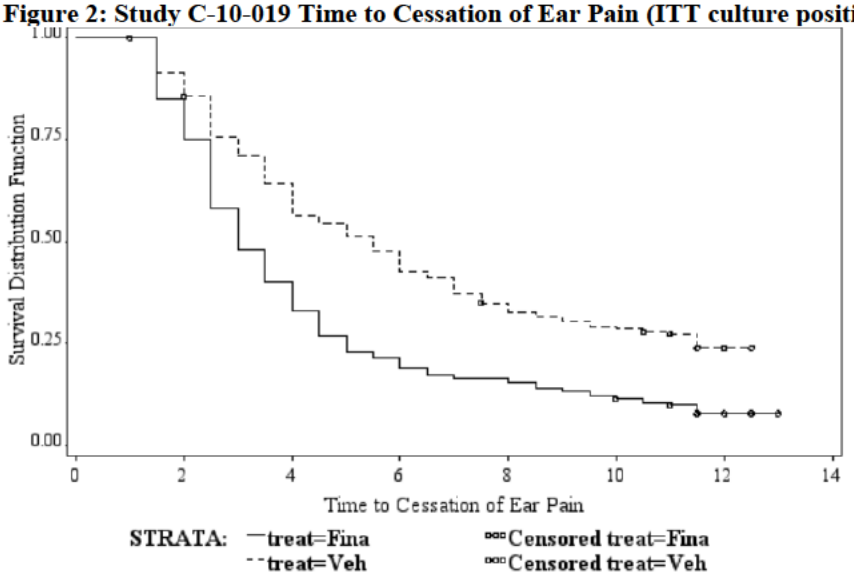
[a] Medians are product-limit estimates.
[b] Difference and 95% confidence interval estimated using bootstrap procedure with 10,000 bootstrap samples, non-stratified analysis.
Source: Tables 14.2-93, 14.2-94, and 14.2-95 of Study C-10-018 report and Tables 14.2-89, 14.2-90, and 14.2-91 of Study C-10-019 report.

Figure 1: Study C-10-018 Time to Cessation of Ear Pain (ITT culture positive subset)



Source: Figure 14.2-49 of Study C-10-018 Report.

Figure 2: Study C-10-019 Time to Cessation of Ear Pain (ITT culture positive subset)



Source: Figure 14.2-49 of Study C-10-019 Report.

In the applicant's analyses presented above, patients who had ear pain reported at baseline but never had subsequent ear pain reported at any diary entry during first 7 days of the study were

excluded from the analysis. There were about 5% to 9% of patients who were excluded (Table 20). Additional sensitivity analyses performed by the statistical reviewer in which those excluded patients were considered as right censored at Day 11; the results of these sensitivity analyses were consistent with applicant's analyses results.

Table 20: Summary of Subjects Who Were Excluded by the Applicant from Time to Cessation of Ear Pain Analysis

	Study C-10-018			Study C-10-019		
	Finafloxacin	**Vehicle**	**Total**	**Finafloxacin**	**Vehicle**	**Total**
Pathogen + Subset	7/145 (4.8%)	10/138 (7.2%)	17/283 (6.0%)	9/147 (6.1%)	5/130 (3.8%)	14/277 (5.1%)
Culture + Subset	25/311 (8.0%)	31/302 (10.3%)	56/613 (9.1%)	17/239 (7.1%)	11/241 (4.6%)	28/480 (5.8%)
ITT	27/344 (7.8%)	33/342 (9.6%)	60/686 (8.7%)	18/274 (6.6%)	16/274 (5.8%)	34/548 (6.2%)

Source: Statistical reviewer's calculation.

Furthermore, it is noted that patients might use pain medication for relief of ear pain at any time during the study. Although majority of subjects who used pain medication on or before study Day 1 (baseline), there were about 9-11% subjects in Study C-10-018 and 13-14% subjects in Study C-10-019 who started using pain medication during the study (Table 21). For both studies, the percentage of subjects in the Vehicle group who used pain medication post-baseline was about twice as much as that in the Finafloxacin group. More patients in Vehicle group having to use pain medication post-baseline indicate the treatment effect of Finafloxacin in reducing ear pain due to AOE.

