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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA # :	208251, SDN 1
Drug Name:	Otovel (cipro 0.3%/fluocinolone 0.025%)
Indication:	Acute Otitis Media with Tympanostomy Tubes in patients aged 6 months and older
Applicant:	SALVAT
Stamp Date:	June 30, 2015
PDUFA Goal Date:	April 30, 2016
Priority or Standard:	Standard
Formulation	Otic Drops
Dosing Regimen	0.25 mL instilled into the affected ear canal twice daily for 7 days
Reviewer Completion Date:	April 13, 2016
Biometrics Division:	Division of Biometrics IV
Medical Division:	Division of Anti-Infective Products (DAIP)
Documents Reviewed:	NDA 208251, \\Cdsesub1\evsprod\NDA208251
Statistical Reviewer:	Christopher Kadoorie, PhD
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1. EXECUTIVE SUMMARY

Studies 02 & 04 with identical designs both met their respective primary objectives of demonstrating the contribution of both the antimicrobial (cipro) and steroid (fluocinolone acetonide) components in the proposed combination drug product, Otovel (cipro with fluocinolone acetonid or CIPRO+FLUO). Both studies also met their respective secondary objectives of demonstrating the contribution of the cipro component by showing the superiority of ciprofloxacin 0.3% with fluocinolone acetonide 0.025% over fluocinolone acetonide 0.025% alone (i.e. CIPRO+FLUO superior to FLUO alone) and the superiority of ciprofloxacin 0.3% alone over fluocinolone acetonide 0.025% alone (i.e. CIPRO alone superior to FLUO alone). In addition to meeting primary and secondary study objectives, Reviewer sensitivity analyses found that primary and secondary analysis findings for efficacy were robust across a variety of assumptions. Reviewer analyses also did not identify any major efficacy, safety or integrity related issues which could compromise overall findings. Only a few minor statistical issues are discussed in **Section 5.1**. The Reviewer considers the overall evidence of efficacy and safety to be acceptable in supporting the use of Otovel in the treatment of pediatric patients with AOMT.

The primary analyses in Studies 02 & 04 were conducted in the clinical intent to treat (CITT) population consisting of all randomized patients assigned to treatment therapy. Primary analyses from both of the studies were observed to be consistent. Both studies showed a reduction in time to cessation of otorrhea with the addition of either the CIPRO or FLUO component with the largest reductions occurring from the addition of the CIPRO component (**Table 5**).

In the Study 02 primary analyses, the median time to cessation of otorrhea was shorter in the CIPRO+FLUO arm at 3.8 days (95% CI: 3.0, 4.4) versus the CIPRO arm at 7.7 days (95% CI: 4.8, 11.4). The median time to cessation in the FLUO arm was not estimable (NE) due to the majority (or 51.8%) of patients failing to achieve cessation and being censored, however, the lower 95% confidence limit of the median was 7.4 days in the FLUO arm which was longer (less favorable) than in the CIPRO+FLUO arm at 3.0 days and the CIPRO arm at 4.8 days. Statistical comparisons using the log rank test showed significantly shorter times to cessation (i.e. the superiority) for CIPRO+FLUO vs. CIPRO alone ($p < 0.001$) and for CIPRO+FLUO vs. FLUO alone ($p < 0.001$). Rates of cessation (the percentage of patients achieving cessation by the end of the study, Day 22) showed similar trends in efficacy across the treatment arms at 88/112 (78.6%) in the CIPRO+FLUO arm, 73/109 (67.0%) in the CIPRO arm and 53/110 (48.2%) in the FLUO arm.

In Study 04 primary analyses, the median time to cessation of otorrhea was shorter in the CIPRO+FLUO arm at 4.9 days (95% CI: 3.7, 5.5) versus the CIPRO arm at 6.8 days (95% CI: 5.5, 7.7). The median time to cessation in the FLUO arm was not estimable due to the majority (or 56.5%) of patients being censored, however, the lower 95% confidence limit of the median was 13.9 days which was longer than in the CIPRO+FLUO arm at 3.7 days and the CIPRO arm at 5.5 days. Statistical comparisons using the log rank test showed the

superiority of CIPRO+FLUO vs. CIPRO alone ($p = 0.028$) and the superiority of CIPRO+FLUO vs. FLUO alone ($p < 0.001$). Rates of cessation showed similar trends in efficacy across treatments at 87/111 (78.4%) in the CIPRO+FLUO arm, 77/112 (68.8%) in the CIPRO arm and 47/108 (43.5%) in the FLUO arm.

The (principal) secondary analyses in Studies 02 & 04 were conducted in the microbiological ITT (MITT) population which included all CITT subjects with a baseline culture that yielded one or more pathogens from ear discharge. In both studies, the addition of the antimicrobial (cipro) component resulted in higher sustained microbiological cure rates (**Table 6**). A 'sustained microbiological cure' was defined as the eradication or presumed eradication in the per subject microbiological response at both Visit 3 and Visit 4. Secondary analyses in Studies 02 & 04 provided consistent results that clearly showed the contribution of the CIPRO component in pre-specified comparisons of CIPRO+FLUO vs. FLUO alone and CIPRO alone vs. FLUO alone. Although these analyses did not pre-specify a statistically controlled test for the contribution of the FLUO component (CIPRO+FLUO vs. CIPRO alone), post-hoc comparisons in both studies were observed to numerically (but not statistically) favor CIPRO+FLUO over CIPRO alone.

In Study 02 secondary analyses, sustained microbiological cure rates based on observed cases were 47/61 (77.0%) in the CIPRO+FLUO arm, 41/63 (65.1%) in the CIPRO arm and 23/52 (44.2%) in the FLUO arm. Statistical comparisons using the stratified Cochran-Mantel-Haenszel (CMH) test (i.e. CMH test stratified by age group: < 3 years and ≥ 3 years) showed the statistical superiority of CIPRO+FLUO vs. FLUO alone ($p < 0.001$) and CIPRO alone vs. FLUO alone ($p = 0.017$). In Study 04 secondary analyses, sustained microbiological cure rates based on observed cases were 47/57 (82.5%) in the CIPRO+FLUO arm, 43/61 (70.5%) in the CIPRO arm and 18/57 (31.6%) in the FLUO arm. Statistical comparisons based the stratified CMH test showed findings of statistical superiority for CIPRO+FLUO vs. FLUO alone ($p < 0.001$) and CIPRO alone vs. FLUO alone ($p < 0.001$).

2. INTRODUCTION

2.1 Overview

Background

SALVAT is seeking approval of Otovel, a combination of a fluroquinolone antimicrobial and a corticosteroid comprising ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% for the treatment of pediatric patients aged 6 months to 12 years with Acute Otitis Media with Tympanostomy Tubes (AOMT). To support the efficacy and safety of Otovel, SALVAT has submitted results from two pivotal, randomized, double-blind multi-center studies (Studies CIFLOTIII/10A02 and CIFLOTIII/10A04 in AOMT, hereafter referred to as Studies 02 & 04). Each of these studies included three treatment arms in order to establish the contribution of both the antimicrobial and steroid components.

Studies 02 & 04 were both superiority studies evaluating the primary endpoint of time to cessation of otorrhea and principal secondary endpoint of sustained microbiological cure in the clinical intent-to-treat (CITT) population.

Reviewer Comment: (b) (4)

Currently, there are two FDA approved treatments for AOMT: Ofloxacin otic solution and CIPRODEX (ciprofloxacin 0.3% with dexamethasone 0.1% otic suspension) in children aged 6 months and older. Ciprofloxacin, the proposed active ingredient, is also currently marketed for use by itself or in combination with a corticosteroid for the treatment of AOE (e.g. Ciprofloxacin 0.2% otic solution, Cipro HC and Ciprodex).

Class and Indication

The proposed drug product is Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution, which is a combination of two active substances: Ciprofloxacin hydrochloride and Fluocinolone acetonide. Ciprofloxacin hydrochloride is a well-characterized fluoroquinolone and Fluocinolone acetonide is a synthetic corticosteroid.

The Applicant seeks the following indication: Treatment of acute otitis media in pediatric patients (aged 6 months and older) with tympanostomy tubes (AOMT) due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa.*

History of Product Development

The following is a timeline of some of the notable events in the history of product development for Otovel for (b) (4) AOMT:

- **Early 2010:** The applicant developed a phase III clinical development program in subjects with AOMT.
- **July 6, 2010:** A Pre-IND meeting was held with the Agency. The Agency recommended conducting two adequate and well controlled studies to support an approval and that the studies would be expected to demonstrate the superiority of the combination over each of the individual components.
- **December 20, 2010**: The original IND (IND 107809) was submitted for ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution.

- **March 17, 2011**: SALVAT resubmitted a Special Protocol Assessment (SPA), following Agency recommendations. These recommendations included showing superiority in time to cessation of otorrhea for both components in the ITT population (primary endpoint) and showing a sustained microbiological eradication rate in each of the ciprofloxacin-containing arms compared to the fluocinolone arm at end of treatment (EOT) and test of cure (TOC) (secondary endpoint).

- **May 2, 2011**: SPA agreement reached.

- (b) (4)

  (b) (4)

- **June 30, 2015***:* The Sponsor submitted the NDA for the AOMT (b) (4) .

- (b) (4)

Brief Overview of Pivotal Trials 02 & 04

The following overview is based on the synopsis provided by the Applicant in the clinical study report. The submission included two identical Phase 3 trials for AOMT, Trials 02 & 04:

Table 1: Identical Phase 3 Trials for AOMT (Trials 02 & 04)

Type of Trials:	Phase 3 multicenter, randomized, double-blind comparative trials to evaluate the safety and efficacy of CIPRO + FLUO in pediatric patients with AOMT.
Objective:	Demonstrate superiority of CIPRO + FLUO versus each of its components (i.e. CIPRO alone and FLUO alone) using a two-sided 0.05 significance level.
Treatment Arms:	Three arms: CIPRO + FLUO, CIPRO, FLUO, otic administration BID.
Sample Size:	331 CITT patients included in each trial.
Primary Endpoint:	Time to cessation of otorrhea in CITT subjects.
Main Inclusion Criteria.	Patients 6 months to 12 years of age having the following: A patent and open tympanostomy tube in the ear that was to be treated, Otorrhea for 3 weeks or less, Moderate or severe purulent otorrhea at inclusion.
Trial Design:	Patients who met the entry criteria were randomly assigned in a 1:1:1 ratio to receive treatment with CIPRO + FLUO, CIPRO alone or FLUO alone. Study medication was administered to the affected ear(s) twice daily for 7 days. Enrollment was stratified by age into 2 groups (patients younger than 3 years old and patients 3 years and older). The study consisted of 4 visits: • Visit 1 at Day 1: Screening, Randomization/Enrollment, Start of treatment • Visit 2 at Day 3-5: During treatment • Visit 3 at Day 8-10: End of Treatment (EOT) • Visit 4 at Day 18-22: Post-treatment/Follow-up, Test of Cure (TOC).
Statistical Methods:	The primary endpoint of 'time to cessation of otorrhea' was estimated using Kaplan-Meier methods and the results were plotted. The treatment groups were compared using the log-rank test stratified by age (patients younger than 3 years old versus patients 3 years and older).

Source: Reviewer Table

Reviewer Comments: *All tables and figures included in this review apply to Trials 02 & 04 unless otherwise stated.*

2.2 Data Sources

The Reviewer primarily considered the clinical summary of efficacy, clinical study reports and selected datasets which are described below for Trials 02 & 04 along with their links. The data formats used in this submission were SDTM and ADAM.

- Clinical Summary of Efficacy :
  - \\Cdsesub1\evsprod\NDA021883\1078\m2\27-clin-sum
- Clinical Study Reports:
  - \\Cdsesub1\evsprod\NDA208251\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acuteotitismedia\5351-stud-rep-contr\ciflotiii-10ia02
  - \\Cdsesub1\evsprod\NDA208251\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acuteotitismedia\5351-stud-rep-contr\ciflotiii-10ia04

Datasets:

- \\Cdsesub1\evsprod\NDA208251\0001\m5\datasets\ciflotiii-10ia02\analysis\adam\datasets
- \\Cdsesub1\evsprod\NDA208251\0001\m5\datasets\ciflotiii-10ia04\analysis\adam\datasets

Datasets of primary interest in Trials 02 & 04 included the following:

- adsl.xpt- Subject Level
- adcm.xpt- Concomitant Medications
- adtte.xpt- Data for Time to Event Analyses
- adisa.xpt- Local signs and symptoms
- adxr.xpt- Efficacy Outcome - Clinical Response
- addv.xpt- Protocol Deviations
- adie.xpt- Inclusion/exclusion criteria not met

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the data quality was acceptable. No errors were noted in any of the submitted datasets. Datasets and variables were clearly described and well-documented. The Reviewer could successfully reproduce all major analyses.

3.2 Evaluation of Efficacy

As stated above, there are two pivotal trials in this submission, Trial CIFLOTIII/10IA02 (Trial 02) and Trial CIFLOTIII/10IA04 (Trial 04) which had identical designs. These trials had only a few minor differences such as the geographical location of the sites, the time period in which the studies conducted and the sample sizes of the individual treatment arms.

Trial 02 was titled "A Multicenter, Randomized, Double-Blind Clinical Trial to Assess the Efficacy and Safety of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution Compared to Ciprofloxacin 0.3% Otic Solution and to Fluocinolone Acetonide 0.025% Otic Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT) in Pediatric Patients." This trial was conducted from July 2011 to June of 2014 in forty-six sites (33 in the United States, 6 in South Africa, 3 in Spain, 1 in the Czech Republic, 1 in Denmark, 1 in Finland, and 1 in Sweden). This trial included a total of 331 randomized subjects (112 in the CIPRO+FLUO arm, 109 in the CIPRO arm and 110 in the FLUO arm).

Trial 04 had the same title and was conducted during a similar time frame, from August 2011 to May 2013. It was conducted in forty-nine sites (35 in the United States, 6 in

South Africa, 5 in Spain, 2 in Canada, and 1 in Finland). This trial also included a total 331 subjects, however, they were randomized slightly differently among the three treatment arms (111 in the CIPRO+FLUO arm, 112 in the CIPRO arm and 108 in the FLUO arm).

Reviewer Comments: *Some of the sites (i.e. 15 sites) that completed participation in the 02 study were also selected to participate in the identical clinical study, Study 04. The sharing of study sites is further discussed in* ***Section 3.2.4.2*** *with the distribution of patients enrolled in each study site shown in* ***Figure 5****.*

3.2.1 Study Design and Endpoints

Study Design

These were Phase III, randomized, double-blind trials designed to assess the efficacy and safety of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution compared with Ciprofloxacin 0.3% otic solution and to Fluocinolone Acetonide 0.025% otic solution in the treatment of AOMT in pediatric patients.

Each of these trials included 331 randomized patients. Patients were aged 6 months to 12 years (less than 13 years) with uncomplicated AOMT in at least one ear.

Patients who met entry criteria were randomly assigned in a 1:1:1 ratio to receive one of the following:

- Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution
- Ciprofloxacin 0.3% otic solution
- Fluocinolone Acetonide 0.025% otic solution.

Study medication was administered to the affected ear(s) twice daily for 7 days. Enrollment was stratified by age into 2 groups (patients younger than 3 years old and patients 3 years and older).

Study Objectives

- **Primary Objective**: Show superiority of CIPRO + FLUO over each of its components (i.e. CIPRO alone and FLUO alone) for the primary endpoint of Time to cessation of otorrhea.

- **Secondary Objective**: Show superiority of CIPRO + FLUO over FLUO alone and CIPRO alone over FLUO alone for the principal secondary endpoint of Sustained microbiological cure.

Inclusion/Exclusion Criteria:

The Reviewer's summary of the inclusion/exclusion criteria for enrollment into the studies are provided below:

Inclusion criteria
1. Patient between 6 months and 12 years of age (both inclusive)
2. Patients with patent tympanostomy tube in the ear that was to be treated
3. Patients suffering from otorrhea for 3 weeks or less
4. Moderate or severe purulent otorrhea at inclusion
5. Signed informed consent from patient or patient's legally authorized representative

Exclusion criteria
1. Tympanostomy tube placement 3 days or less before study entry
2. Tympanostomy tubes containing antiseptic or antibacterial activity (silver oxide or silver salts), T-type tubes
3. Acute otitis externa or malignant otitis externa
4. Suspected viral, fungal, or mycobacterial ear infection
5. Otologic surgery within the previous year (other than tympanostomy tube placement)
6. Mastoiditis
7. Known or suspected quinolone and/or corticoids hypersensitivity
8. History of an immunosuppressive disorder, current immunosuppressive therapy, or diabetes
9. Acute or chronic renal disease, active hepatitis
10. Chronic nasal obstruction and/or persistent rhinorrhea
11. Craniofacial anomalies
12. Patient predisposed to neurosensory hearing loss
13. Use of topical non-steroidal otic agents within 1 day of study entry.
14. Use of topical or otic steroids within 3 days of enrollment or systemic steroids within 7 days of enrollment
15. Use of intranasal or inhaled steroids within 3 days of enrollment
16. Any infection requiring systemic antimicrobial therapy
17. Use of topical or systemic antimicrobial or antifungal agents within the previous 7 days of study entry or antimicrobial therapy for the current episode of AOMT
18. Concurrent use of oral anti-inflammatory agents, except ibuprofen

Visit Schedule

The study consisted of 4 visits:

- Visit 1 at Day 1: Screening, Randomization/Enrollment, Start of treatment
- Visit 2 at Day 3-5: During treatment
- Visit 3 at Day 8-10: End of Treatment (EOT)
- Visit 4 at Day 18-22: Post-treatment/Follow-up, Test of Cure (TOC)

Table 2 provides a summary of the observations and assessments that occurred at each study visit in Trials 02 and 04.