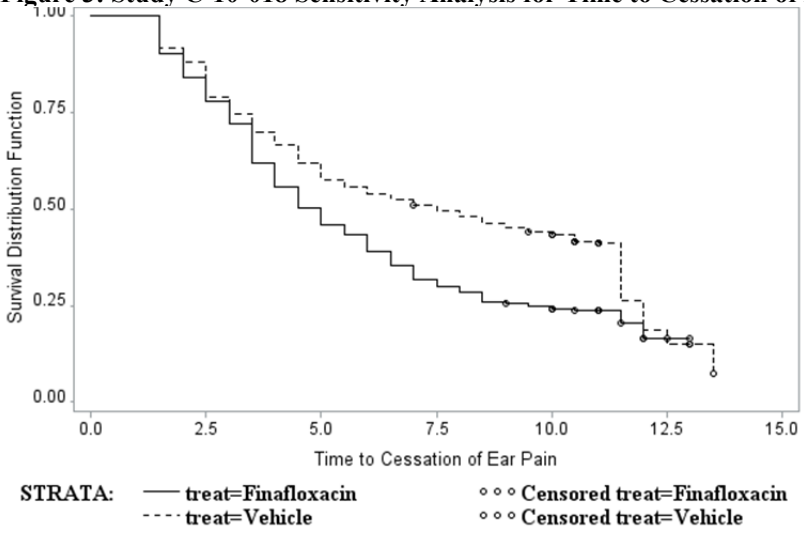
Table 21: Summary of Subjects Who Used Pain Medication Post-Baseline

	Study C-10-018			Study C-10-019		
	Finafloxacin	**Vehicle**	**Total**	**Finafloxacin**	**Vehicle**	**Total**
Pathogen + Subset	10/145 (6.9%)	21/138 (15.2%)	31/283 (11.0%)	14/147 (9.5%)	26/130 (20%)	40/277 (14.4%)
Culture + Subset	20/311 (6.4%)	33/302 (10.9%)	53/613 (8.6%)	21/239 (8.8%)	42/241 (17.4%)	63/480 (13.1%)
ITT	22/344 (6.4%)	36/342 (10.5%)	58/686 (8.7%)	24/274 (8.8%)	45/274 (16.4%)	69/548 (12.6%)

Source: Statistical reviewer's calculation

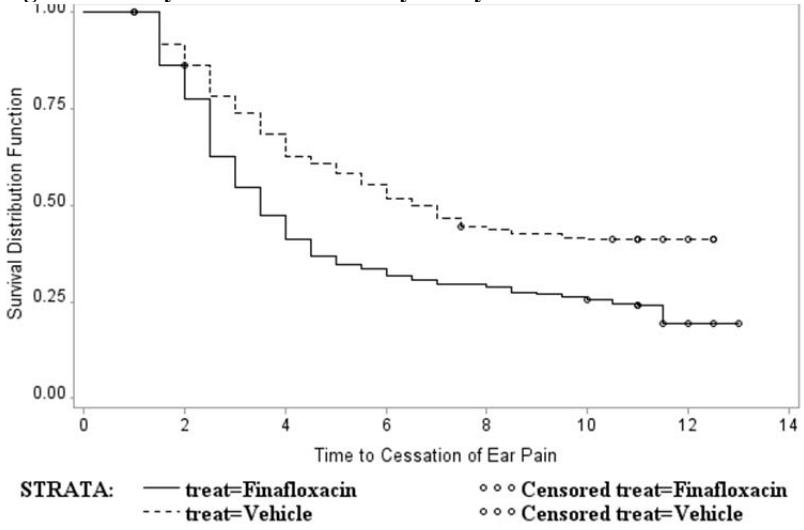
Additional sensitivity analysis was performed by the statistical reviewer where any subjects who took pain medication post-baseline were considered as right censored at Day 11; in addition, for this sensitivity analysis, those excluded patients described above were also considered as right censored at Day 11. Kaplan-Meier survival curves of time of cessation of ear pain in this sensitivity analysis were consistent with the primary analysis and also indicated the treatment effect of Finafloxacin over Vehicle (Figure 3 and Figure 4).

Figure 3: Study C-10-018 Sensitivity Analysis for Time to Cessation of Ear Pain (ITT culture positive subset)



Source: Statistical Reviewer's Analysis.