Table 2: Schedule of Observations and Assessments, Trials 02 and 04

Evaluation	Visit 1 Screening/ Study Entry	Visit 2 On treatment	Visit 3 End of Treatment	Visit 4 Post-Treatment Follow-Up
Study Day	**1**	**3-5**	**8-10**	**18-22**
Informed consent	X			
Inclusion/exclusion criteria	X			
Medical history	X			
Concurrent symptoms/conditions	X			
Physical examination	X	X	X	X
Signs and symptoms of otitis	X	X	X	X
Audiometric evaluation	X			X
Clinical response		X	X	X
Pharmacokinetic sample collection	X		X	
Microbiological culture of ear discharge	X		X	X
Randomization through IWRS	X			
Dispense study medication, explain its use	X	X		
Collect used/unused study medication containers			X	
Dispense diary card and explain its use	X			

Source: Partially Adapted from Applicant's Table in Study Report.

Analysis Populations:

The protocol defined five analysis populations. The CITT population was the primary population used for the assessment of efficacy and will be the focus of this review.

Clinical Intent-to-Treat (CITT) population: all patients who were randomly assigned to study medication.

Clinical Per-Protocol (CPP) population: all CITT patients who did not have any major protocol deviations leading to exclusion from the CPP population.

Microbiological Intent-to-Treat (MITT) population: The MITT population included all CITT patients who had a baseline (Visit 1) microbiological culture that yielded one or more pathogens from ear discharge.

Microbiological Per-Protocol (MPP) population: all CPP patients who had a baseline (Visit 1) microbiological culture that yielded one or more pathogens and who had microbiological results (when patient had material to culture) from Visit 3 and/or Visit 4. Patients who had an infection that resolved to the extent that no culturable exudate was available were included in the MPP. Patients who were deemed a clinical failure at an earlier visit than Visit 4 were also included.

Safety population: all patients who received any amount of study medication.

Primary Efficacy Endpoint:

The primary efficacy endpoint was to demonstrate the superiority of CIPRO+FLUO over CIPRO alone and the superiority of CIPRO+FLUO over FLUO alone for time to cessation of otorrhea in patients suffering from AOMT. Otorrhea was defined as ending on the first day on which the otorrhea was absent and remained absent until the end of the study.

Caregivers evaluated the presence of otorrhea twice daily (just prior to each dose administration during the treatment period) each day during study participation and entered this information in the diary card.

Investigators used diary card information together with the information gathered during the otoscopic examination to ascertain the time to cessation of otorrhea. Caregiver observations and the status of the tympanostomy tube (blockage, presence, permeability, etc) were taken into account. This information was recorded in the eCRF and used for the primary endpoint calculation (time to cessation of otorrhea).

At the end of study, the investigator chose one of the following options:

- Otorrhea still persists
- Otorrhea finished on dd/mmm/yyy at hh:mm

Principal Secondary Endpoint:

The principal secondary endpoint was to demonstrate the superiority of CIPRO+FLUO over FLUO alone and the superiority of CIPRO alone over FLUO alone with respect to sustained microbiological cure. A 'sustained microbiological cure' was defined as a favorable response (i.e. the eradication or presumed eradication in the per subject microbiological response) at both Visit 3 and Visit 4. 'Per-Patient Microbiological Response' is described further below:

Per-Patient Microbiological Response

Each investigator rendered a patient bacteriologic response based on the definitions provided in the protocol, but the sponsor's assessment was used in the analysis. During the Sponsor medical review, the per-patient microbiological response at Visit 3 and Visit 4 was determined by the per-pathogen microbiological outcomes as follows:

- For patients from whom only 1 pathogen was isolated, the patient microbiological response was based on the assessment for that pathogen.
- For patients from whom more than 1 pathogen was isolated, the patient microbiological response reflected the worst response present amongst all baseline pathogens.

For each patient, the microbiological response was further summarized as 'Favorable', 'Unfavorable' or 'Indeterminate' as follows:

Favorable

- Eradication
- Presumed Eradication: Elimination or reduction of all baseline/study entry

pathogen(s) in accordance with the definitions for pathogen eradication or presumed eradication.

Unfavorable

- Persistence
- Presumed Persistence: Microbiological response of persisted or presumed persisted of any admission pathogen(s)
- Superinfection: Presence of a pathogen at Visit 3 not present at Visit 1 (presence of a non-pathogenic organism was not considered superinfection)
- Reinfection: Presence of a new pathogen at Visit 4 different from the one eradicated or presumably eradicated at Visit 3
- Recurrence: Reappearance of a pathogen eradicated or presumably eradicated at Visit 3

Indeterminate

- Indeterminate: Entry culture either not obtained or no baseline pathogen identified
  - No culture obtained because patient was lost to follow-up or withdrew from the study prematurely.
  - Microbiologic response could not be assessed for a patient who was clinically improving but took potentially effective non-study systemic concomitant antibacterial therapy for an indication other than otitis media.

Other Secondary Efficacy Endpoints:

Clinical Response

The investigator made the assessment of clinical response for each patient at Visits 2, 3, and 4. Clinical response categories included the following:

- Clinical Success: complete resolution of clinical signs (otorrhea, eardrum edema, otalgia, and eczema of the external auditory) that were present at baseline and absence of any new findings. Granulation tissue was no worse in comparison with baseline.

- Clinical Failure:
  - Worsened: signs and symptoms of otitis media that warranted change in antimicrobial theapy or development of complications of AOMT (e.g. mastoiditis or meningitis)
  - Not changed: clinical signs or symptoms were unchanged compared with baseline
  - Improved: significant improvement without complete resolution in clinical signs or symptoms compared with baseline

Other Efficacy Assessments

- Volume of Otorrhea, Granulation tissue, Type/Color of Otorrhea, Eardrum Edema, Pain (Otalgia), Eczema of the External Auditory Canal, Presence of Tympanostomy Tubes were assessed at Visits 1, 2, 3 and 4 by the investigator.
- Quality of Life Questionnaire OM-6 was completed by the caregiver at Visits 1, 3, and 4.

- The AOM-SOS questionnaire was completed by the caregiver twice daily during the whole study.

Safety Endpoints:

Safety was assessed by AE incidence, physical examination (including vital signs), audiometric assessments, and Ciprofloxacin and/or Fluocinolone Acetonide plasma levels.

Sample Size Determination:

The sample size was determined based on a clinical trial comparing Ciprofloxacin plus dexamethasone with Ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea with tympanostomy tubes, as reported by Roland (2003). Based on Roland's Table II which gave summary statistics for the number of patients with cessation of otorrhea (without recurrence) at Day 3 and Day 8, a total of 90 microbiological patients per group would be necessary for a two-sided log-rank test stratified by age (younger than 3 years old, 3 years and older) at a significance level of 0.05% to have 90% power.

Prior Medication:

Prior medication was defined as any medication taken within the prior 30 Days of Visit 1 and stopped prior to Visit 1. Patients were asked to identify any prior medications used on Visit 1.

Concomitant Medication:

Concomitant medication was defined as any medication taken after Visit 1. Patients were asked to identify any concomitant medications used on Visits 2, 3 and 4. 'Effective concomitant therapy' was defined as any otic or systemic treatment with an antibacterial or other therapy that had the potential for interfering with the assessment of the study medication's performance in the patient. For systemic antibacterial or steroid treatment this included therapies administered for reasons not associated with otitis media. Treatment for otitis media would be considered a treatment failure.

The Applicant states that the following concomitant medications were prohibited during the study:

- Topical non-steroidal otic agents,
- Topical or otic steroids and systemic steroids, intranasal or inhaled steroids,
- Topical (when applied to the ear or surrounding area) or systemic antimicrobial or antifungal agents,
- Oral or topical anti-inflammatory agents, except ibuprofen (analgesics without anti-inflammatory properties, such as acetaminophen, were allowed),
- Antihistamines and decongestants,
- Any investigational drug,
- Drugs for curative treatment of otitis externa or otitis media,
- Any compound, agent, or substance that was applied to the external ear or instilled in the ear canal, other than study medication.

3.2.2 Subject Disposition, Demographic and Baseline Characteristics

Table 3 shows the disposition of randomized patients in Trials 02 and 04. Both trials included 331 randomized patients and showed similar overall rates with respect to the percentage of CITT patients included the Safety, CPP, MITT and MPP analysis populations. Study completion rates in Trials 02 & 04 respectively were observed to be highest in the CIPRO+FLUO arm (92.9% & 95.5%) and slightly lower in the CIPRO arm (90.8% & 92.9%) and substantially lower in the FLUO arm (82.7% & 82.4%). The percentage of CITT patients included in the MITT population was similar across the trials (58.9% & 56.5%). There were no other notable observations with respect to patient disposition across treatment arms and between trials.

Table 3: Disposition of Randomized Patients (CITT)

	CIPRO+FLUO	CIPRO	FLUO	Total
Trial 02				
Randomized (CITT)	112 (100)	109 (100)	110 (100)	331 (100)
Safety	113[1] (100)	108 (99.1)	106 (96.4)	327 (98.8)
CPP	83 (74.1)	80 (73.4)	82 (74.5)	245 (74.0)
MITT	65 (58.0)	70 (64.2)	60 (54.5)	195 (58.9)
MPP	49 (43.8)	54 (49.5)	45 (40.9)	148 (44.7)
Completed Study	104 (92.9)	99 (90.8)	91 (82.7)	294 (88.8)
Trial 04				
Randomized (CITT)	111 (100)	112 (100)	108 (100)	331 (100)
Safety	111 (100)	112 (100)	107 (99.1)	330 (99.7)
CPP	77 (69.4)	89 (79.5)	73 (67.6)	239 (72.2)
MITT	60 (54.1)	65 (58.0)	62 (57.4)	187 (56.5)
MPP	40 (36.0)	56 (50.0)	46 (42.6)	142 (42.9)
Completed Study	106 (95.5)	104 (92.9)	89 (82.4)	299 (90.3)

Source: Reviewer Table

[1]Patient 033-018 was given an incorrect kit and was included in the FLUO arm for the CITT population and the CIPRO+FLUO arm (i.e. the actual treatment arm) in the safety population.

Reviewer Comments: *The 02 study was conducted from July 2011 to June 2014 and the 04 study was conducted from August 2011 to May 2013. There were 15 sites which completed enrollment in the 02 study that were also selected to participate in the 04 study. These 15 shared sites included a combined total of 246 patients (172 patients (52%) of patients in the 02 study and 74 patients (22%) of patients in the 04 study.*

Table 4 shows the demographic and baseline characteristics in Trials 02 and 04. In Trials 02 & 04 respectively, patients were mostly male (60% & 58%), white/caucasian (75% & 80%) and non-hispanic (83% & 90%). The mean (median) age of the study population was 3.4 (2.6) years & 3.2 (2.4) years. The treatment arms appeared to be generally similar and balanced with respect to demographic and baseline characteristics.

Table 4: Demographics and Baseline Characteristics (CITT)

Demographics	CIPRO+FLUO	CIPRO	FLUO	Total
Trial 02				
	N=112	**N=109**	**N=110**	**N=331**
Gender				
Male	64 (57.1)	66 (60.6)	68 (61.8)	198 (59.8)
Female	48 (42.9)	43 (39.4)	42 (38.2)	133 (40.2)
Age (years)				
Mean ± SD	3.2 ± 2.1	3.5 ± 2.6	3.5 ± 2.4	3.4 ± 2.4
Median (min, max)	2.5 (0.6, 11.8)	2.7 (0.6, 11.6)	2.6 (0.8, 12.7)	2.6 (0.6, 12.7)
Race				
White/Caucasian	81 (72.3)	79 (72.5)	87 (79.1)	247 (74.6)
Black/African American	21 (18.8)	21 (19.3)	12 (10.9)	54 (16.3)
Asian	2 (1.8)	4 (3.7)	2 (1.8)	8 (2.4)
Other	8 (7.1)	5 (4.6)	9 (8.2)	22 (6.6)
Ethnicity				
Hispanic or Latino	22 (19.6)	16 (14.7)	18 (16.4)	56 (16.9)
Not Hispanic or Latino	90 (80.4)	93 (85.3)	92 (83.6)	275 (83.1)
Prior Antibiotic Use				
Yes[1]	6 (5.4%)	4 (3.7%)	6 (5.5%)	16 (4.8%)
No	106 (94.6%)	105 (96.3%)	104 (94.5%)	315 (95.2%)
Trial 04				
	N=111	**N=112**	**N=108**	**N=331**
Gender				
Male	65 (58.6)	69 (61.6)	59 (54.6)	193 (58.3)
Female	46 (41.4)	43 (38.4)	49 (45.4)	138 (41.7)
Age (years)				
Mean ± SD	3.2 ± 2.5	3.3 ± 2.4	3.2 ± 2.3	3.2 ± 2.4
Median (min, max)	2.3 (0.7, 12.7)	2.5 (0.7, 12.0)	2.2 (0.6, 12.2)	2.4 (0.6, 12.7)
Race				
White/Caucasian	86 (77.5)	89 (79.5)	89 (82.4)	264 (79.8)
Black/African American	12 (10.8)	11 (9.8)	11 (10.2)	34 (10.3)
Asian	3 (2.7)	4 (3.6)	2 (1.9)	9 (2.7)
Other	10 (9.0)	8(7.1)	6 (5.6)	24 (7.3)
Ethnicity				
Hispanic or Latino	13 (11.6)	8 (7.2)	12 (11.1)	33 (10.0)
Not Hispanic or Latino	99 (88.4)	103 (92.8)	96 (88.9)	298 (90.0)
Prior Antibiotic Use				
Yes[1]	10 (9.0%)	5 (4.5%)	2 (1.9%)	17 (5.1%)
No	101 (91.0%)	107 (95.5%)	106 (98.1%)	314 (94.8%)

Source: Partially Adapted from Applicant Table 10-1 in study report

[1] One patient in Study 02 from the CIPRO+FLUO and one patient in Study 04 from the CIPRO arm had prior antibiotic use within 48 hours of the initiation of study drug.

Reviewer Comment: *The number of patients with prior antibiotic within 48 hours of the initiation of study drug was small and was not a factor in the primary analysis.*

3.2.3 Statistical Methodologies

3.2.3.1 Statistical Methodologies (Applicant)

Primary analysis: The primary analysis was carried out on the CITT population. In order to satisfy the primary endpoint, both comparisons of the combination to the components alone must have shown the combination to be statistically superior to the component alone using a two-sided 0.05 significance level. Time to cessation of otorrhea was calculated in days as (Date/Time otorrhea ended minus Date/Time of first dose of study medication). Time to cessation of otorrhea was estimated using Kaplan-Meier estimates and results were plotted. The treatment groups were compared for time to cessation of otorrhea by using the log-rank test stratified by age (patients younger than 3 years old versus patients 3 years and older). A difference would be claimed if the null hypothesis was rejected at the two-sided 0.05 level. The Wilcoxon test was also performed as a supportive analysis.

Censoring Used in Primary Analysis: Patients who did not discontinue prematurely from the study and for whom the otorrhea still persisted at the end of the study were censored at the maximum evaluation (i.e. Day 22). Patients who discontinued for any reason were censored at the maximum evaluation (i.e. Day 22). Patients discontinued for lack of efficacy or rescue medication use were censored at the maximum evaluation (i.e. Day 22). Lost to follow-up patients were censored at the maximum evaluation (i.e. Day 22) regardless of the status of otorrhea at the last observation. Randomized and non-dosed patients were censored at the maximum evaluation (i.e. Day 22).

Robustness of Efficacy Results: To assess the robustness of the efficacy results, four sensitivity analyses were conducted. To explore the impact of missing data, the first sensitivity analysis repeated the primary analysis for the CITT population censoring all discontinued patients at Day 1, regardless of the reason for discontinuation. In the second sensitivity analysis, the primary endpoint of time to cessation of otorrhea was repeated for the MITT population. To explore the impact of the presence of viral and bacterial pathogens on the time to cessation of otorrhea in the MITT population, the third sensitivity analysis repeated the primary analysis of the primary endpoint for patients with only bacterial pathogens identified at Visit 1, and the fourth sensitivity analysis repeated the same analysis for patients with both bacterial and viral pathogens identified at Visit 1.

Multiple Comparisons Adjustment: No multiple comparison adjustments were needed in these trials. Demonstration of the contribution of both components had to be shown in order to satisfy the primary objective.

Covariates: The Sponsor's log rank test did not include any covariates.

Principal Secondary Analyses: The Sponsor's secondary objective was to demonstrate therapeutic superiority of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% over Fluocinolone Acetonide 0.025% alone as well as to demonstrate therapeutic superiority of Ciprofloxacin 0.3% alone over Fluocinolone Acetonide 0.025% alone with respect to sustained microbiological cure. Sustained microbiological cure rates were

compared among the three treatment arms by using a CMH test stratified by age (< 3 years vs. ≥ 3 years).

Missing Data (Principal Secondary Analyses): Missing data at Visit 3 and/or at Visit 4 were replaced using last observation carried forward (LOCF). Missing data at Visit 1 and Visit 2 were not replaced. In patients who received rescue medication, missing data after receiving rescue medication were not replaced. The only exception was for the clinical 2-level response, which was set to "Failure" after use of rescue medication.

Other Secondary Analyses: Other secondary analyses of the primary endpoint, using the same methods as the primary analysis, were performed for the CPP population, for each of the 2 age strata (patients younger than 3 years versus 3 years and older) on the CITT and CPP populations, for the safety, CITT, and CPP populations that did not take out-of-specification medication, and for the CITT population for each batch of study medication. Secondary analysis of the primary endpoint was also performed for the subgroups of patients with titanium tubes and without titanium tubes in the CITT and CPP populations to evaluate time to cessation of otorrhea in the absence of any potential effect from antibacterial or antiseptic properties of titanium tubes.