Figure 4: Study C-10-019 Sensitivity Analysis for Time to Cessation of Ear Pain (ITT culture positive subset)



Source: Statistical Reviewer's Analysis.

Based on all the above analysis results, Finafloxacin otic suspension 0.3% was also superior to Vehicle in regard to the median time to cessation of ear pain.

3.3 Evaluation of Safety

For Study C-10-018, all 686 subjects who were exposed to the study treatment were included in the safety analysis set. For Study C-10-019, all 548 subjects who were exposed to the study treatment were included in the safety analysis set. The following tables present the treatment-emergent adverse events for both studies. Overall, Finafloxacin had similar adverse events rates

as Vehicle-treated groups. Please see the review of the medical reviewer for details of the safety evaluation.

Table 22: Summary of Treatment-Emergent Adverse Events of Studies C-10-018 and C-10-019 (Safety Analysis Set)

	Study C-10-018		Study C-10-019	
	Finafloxacin (N=344)	**Vehicle (N=342)**	**Finafloxacin (N=274)**	**Vehicle (N=274)**
Patients discontinued due to an adverse event	**6 (1.7%)**	**15 (4.4%)**	**12 (4.4%)**	**7 (2.6%)**
Discontinued due to nonfatal serious adverse events	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discontinued due to nonserious adverse events	6 (1.7%)	15 (4.4%)	12 (4.4%)	7 (2.6%)
Treatment-related	1 (0.3%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Not related to treatment	5 (1.5%)	13 (3.8%)	12 (4.4%)	7 (2.6%)
Patients with at least 1 treatment-emergent adverse event (related and not related combined)	**51 (14.8%)**	**51 (14.9%)**	**40 (14.6%)**	**48 (17.5%)**
Most frequent treatment-emergent adverse events (reported by 1% or more of the patients in either Treatment group)				
Ear pruritus	6 (1.7%)	4 (1.2%)	n/a	
Ear Pain	3 (0.9%)	5 (1.5%)	0	4 (1.5%)
Ear discomfort	2 (0.6%)	5 (1.5%)	0	4 (1.5%)
Nausea	5 (1.5%)	0 (0.0%)	n/a	n/a
Otitis externa	n/a	n/a	9 (3.3%)	6 (2.2%)
Otitis media	4 (1.2%)	11 (3.2%)	4 (1.5%)	3 (1.1%)
Headache	7 (2.0%)	10 (2.9%)	4 (1.5%)	8 (2.9%)
Dizziness	4 (1.2%)	2 (0.6%)	n/a	n/a
Patients with at least 1 treatment-emergent adverse event related to treatment (ADR; adverse drug reaction)	**9 (2.6%)**	**4 (1.2%)**	**2 (0.7%)**	**3 (1.1%)**
Ear pruritus	2 (0.6%)	2 (0.6%)	1 (0.4%)	1 (0.4%)
Cerumen impaction	1 (0.3%)	0 (0.0%)	n/a	n/a
Ear congestion	0 (0.0%)	1 (0.3%)	n/a	n/a
Ear discomfort	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.4%)
Nausea	1 (0.3%)	0 (0.0%)	n/a	n/a
Ear infection fungal	1 (0.3%)	0 (0.0%)	n/a	n/a
Otitis externa candida	1 (0.3%)	0 (0.0%)	n/a	n/a
Dizziness	3 (0.9%)	0 (0.0%)	n/a	n/a
Headache	1 (0.3%)	0 (0.0%)	n/a	n/a
Rash	0	1 (0.3%)	n/a	n/a
Hypoacusis	n/a	n/a	1 (0.4%)	0 (0.0%)
Otorrhoea	n/a	n/a	0 (0.0%)	1 (0.4%)

Source: Table 12.2.2-1 of Study C-10-018 report and Table 12.2.2-1 of Study C-10-019 report.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