Integrated Analyses: Sensitivity analyses were performed for several variables of interest among patients from Trials 02 & 04 (combined).

3.2.3.2 Statistical Methodologies (Reviewer)

The statistical methodologies of the reviewer generally followed the methodologies used by the Applicant with a few differences:

- The Reviewer primarily focused on the primary endpoint of time to cessation of otorrhea and the principal secondary endpoint of sustained microbiological cure in the CITT and MITT analysis populations, respectively, with less of an emphasis on other supportive analyses.
- The Reviewer generally disagrees with the approaches used by the Applicant for missing data in the principal secondary analysis such as consideration of observed cases only and imputation using last observation carried forward (LOCF). However, for these data, such approaches were considered acceptable since they would tend to be conservative given the patterns of missing data (i.e. CIPRO+FLUO arm had the least missing data).
- The Reviewer primarily considers sensitivity analyses separately for each trial whereas the Applicant performs several sensitivity analyses in an integrated study population (Trials 02 & 04 combined) which are presented in the summary of clinical efficacy.

3.2.4 Efficacy Results and Conclusions

3.2.4.1 Results of Applicant's Primary and Secondary Analysis

<u>Primary Analysis</u>

Table 5 shows results of the primary analysis of time to cessation of otorrhea in the CITT population. Findings were consistent across both trials. When comparing treatments in Trials 02 & 04 respectively, the median number of days at which cessation of otorrhea was achieved was 3.8 & 4.9 days for the CIPRO+FLUO arm and 7.7 & 6.8 days for the CIPRO arm. The median number of days was not estimable in the FLUO arm in either of the studies due to the majority (i.e. 51.8% & 56.5%) of patients being censored, however, the lower 95% confidence limit of the median in the FLUO arm was estimated at 7.4 & 13.9 days which was considerably longer than the lower 95% confidence limit in the CIPRO+FLUO arm at 3.0 & 3.7 days and the CIPRO arm at 4.8 & 5.5 days. When performing statistical testing using the log rank test, results showed the superiority of CIPRO+FLUO vs. CIPRO (p-value < 0.001 in Trial 02, p-value =0.028 in Trial 04) and the superiority of CIPRO+FLUO vs. FLUO (p-value < 0.001 in both trials). Similar findings were observed when using Wilcoxon test.

Cessation rates in Trials 02 & 04, respectively, showed similar trends in efficacy across the treatment arms at 78.6% & 78.4% in the CIPRO+FLUO arm, 67.0% & 68.8% in the CIPRO arm and 48.2% to 43.5% in the FLUO arm. The results of these analyses supported the Sponsor's primary objective of demonstrating the contribution of both the CIPRO component and the FLUO component in the combination drug product (CIPRO+FLUO).

Reviewer Comment: *No adjustment for multiplicity is needed in these analyses since the Applicant must show the contribution of both components in order to satisfy the primary objective.*

Table 5: Primary Analysis: Time to Cessation of Otorrhea (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Number (%) of patients censored at Day 22 (no cessation of otorrhea)	24 (21.4%)	36 (33.0%)	57 (51.8%)
Time to cessation of otorrhea (days): Mean (SE) Median (95% CI)	 6.9 (0.61) 3.8 (3.0, 4.4)	 10.8 (0.78) 7.7 (4.8, 11.4)	 12.6 (0.77) NE (7.4, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)
Number of patients censored (no cessation of otorrhea)	24 (21.6%)	35 (31.3%)	61 (56.5%)

Time to cessation of otorrhea (days): Mean (SE) Median (95% CI)	 7.6 (0.63) 4.9 (3.7, 5.5)	 10.5 (0.78) 6.8 (5.5, 7.7)	 13.7 (0.70) NE (13.9, NE)
Log rank test p-value[1]		0.028	< 0.001
Wilcoxon test p-value[2]		0.018	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Reviewer Comment: *Kaplan-Meier methods were used in the primary analysis with the assumption that patients who did not achieve cessation would be censored at Day 22 (i.e. end of study). Using this methodology, time to cessation based on the median number of days (with 95% confidence limits) and the mean number of days (with standard error) could be estimated. However, since the time variable may not follow a normal distribution, estimates made using the median number of days was considered to be more informative. Therefore, Reviewer sensitivity and subgroup analyses do not report mean changes in time to cessation of otorrhea but rather median changes with the corresponding 95% CI.*

Figure 1 shows the cumulative percentage patients in each treatment arm of Trial 02 achieving cessation of otorrhea over the study period (22 days). The CIPRO+FLUO arm showed the highest rates of cessation over the study period after 2 days (or by start of Day 3) through Day 22. The difference in cessation rates between CIPRO+FLUO and the other arms appeared to be substantial throughout most of the trial. The CIPRO arm showed cessation rates that were higher than in the FLUO arm and tended to widen after 4 days (or by the start of Day 5) through Day 22. Overall, patients tended to achieve their cessation within the first 10 days of the trial with only a few subjects achieving cessation after 10 days.

Figure 1: Comparison of the Percentage of Patients in Each Study Arm Achieving Cessation of Otorrhea Over Time, Trial 02

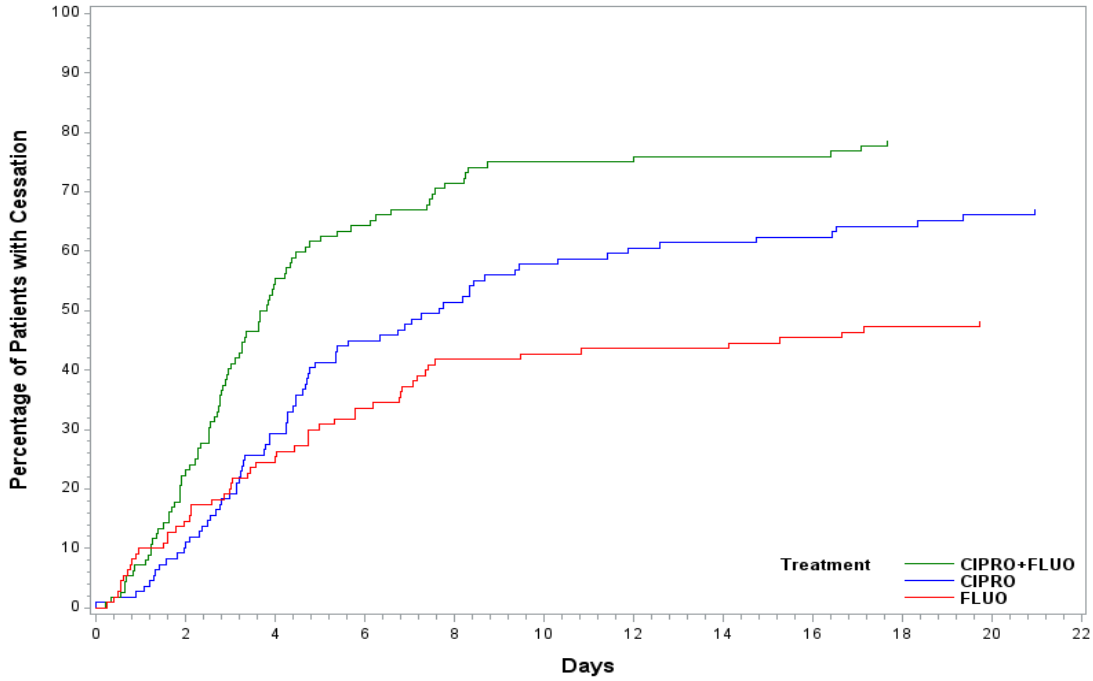
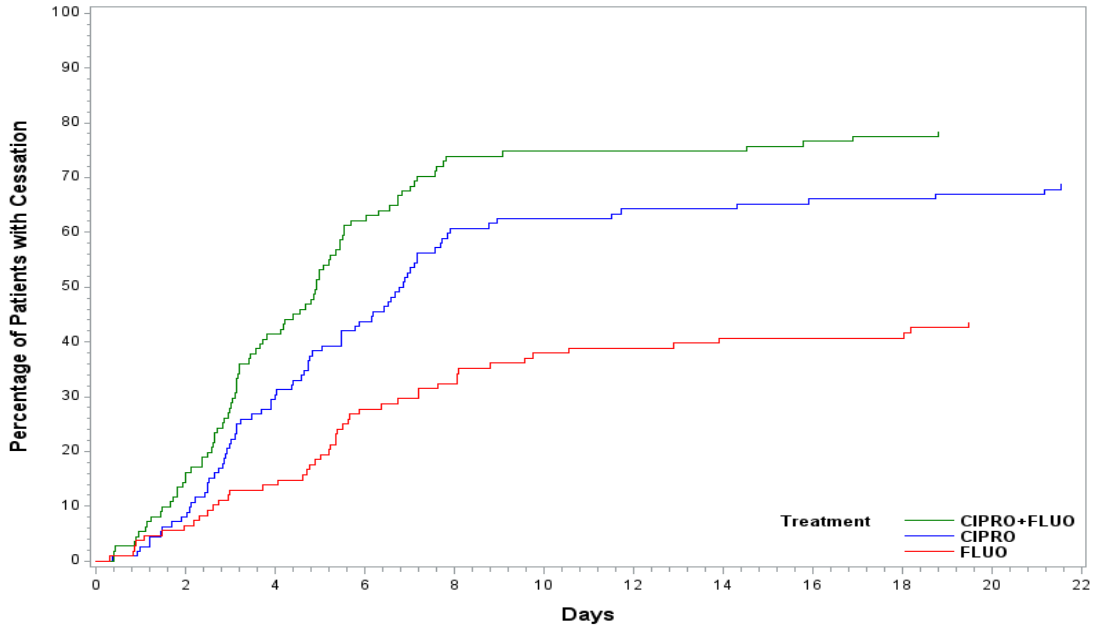