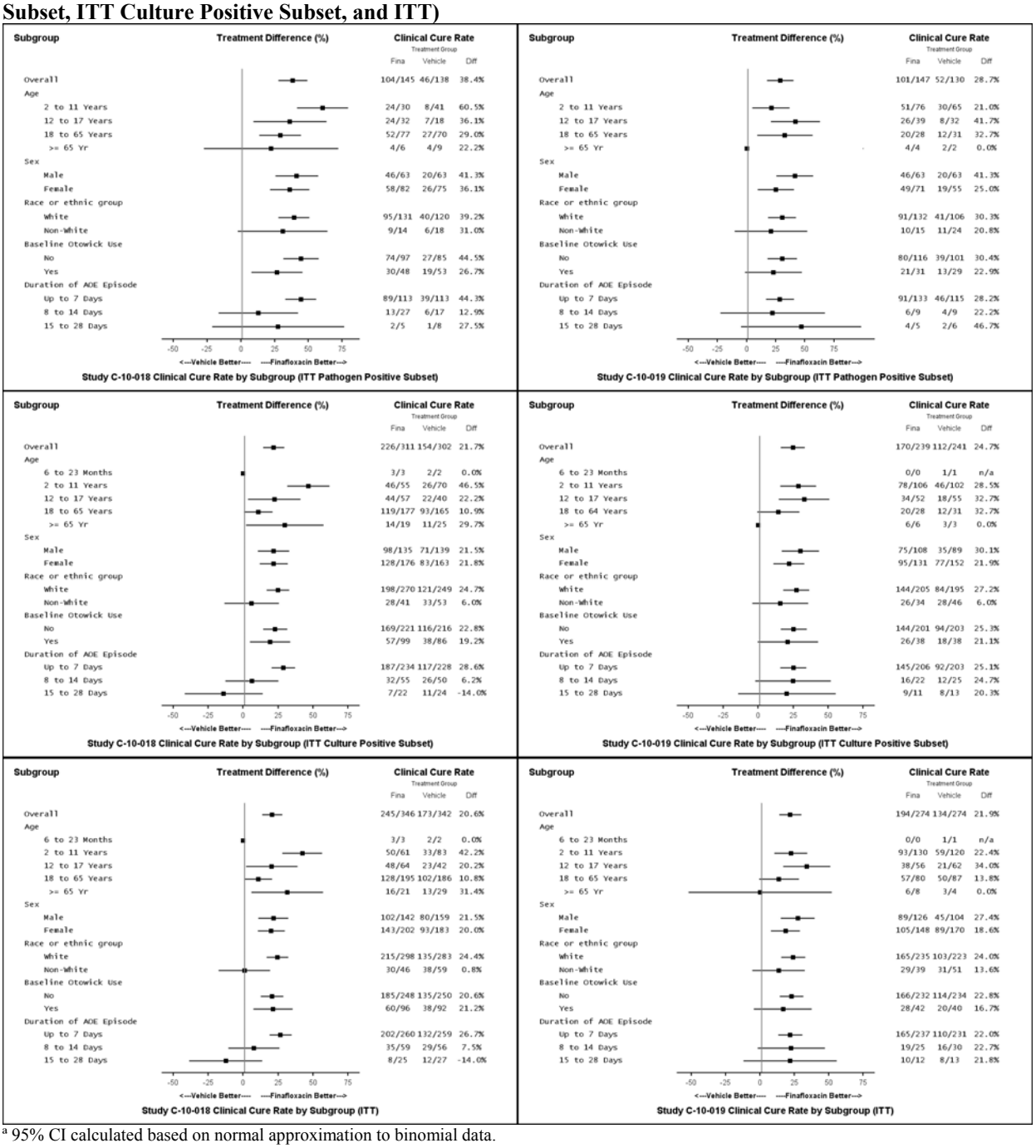
4.1 Gender, Race, Age, Baseline Otowick Use, and Duration of Current Episode

Subgroup analyses based on gender, race, and age were performed. Treatment effects might be different for subjects with or without baseline otowick use, and for subjects with difference duration of current AOE episode; therefore subgroup analyses based on these two parameters were also conducted.

In Study C-10-018, for the ITT culture positive subset and ITT set, Vehicle had higher clinical cure rate compared to Finaflaxcin in subjects who had duration of current episode between 15 to

28 days. Other than this sub-group in Study C-10-018, in general, there were no marked differences in the efficacy results among the various subpopulations.

Figure 5: Forest Plots of Subgroup Analyses for Studies C-10-018 and C-10-019 (ITT Pathogen Positive Subset, ITT Culture Positive Subset, and ITT)



[a] 95% CI calculated based on normal approximation to binomial data.
Source: Statistical reviewer's analyses.