Figure 2 shows the percentage patients in each treatment arm of Trial 04 achieving cessation of otorrhea over the study period (22 days). The CIPRO+FLUO arm showed the highest rates of cessation after 1 day (or by the start of Day 2) through Day 22. The difference in cessation rates between CIPRO+FLUO and the other arms appeared to be substantial throughout most of the study period. The CIPRO arm showed cessation rates that were higher than in the FLUO arm after 2 days (or by the start of Day 3) through Day 22. The CIPRO arm was observed to perform relatively better against the other arms in Trial 04 compared to Trial 02. Similar to Trial 02, patients in Trial 04 tended to achieve their cessation within the first 10 days of the trial with only a few subjects achieving cessation after 10 days.

Figure 2: Comparison of the Percentage of Patients in Each Study Arm Achieving Cessation of Otorrhea Over Time, Trial 04



Source: Reviewer Figure

Principal Secondary Analysis

The Principal Secondary Analysis was considered by the Applicant to be the only confirmatory secondary analysis with all other secondary analyses being considered as supportive. The principal secondary endpoint considered in this analysis was sustained microbiological cure. Sustained microbiological cure was defined as Eradication or Presumed Eradication in the per-patient microbiological response at both Visit 3 and Visit 4. The primary analysis of sustained microbiological cure was performed on the MITT population.

As shown in **Table 6**, the MITT analysis in Trial 02 showed sustained microbiological cure rates of 47/61 (77.0%) of patients in the CIPRO+FLUO group, 41/63 (65.1%) in the CIPRO group, and 23/52 (44.2%) of patients in the FLUO group. Pairwise comparisons of the CMH test, stratified by age showed a statistically significant difference in sustained microbiological cure between the CIPRO+FLUO group compared with the FLUO group ($p < 0.001$) and for the CIPRO group compared with the FLUO group ($p = 0.017$).

In Trial 04, microbiological cure rates were 47/57 (82.5%) in the CIPRO+FLUO group, 43/61 patients (70.5%) in the CIPRO group, and 18/57 patients (31.6%) in the FLUO group. Pairwise comparisons showed a significant difference in sustained microbiological cure between the CIPRO+FLUO group compared with the FLUO group ($p < 0.001$) and for the CIPRO group compared with the FLUO group ($p < 0.001$).

Table 6: Principal Secondary Endpoint Analysis: Sustained Microbiological Cure Rate in Observed Subjects (MITT)

Trial 02	CIPRO+FLUO (N = 65)	CIPRO (N = 70)	FLUO (N = 60)
Sustained Cure, n/N_{obs} (%)	47/61 (77.0)	41/63 (65.1)	23/52 (44.2)
No Sustained Cure, n/N_{obs} (%)	14/61 (23.0)	22/63 (34.9)	29/52 (55.8)
Missing, n/N_{MITT} (%)	4/65 (6.2)	7/70 (10.0)	8/60 (13.3)
p-value[1] vs. CIPRO+FLUO		0.173	< 0.001
p-value[2] vs. CIPRO			0.017
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Sustained Cure, n/N_{obs} (%)	47/57 (82.5)	43/61 (70.5)	18/57 (31.6)
No Sustained Cure, n/N_{obs} (%)	10/57 (17.5)	18/61 (29.5)	39/57 (68.4)
Missing, n/N_{MITT} (%)	3/60 (5.0)	4/65 (6.2)	5/57 (8.1)
p-value[1] vs. CIPRO+FLUO		0.129	< 0.001
p-value[2] vs. CIPRO			< 0.001

Source: Reviewer Table
Analysis is based on observed cases (excluding missing data) which may be conservative given the relatively low rates of missing data in the CIPRO+FLUO arm.
[1]Pairwise comparisons versus CIPRO+FLUO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)
[2]Pairwise comparisons versus CIPRO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)

3.2.4.2 Additional Reviewer Analyses

Primary Endpoint

The Reviewer conducted several additional exploratory/sensitivity analyses of the primary endpoint. These analyses were conducted in the CITT population under a variety of different assumptions. These analyses aimed to assess the robustness of primary analysis results by controlling for potential confounding variables. Findings from Reviewer exploratory/sensitivity analyses were generally supportive of findings reported for the primary analysis.

Exploratory/sensitivity analyses of the primary endpoint considered various changes of assumptions in the primary analysis:

- Analysis of rates of cessation of ottorhea (rather than time to cessation of otorrhea)
- Analysis without stratification (rather than with stratification by age group, < 3yrs and ≥ 3 yrs)
- Analysis including only uncensored patients (rather than all CITT patients)
- Analysis censoring discontinued patients at Day 1 (rather than censoring at Day 22)
- Analysis including only the MITT population (rather than the CITT population)
- Analysis including only unshared study sites (rather than all study sites)

Additional Reviewer exploratory/sensitivity analyses are shown in the **Appendix.** These analyses considered the following groups of patients:

- Per protocol patients
- Patients not using effective prior antibacterial therapies
- Patients not using prohibited concomitant antibacterial therapies
- Patients not using titanium tubes
- Patients not using out of specification study medication

Secondary Endpoint

The Reviewer conducted the following exploratory/sensitivity analyses related to the secondary endpoint:

- Microbiological outcomes at Visit 3 and Visit 4 separately
- Microbiological outcomes at Visit 3 and Visit 4 by target pathogen.

Sensitivity Analysis: Rates of Cessation of Otorrhea by Day 22

Sensitivity/exploratory analyses were performed to observe the rates of cessation of otorrhea by Day 22. These analyses assessed whether the contribution of the components observed in the primary analysis is being driven more by faster times to cessation of otorrhea or by higher rates of cessation of otorrhea by Day 22. **Table 7** and **Figure 3** shows that patients in the CIPRO+FLUO arm had the highest rates of cessation by Day 22. The rates across in Trials 02 & 04, respectively, were 78.6% & 78.4% for the CIPRO+FLUO arm, 67.0% & 68.8% for the CIPRO arm and 48.2% & 43.5% for the FLUO arm.

In both studies, statistical comparisons of CIPRO+FLUO vs. FLUO using Fisher's exact test were significant ($p < 0.001$) indicating that findings of superiority in the primary analysis were highly robust and did not depend upon whether a time component is factored in. When comparing CIPRO+FLUO vs. CIPRO, rates of cessation consistently favored CIPRO+FLUO, however, the treatment differences in Trials 02 & 04 of 11.6% & 9.6% were not significant ($p=.069$ & $p=.129$). This indicated that findings of superiority for CIPRO+FLUO vs. CIPRO in the primary analysis were less robust and were dependent upon whether a time component is factored in.

Table 7: Sensitivity Analysis: Rates of Cessation of Otorrhea by Day 22 (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Treatment Difference (95% CI)[1]		11.6% (-0.1%, 23.2%)	30.4% (18.4%, 42.4%)
Binomial test, p-value[2]		0.069	<0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number (%) of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)

Treatment Difference (95% CI)[1]		9.6% (-1.9%, 21.1%)	34.9% (22.8%, 47.0%)
Binomial test, p-value[2]		0.129	<0.001

Source: Reviewer Table

[1] Treatment difference (95% CI) of 'CIPRO+FLUO – Component'

[2] Pairwise comparisons versus CIPRO+FLUO using Fisher's exact test

Sensitivity Analysis: Primary Analysis without Stratification

Sensitivity analyses were conducted to assess the potential impact of stratification on primary analysis findings. The statistical tests used in the primary analyses, log rank test and Wilcoxon test, were stratified according the patient's age group at baseline (patients less than 3 years old and patients 3 years and older). The sensitivity analyses shown in **Table 8** consider these statistical tests without using any stratification. Findings in these analyses appeared be similar to the findings observed in the primary analysis and were not meaningfully affected by assumptions regarding stratification by age.

Reviewer Comments: *Since the initial randomization was already stratified by age group (patients less than 3 years old and patients 3 years and older), the use of statistical tests stratified by age group vs. not stratified had a minimal impact on findings.*

Table 8: Sensitivity Analysis: Time to Cessation of Otorrhea without Stratification (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Time to cessation of otorrhea (days): Median (95% CI)	3.8 (3.0, 4.4)	7.7 (4.8, 11.4)	NE (7.4, NE)
Log rank test p-value[1]		0.003	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number (%) of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)
Time to cessation of otorrhea (days): Median (95% CI)	4.9 (3.7, 5.5)	6.8 (5.5, 7.7)	NE (13.9, NE)
Log rank test p-value		0.028	< 0.001
Wilcoxon test p-value		0.019	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test without stratification

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test without stratification

Sensitivity Analysis: Uncensored Patients Only

Exploratory/sensitivity analyses were conducted to compare treatment arms with respect to reductions in time to cessation of otorrhea among only uncensored patients (i.e. those patients achieving cessation by Day 22). Although these analyses involve some clear

biases since only the patients with the most favorable outcomes are being compared and there are differences in the proportions of patients selected from each of the treatment groups, they may provide insight into the ability of the components to reduce time to cessation of otorrhea. **Table 9** shows that patients in the CIPRO+FLUO arm had the shortest time to cessation and that comparisons for CIPRO and FLUO varied across trials, showing FLUO with a shorter median time to cessation than CIPRO in Trial 02 and CIPRO as having the shorter median time to cessation than FLUO in Trial 04. These analyses indicate that the addition of either of the components may lead to modest reductions in the time to cessation in uncensored patients but it is not clear as to which component is resulting in larger reductions.

Table 9: Sensitivity Analysis: Time to Cessation of Otorrhea Using Uncensored Patients Only (CITT)

Trial 02	**CIPRO+FLUO (N = 88)**	**CIPRO (N = 73)**	**FLUO (N = 53)**
Time to cessation of otorrhea (days): Median (95% CI)	2.9 (2.6, 3.6)	4.4 (3.3, 4.9)	3.6 (2.1, 5.0)
Log rank test p-value[1]		0.003	0.207
Wilcoxon test p-value[2]		0.002	0.361
Trial 04	**CIPRO+FLUO (N = 87)**	**CIPRO (N = 77)**	**FLUO (N = 47)**
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (3.1, 4.8)	4.6 (3.5, 5.5)	5.4 (4.6, 5.9)
Log rank test p-value[1]		0.062	0.016
Wilcoxon test p-value[2]		0.088	0.018

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)

Sensitivity Analysis: Censoring All Discontinued Patients at Day 1

In order to assess the effect of censoring on primary analysis results, sensitivity analyses were conducted where all discontinued patients were censored at Day 1. While this sensitivity analysis may not be useful by itself, a comparison of findings from the primary analysis which censored patients at Day 22 (essentially considering them as having no cessation) and this sensitivity analysis which censored patients at Day 1 (essentially excluding them from the analysis) can help to determine whether primary analysis findings are robust to assumptions regarding censoring. As shown in **Table 10**, there is a significant contribution of each of the components of CIPRO+FLUO which shows that primary analysis findings (shown earlier in **Table 5)** are likely to be robust to the assumptions used for censoring discontinued patients.

Table 10: Sensitivity Analysis: Time to Cessation of Otorrhea Censoring All Discontinued Patients at Day 1 (CITT)

Trial 02	CIPRO+FLUO (N = 112)	CIPRO (N = 109)	FLUO (N = 110)
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Time to cessation of otorrhea (days): Median (95% CI)	3.6 (2.9, 4.3)	7.1 (4.8, 9.4)	17.1 (7.1, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)
Time to cessation of otorrhea (days): Median (95% CI)	4.9 (3.7, 5.5)	6.7 (5.0, 7.7)	NE (NE, NE)
Log rank test p-value		0.023	< 0.001
Wilcoxon test p-value		0.015	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Sensitivity Analysis: Analysis of MITT Population Only

In **Table 11**, sensitivity analyses were conducted in an analysis population of MITT patients only. These analyses determine whether the inclusion of patients without a baseline pathogen in the primary analysis could have potentially influenced treatment comparisons. Although there is a loss in statistical power associated with using the smaller MITT population (58.9% & 56.1% of CITT patients in Trials 02 & 04 were included in the MITT, **Table 3**), statistical comparisons showed similar degrees of significance. This indicates that primary analysis results were robust to assumptions regarding the analysis population considered (i.e. CITT or MITT).

Table 11: Sensitivity Analysis: Time to Cessation of Otorrhea (MITT)

Trial 02	CIPRO+FLUO (N = 65)	CIPRO (N = 70)	FLUO (N = 60)
Number (%) of patients with cessation of otorrhea	51 (88.5)	45 (64.3)	26 (43.3)
Time to cessation of otorrhea (days): Median (95% CI)	4.3 (3.3, 6.3)	8.1 (4.9, 16.4)	NE (9.5, NE)
Log rank test p-value[1]		0.009	< 0.001
Wilcoxon test p-value[2]		0.008	< 0.001
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Number of patients with cessation of	48 (80.0)	43 (66.1)	23 (37.1)

otorrhea			
Time to cessation of otorrhea (days): Median (95% CI)	4.6 (3.2, 6.8)	7.0 (5.9, 11.8)	NE (19.5, NE)
Log rank test p-value[1]		0.030	< 0.001
Wilcoxon test p-value[2]		0.029	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

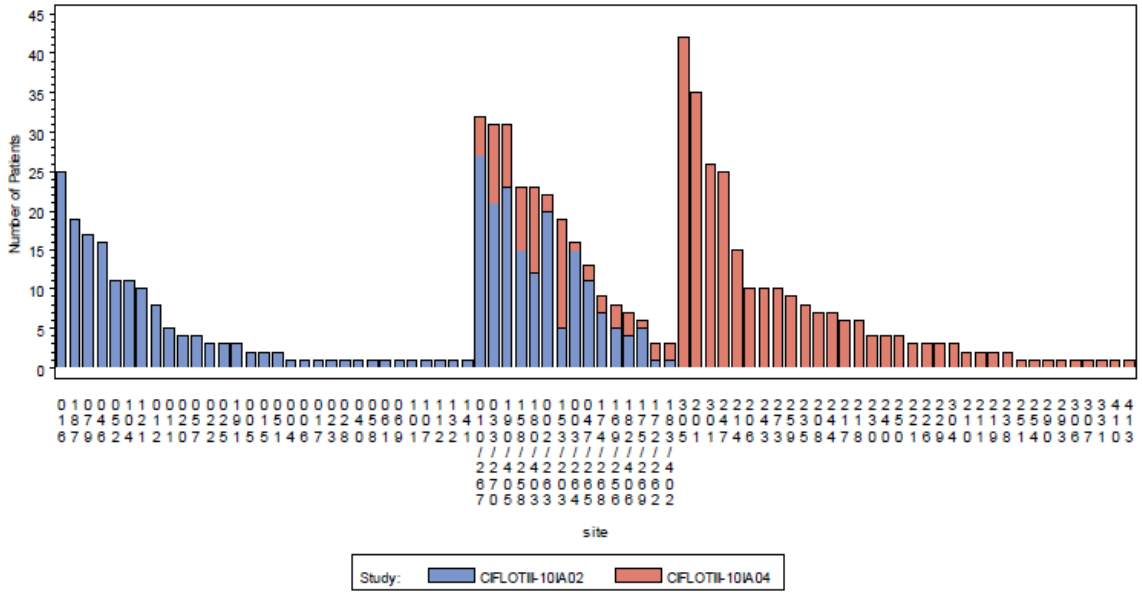
[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Sensitivity Analysis: Patients from Sites Not Shared Across Trials 02 & 04

In this submission, the Applicant provided **Figure 4** which shows all the study sites used in Studies 02 and 04, including those sites used in Study 02 only, those sites used in Study 04 only and those sites used in both Study 02 and Study 04. Reviewer sensitivity analyses assessed the influence of the sharing of study sites on primary analysis findings. From **Table 12**, treatment comparisons did not meaningfully change when excluding all shared sites.