4.2 Region

Clinical cure rates at TOC by region were conducted by the statistical reviewer. In general, the magnitude of treatment effect for patients in Puerto Rico and Canada was less than patients in U.S.

Table 23: Clinical Cure Rate at TOC Visit by Region for Studies C-10-018 and C-10-019 (ITT pathogen positive subset, ITT culture positive subset, and ITT)

	ITT pathogen positive subset					
	Study C-10-018			Study C-10-019		
Region	Finafloxacin (N=145)	Vehicle (N=138)	Fina vs. Vehicle Difference (95% CI)[a]	Finafloxacin (N=147)	Vehicle (N=130)	Fina vs. Vehicle Difference (95% CI)[a]
U.S.	94/128 (73.4%)	35/116 (30.2%)	43.3% (31.9%, 54.6%)	90/135 (66.7%)	40/114 (35.1%)	31.6% (19.8%, 43.4%)
Canada	5/12 (41.7%)	3/9 (33.3%)	8.3% (-33.2%, 49.9%)	n/a	0/1 (0.0%)	n/a
Puerto Rico	5/5 (100.0%)	8/13 (61.5%)	38.5% (12.0%, 64.9%)	11/12 (91.7%)	12/15 (80.0%)	11.7% (-13.9%, 37.3%)
	ITT culture positive subset					
	Study C-10-018			Study C-10-019		
	Finafloxacin (N=311)	Vehicle (N=302)	Fina vs. Vehicle Difference (95% CI)[a]	Finafloxacin (N=239)	Vehicle (N=241)	Fina vs. Vehicle Difference (95% CI)[a]
U.S.	193/254 (76.0%)	123/244 (50.4%)	25.6% (17.4%, 33.8%)	152/213 (71.4%)	93/208 (44.7%)	26.7% (17.6%, 35.7%)
Canada	17/33 (51.5%)	12/30 (40.0%)	11.5% (-12.9%, 36.0%)	1/1 (100.0%)	1/3 (33.3%)	66.7% (13.3%, 100.0%)
Puerto Rico	16/24 (66.7%)	19/28 (67.9%)	-1.2% (-26.8%, 24.4%)	17/25 (68.0%)	18/30 (60.0%)	8.0% (-17.3%, 33.3%)
	ITT					
	Study C-10-018			Study C-10-019		
	Finafloxacin (N=344)	Vehicle (N=342)	Fina vs. Vehicle Difference (95% CI)[a]	Finafloxacin (N=274)	Vehicle (N=274)	Fina vs. Vehicle Difference (95% CI)[a]
U.S.	209/278 (75.2%)	141/279 (50.5%)	24.6% (16.9%, 32.4%)	174/243 (71.6%)	114/239 (47.7%)	23.9% (15.4%, 32.4%)
Canada	17/36 (47.2%)	12/31 (38.7%)	8.5% (15.2%, 32.2%)	1/2 (50.0%)	1/3 (33.3%)	16.7% (-70.8%, 100.0%)
Puerto Rico	19/30 (63.3%)	20/32 (62.5%)	0.8% (-23.2%, 24.9%)	19/29 (65.5%)	19/32 (59.4%)	6.1% (-18.1%, 30.4%)

[a] 95% CI calculated based on normal approximation to binomial data.
Source: Statistical Reviewer's calculation.

4.3 Other Fluoroquinolone Resistant Bacteria

Post-hoc analyses based on a subset of patients who had at least one fluoroquinolone-resistant organism at baseline were conducted by the applicant. (b) (4) [redacted] For both studies,

the results of clinical cure and microbiological success in this subset were consistent with the results of the overall population.

The applicant proposed to include the results for this subset of patients in the clinical studies section of the label. Although the results were statistically significant, whether to include efficacy results for this subset in the final label would be a clinical judgment based on whether the (b) (4) had any clinical significance. Therefore, the statistical reviewer would like to defer the decision of including efficacy results for this subset in the final label to the clinical review team.

Table 24: Clinical Cure and Microbiological Success at TOC visit in Patients with Fluoroquinolone Resistant Organisms (ITT culture positive subset)

	Study C-10-018			Study C-10-019		
	Finafloxacin	Vehicle	Fina vs. Vehicle Difference (95% CI)[a]	Finafloxacin	Vehicle	Fina vs. Vehicle Difference (95% CI)[a]
Clinical Cure	42/54 (77.8%)	31/58 (53.4%)	24.3% (7.4%, 41.3%)	32/45 (71.1%)	14/43 (37.2%)	33.9% (14.3%, 53.5%)
Microbiological Success	32/54 (59.3%)	6/58 (10.3%)	48.9% (33.6%, 64.2%)	27/45 (60.0%)	5/43 (11.6%)	48.4% (31.1%, 65.6%)

[a] 95% CI calculated based on normal approximation to binomial data.
Source: Tables 11.4.1.5-7 and 11.4.1.5-8 of Study C-10-018 report, and Tables 11.4.1.5-7 and 11.4.1.5-8 of Study C-10-019 report.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for the two pivotal studies submitted.

For the analysis of the primary efficacy endpoint, the outcome of clinical cure at Day 11 was imputed as a "failure" for any patient who did not complete the study or who had missing scores for 1 or more of the components of clinical cure. In Study C-10-018, for the ITT culture positive subset, 13.5% (42/311) subjects in the Finafloxacin group had their clinical cure scores missing at TOC visit; and 26.5% (80/302) subjects in the Vehcile group had their clinical cure scores missing at TOC visit. In Study C-10-019, the rates of subjects who had clinical cure scores missing at TOC visit were 13.0% (31/239) and 36.1 (87/241) for Finaflaxacin and Vehicle respectively. For majority of these patients, the reason for them not completing the study and therefore having missing clinical cure scores was treatment failure. In Study C-10-018, the percentages of subjects who had clinical cure rates missing due to treatment failure were 71.4% (30/42) for the Finafloxacin group and 71.3% (57/80) in the Vehicle group; in Study C-10-019, these percentages were 58.1% (18/31) and 86.2% (75/87) for Finaflaxacin and Vehicle respectively. Therefore imputing "failure" for clinical cure for these treatment failure patients with missing data was considered by the statistical reviewer as appropriate.

For the remaining subjects who had missing scores of clinical cure for reasons other than treatment failure (adverse events, lost to follow-up, etc.), additional sensitivity analyses were

performed by the statistical reviewer where Finafloxacin-treated patients with missing data had their clinical cure outcomes imputed as failures at TOC and Vehicle-treated patients with missing data in the Vehicle group had their clinical cure outcomes imputed as successes at TOC (ie, a worst case scenario analysis); the results of this analysis were supportive of the primary analysis results.

5.2 Collective Evidence

Clinical Cure at TOC Visit – Primary Efficacy Endpoint

In Study C-10-018, at the TOC visit, for the ITT pathogen positive subset, 71.7% (104/145) of the patients in the Finafloxacin group had a clinical cure compared with 33.3% (46/138) of the patients in the Vehicle group; the treatment difference (38.4%) was statistically significant ($p<0.001$) with a 95% CI of (27.6%, 49.1%). For the ITT culture positive subset, more patients in the Finafloxacin group had clinical cure compared to the Vehicle group (72.7% [226/311], 51.0% [154/302] respectively); the treatment difference was 21.7% with a 95% CI of (14.2%, 29.2%).

In Study C-10-019, at the TOC visit, for the ITT pathogen positive subset, 68.7% (101/147) of the patients in the Finafloxacin group had a clinical cure compared with 40.0% (52/130) of the patients in the Vehicle group; the treatment difference (28.7%) was statistically significant ($p<0.001$) with a 95% CI of (17.4%, 40.0%). For the ITT culture positive subset, more patients in the Finafloxacin group had clinical cure compared to the Vehicle group (71.1% [170/239], 46.5% [112/241] respectively); the treatment difference was 24.7% with a 95% CI of (16.1%, 33.2%).

Microbiological Success at TOC Visit – Secondary Efficacy Endpoint #1

In Study C-10-018, at the TOC visit, for the ITT pathogen positive subset, 66.9% (97/145) of the patients in the Finafloxacin group had microbiological success compared with 13.0% (18/138) of the patients in the Vehicle group; the treatment difference (53.9%) was statistically significant ($p<0.001$) with a 95% CI of (44.4%, 63.4%). For the ITT culture positive subset, more patients in the Finafloxacin group had microbiological success compared to the Vehicle group (60.8% [189/311], 16.6% [50/302] respectively); the treatment difference was 44.2% with a 95% CI of (37.4%, 51.1%).

In Study C-10-019, at the TOC visit, for the ITT pathogen positive subset, 66.0% (97/147) of the patients in the Finafloxacin group had microbiological success compared with 11.5% (15/130) of the patients in the Vehicle group; the treatment difference (54.4%) was statistically significant ($p<0.001$) with a 95% CI of (45.0%, 63.9%). While for the ITT culture positive subset, more patients in the Finafloxacin group had microbiological success compared to the Vehicle group (64.9% [155/239], 17.0% [41/241] respectively); the treatment difference was 47.8% with a 95% CI of (40.2%, 55.5%).

Time to cessation of ear pain – Secondary Efficacy Endpoint #2

In Study C-10-018, for the ITT pathogen positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 4.0 days and 7.0 days respectively; the treatment difference was -3.0 with a 95% CI of (-5.0, -0.8). For the ITT culture positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 4.0 days and 5.0 days respectively; the treatment difference was -1.0 ($p<0.001$) with a 95% CI of (-2.0, 0.0).

In Study C-10-019, for the ITT pathogen positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 3.0 days and 6.5 days respectively; the treatment difference was -3.6 with a 95% CI of (-5.0, -2.0). For the ITT culture positive subset, the median time to cessation of ear pain in the Finafloxacin group and Vehicle group was 3.0 days and 5.5 days respectively; the treatment difference was -2.3 ($p<0.001$) with a 95% CI of (-3.0, -1.0).

Table 25: Summary of the Primary and Secondary Efficacy Results (ITT pathogen positive subset, ITT culture positive subset, and ITT)

Clinical Cure at TOC						
	Study C-10-018			**Study C-10-019**		
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**
Pathogen + Subset	104/145 (71.7%)	46/138 (33.3%)	38.4% (27.6%, 49.1%)	101/147 (68.7%)	52/130 (40.0%)	28.7% (17.4%, 40.0%)
Culture + Subset	226/311 (72.7%)	154/302 (51.0%)	21.7% (14.2%, 29.2%)	170/239 (71.1%)	112/241 (46.5%)	24.7% (16.1%, 33.2%)
ITT	245/346 (71.2%)	173/342 (50.6%)	20.6% (13.5%, 27.8%)	194/274 (70.8%)	134/274 (48.9%)	21.9% (13.9%, 29.9%)
Microbiological Success at TOC						
	Study C-10-018			**Study C-10-019**		
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[a]**
Pathogen + Subset	97/145 (66.9%)	18/138 (13.0%)	53.9% (44.4%, 63.4%)	97/147 (66.0%)	15/130 (11.5%)	54.4% (45.0%, 63.9%)
Culture + Subset	189/311 (60.8%)	50/302 (16.6%)	44.2% (37.4%, 51.1%)	155/239 (64.9%)	41/241 (17.0%)	47.8% (40.2%, 55.5%)
Median Time to Cessation of Ear Pain						
	Study C-10-018			**Study C-10-019**		
	Finafloxacin	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[b]**	**Finafloxacin**	**Vehicle**	**Finafloxacin vs. Vehicle Difference (95% CI)[b]**
Pathogen + Subset	4.0	7.0	-3.0 (-5.0, -0.8)[b]	3.0	6.5	-3.6 (-5.0, -2.0)[b]
Culture + Subset	4.0	5.0	-1.0 (-2.0, 0.0)[b]	3.0	5.5	-2.3 (-3.0, -1.0)[b]

[a] 95% CI calculated based on normal approximation to binomial data.
[b] Difference and 95% confidence interval estimated using bootstrap procedure with 10,000 bootstrap samples, non-stratified analysis.

Source: Tables 11.4.1.3-2, 11.4.1.2-1, 14.2-24, 14.2-93, and 14.2-94 of Study C-10-018 report; and Tables 11.4.1.3-2, 11.4 1 2-1, 14.2-24, 14.2-89, and 14.2-90 of Study C-10-019 report.

5.3 Conclusions and Recommendations

In conclusion, Finafloxcin otic suspension 0.3% is superior to Vehicle in terms of:

- The percentage of patients who achieved a clinical cure at Day 11 (the TOC visit);
- The percentage of patients who achieved microbiological success at the TOC visit;
- And the median time to cessation of ear pain as reported by patients (or parents/guardians) in half (1/2) day increments.

Therefore, the statistical reviewer recommends the approval of Finafloxcin otic suspension 0.3% for the treatment of AOE.

5.4 Labeling Recommendations

The statistical reviewer recommended that studies' results be presented as follows for Section 14 CLINICAL STUDIES of the labeling:

In two randomized multicenter, vehicle controlled clinical trials, TRADENAME dosed four drops twice daily for 7 days was superior to its vehicle for both clinical and microbiological outcomes as well as in time to cessation of ear pain in patients with acute otitis externa (AOE).

Among 560 patients (161 with an otowick) that were pathogen positive (baseline microbiological specimen that contained Staphylococcus aureus and/or Pseudomonas aeruginosa), clinical cure on Day 11 was (b) (4) *in TRADENAME versus* (b) (4) *in Vehicle. Among* (b) (4) [redacted]

Clinical Cures at Day 11 (Pathogen Positive Subset, and Culture Positive Subset)

	Study 1			*Study 2*		
	TRADENAME	***Vehicle***	***TRADENAME vs. Vehicle Difference (95% CI)[a]***	***TRADENAME***	***Vehicle***	***TRADENAME vs. Vehicle Difference (95% CI)[a]***
Pathogen + Subset	*104/145 (71.7%)*	*46/138 (33.3%)*	*38.4% (27.6%, 49.1%)*	*101/147 (68.7%)*	*52/130 (40.0%)*	*28.7% (17.4%, 40.0%)*
[redacted]						(b) (4)

Among the pathogen positive patients, microbiological success (eradication of all baseline organisms) was achieved on Day 11 in 67% (b) (4) *in TRADENAME versus 13%* (b) (4) *in the Vehicle treated patients.* (b) (4) [redacted]

Microbiological Success at Day 11 (Pathogen Positive Subset, [redacted])

	Study 1			Study 2		
	TRADENAME	*Vehicle*	*TRADENAME vs. Vehicle Difference (95% CI)*	*TRADENAME*	*Vehicle*	*TRADENAME vs. Vehicle Difference (95% CI)[a]*
Pathogen + Subset	*97/145 (66.9%)*	*18/138 (13.0%)*	*53.9% (44.4%, 63.4%)*	*97/147 (66.0%)*	*15/130 (11.5%)*	*54.4% (45.0%, 63.9%)*
[redacted]						

The median time to cessation of ear pain in pathogen positive patients treated with TRADENAME was [redacted] days compared to [redacted] days in Vehicle. [redacted] the median time to cessation of ear pain in [redacted] patients treated with TRADENAME was [redacted] days compared to [redacted] days in Vehicle.

Median Time (day) to Cessation of Ear Pain (Pathogen Positive Subset, and [redacted])

	Study 1			Study 2		
	TRADENAME	*Vehicle*	*TRADENAME vs. Vehicle Difference (95% CI)*	*TRADENAME*	*Vehicle*	*TRADENAME vs. Vehicle Difference (95% CI)*
Pathogen + Subset	*4.0*	*7.0*	*-3.0 (-5.0, -0.8)*	*3.0*	*6.5*	*-3.6 (-5.0, -2.0)*
[redacted]	*4.0*	*5.0*	*-1.0 (-2.0, [redacted])*	*3.0*	*5.5*	*[redacted] (-3.0, -1.0)*

The applicant also proposed to include efficacy results for a subset of patients who had [redacted] at baseline in the clinical studies section of the label. The applicant [redacted] Although the results of this subset were statistically significant, [redacted] had any clinical significance was beyond the scope of this statistical review. Therefore, the statistical reviewer would like to defer the decision of including efficacy results for this subset in the final label to the clinical review team.

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/s/

YUNFAN DENG
09/24/2014

YAN WANG
09/24/2014
Concur with overall conclusion.