Reviewer Comments: *Some sites that completed participation in the 02 study were also selected to participate in the identical clinical study, Study 04. However, based on Agency recommendations, the rollover of sites would be minimized and high enrolling sites from Study 04 were not permitted to continue and/or be initiated in Study 02. In addition, Study 04 would remain blinded until Study 02 was completed.*

Figure 3: Distribution of Patients Enrolled in each Study Site, Trials 02 & 04 (CITT)



Source: Applicant Figure 14.2.1.13 in SCE

Table 12: Time to Cessation of Otorrhea in Patients from Sites Not Shared Across Trials 02 & 04 (CITT)

Trial 02	CIPRO+FLUO (N = 50)	CIPRO (N = 58)	FLUO (N = 51)
Number (%) of patients with cessation of otorrhea	39 (78.0)	36 (62.1)	23 (45.1)
Time to cessation of otorrhea (days): Median (95% CI)	3.8 (3.0, 6.3)	10.4 (6.4, NE)	NE (6.2, NE)
Log rank test p-value[1]		0.006	0.003
Wilcoxon test p-value[2]		0.002	0.019
Trial 04	**CIPRO+FLUO (N = 93)**	**CIPRO (N = 84)**	**FLUO (N = 80)**
Number of patients with cessation of otorrhea	72 (77.4)	53 (63.1)	36 (45.0)
Time to cessation of otorrhea (days): Median (95% CI)	4.9 (3.7, 5.7)	7.1 (5.5, 15.9)	NE (8.8, NE)
Log rank test p-value[1]		0.016	< 0.001
Wilcoxon test p-value[2]		0.016	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

3.2.4.3 Efficacy Conclusions

The primary analyses of these trials showed that time to cessation of otorrhea by Day 22 (end of study) was significantly shorter in the CIPRO+FLUO arm versus the CIPRO alone and FLUO alone arms. This demonstrated the effect of each component in CIPRO+FLUO (i.e., CIPRO and FLUO). In Studies 02 & 04, respectively, the median time to cessation was 3.8 days (95% CI: 3.0, 4.4) & 4.9 days (95% CI: 3.7, 5.5) in the CIPRO+FLUO arm and 7.7 days (95% CI: 4.8, 11.4) & 6.8 days (95% CI: 5.5, 7.7) in the CIPRO arm. In both studies, the median time was not estimable in the FLUO arm due to the majority of patients failing to achieve cessation and being censored, however, the lower 95% confidence limit of the median was 7.4 & 13.9 days in the FLUO arm which was longer than in the CIPRO+FLUO arm at 3.0 & 3.7 days and the CIPRO arm at 4.8 & 5.5 days. In Studies 02 & 04, statistical comparisons using the log rank test showed the superiority of CIPRO+FLUO vs. CIPRO ($p < 0.001$ & $p = 0.028$) and CIPRO+FLUO vs. FLUO ($p < 0.001$ & $p < 0.001$). Rates of cessation showed similar trends in efficacy across treatments at 88/112 (78.6%) & 87/111 (78.4%) in the CIPRO+FLUO arm, 73/109 (67.0%) & 77/112 (68.8%) in the CIPRO arm and 53/110 (48.2%) & 47/108 (43.5%) in the FLUO arm.

Secondary analyses in Studies 02 & 04 provided consistent results that clearly showed the contribution of the CIPRO component in pre-specified comparisons of CIPRO+FLUO vs. FLUO alone and CIPRO alone vs. FLUO alone. Although these analyses did not pre-specify a statistically controlled test for the contribution of the FLUO component

(CIPRO+FLUO vs. CIPRO alone), post-hoc comparisons in both studies were observed to numerically (but not statistically) favor CIPRO+FLUO over CIPRO alone. In Trials 02 & 04, respectively, sustained microbiological cure rates were 47/61 (77.0%) & 47/57 (82.5%) in the CIPRO+FLUO arm, 41/63 (65.1%) & 43/61 (70.5%) in the CIPRO arm and 23/52 (44.2%) & 18/57 (31.6%) in the FLUO arm. Statistical comparisons based the stratified CMH test showed findings of statistical superiority for CIPRO+FLUO vs. CIPRO ($p = 0.017$ in Study 02 and $p < 0.001$ in Study 04) and CIPRO vs. FLUO ($p < 0.001$ in both studies)

In addition to the above primary and secondary analyses, the Reviewer conducted several sensitivity analyses. These analyses showed that primary and secondary analysis results were generally robust to key assumptions such as differences in analysis populations, subgroups based on possible confounding variables as well as other assumptions (e.g. prior/concomitant medications). The Reviewer also conducted exploratory analyses such as analyses of sites that were not shared across studies. All of these analyses showed results that were consistent with overall results. Details of these analyses are included in **Section 3.2.4.2** and in the **Appendix**.

3.3 Evaluation of Safety

Deaths and Serious Adverse Events

In Trial 02 and Trial 04 (combined), there were no deaths reported. Three patients (one per arm) were identified as having treatment emergent nonfatal events. All these cases required hospitalization but were not related to study drug treatment.

Study Withdrawals

The number of patients who withdrew due to adverse events was generally low at 1.3%, 2.3% and 3.3% in the CIPRO+FLUO, CIPRO and FLUO groups, respectively. Overall, there were substantially more withdrawals from the FLUO group at 16.0% compared to the CIPRO+FLUO (5.8%) and CIPRO (7.7%) groups. The primary reason for this treatment difference was 'lack of efficacy and/or use of rescue medication' which was observed more frequently in the FLUO subjects.

Table 13: Reasons for Withdrawal in Trials 02 and 04 (Pooled), Safety Population

Reason	**CIPRO+FLUO N=224 n (%)**	**CIPRO N=220 n (%)**	**FLUO N=213 n (%)**
Study Withdrawals	**13 (5.8%)**	**17 (7.7%)**	**34 (16.0%)**
Reason:			
Adverse Event	3 (1.3%)	5 (2.3%)	7 (3.3%)
At the discretion of the Investigator	0	0	3 (1.4%)
Lack of efficacy and/or use of rescue medication	1 (0.4%)	8 (3.6%)	17 (8.0%)
Lost to follow-up	4 (1.8%)	1 (0.5%)	5 (2.3%)
Violation of eligibility criteria	2 (0.9%)	1 (0.5%)	0

Withdrew Consent	1 (0.4%)	2 (0.9%)	2 (0.9%)
Other	2 (0.9%)	0	0

Source: Reviewer Table

Common Treatment Emergent Adverse Events

The most frequently reported AE was pyrexia which is a common symptom of acute otitis media. Overall, rates for each AE tended be highest in the FLUO group. When comparing the CIPRO+FLUO group vs. CIPRO group, AEs tended to be slightly higher in the CIPRO + FLUO group for many of the commonly reported AEs including pyrexia (7.1% vs. 5.5%), rhinorrhoea (6.3% vs. 2.7%), otitis media (6.3% vs. 4.1%), cough (4.5% vs. 2.7%), otorrhoea (5.4% vs. 4.1%), vomiting (1.8% vs. 0.5%), nasopharyngitis (1.3% vs. 0.5%) and upper respiratory infection (4.5% vs. 4.1%).

Table 14: Patients with Commonly Reported Treatment Emergent Adverse Events, Safety Population

	CIPRO+FLUO N=224	**CIPRO N=220**	**FLUO N=213**
Number of patients with ≥1 TEAE	96 (42.9%)	94 (42.7%)	110 (51.6%)
Commonly Reported TEAEs			
Pyrexia	16 (7.1%)	12 (5.5%)	23 (10.8%)
Otitis media	14 (6.3%)	9 (4.1%)	15 (7.0%)
Upper respiratory tract infection	10 (4.5%)	9 (4.1%)	8 (3.8%)
Nasopharyngitis	3 (1.3%)	1 (0.5%)	9 (4.2%)
Rhinorrhoea	14 (6.3%)	6 (2.7%)	16 (7.5%)
Cough	10 (4.5%)	6 (2.7%)	7 (3.3%)
Ear pain	4 (1.8%)	4 (1.8%)	8 (3.8%)
Otorrhoea	12 (5.4%)	9 (4.1%)	12 (5.6%)
Vomiting	4 (1.8%)	1 (0.5%)	9 (4.2%)

Source: Reviewer Table

Conclusions

Overall, the Reviewer did not have any concerns with respect to the safety of CIPRO+FLUO. Overall, serious adverse events and adverse events leading to study withdrawal were generally low. Commonly reported AEs were also generally low in the CIPRO and CIPRO+FLUO groups but tended to be slightly higher in the FLUO arm. When comparing the CIPRO+FLUO and CIPRO groups, the CIPRO+FLUO group more frequently reported several adverse events which included pyrexia, otitis media, rhinorrhea, cough, upper respiratory tract infection and otorrhoea, however differences were generally modest. For more details regarding the safety review of Otovel, please refer to the Clinical Review conducted by Dr. Mayurika Ghosh.

4. SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analyses by Age, Gender, Race and Geographic Region

The Reviewer considered the primary analysis of 'time to cessation of otorrhea' in various subgroups of the CITT including age group (<3 years old, ≥ 3 years old), gender (male, female), race (white, non-white) and geographic region (US vs. non-US).

In **Table 15**, a subgroup analysis is performed by age group (patients < 3 years and patients ≥ 3 years) for both trials. This age group variable was used as a stratification variable in the randomization and analyses of both trials. In comparison to patients < 3 years, patients ≥ 3 years tended to have shorter a time to cessation of otorrhea with a larger percentage of patients achieving cessation by Day 22. The CIPRO+FLUO arm also showed a shorter time to cessation in both of the age subgroups in both studies. Comparisons of CIPRO+FLUO vs. FLUO showed p-values of < 0.001 using the log rank test regardless of the subgroup or study considered. Comparisons of CIPRO+FLUO vs. CIPRO were generally not significant except in Trial 02 for the subgroup of patients ≥ 3 years (p = 0.001).

Reviewer Comments: *It is important to note that this analysis and all other subgroup analyses presented in this section of the review are exploratory/sensitivity analyses involving a large number of comparisons and there is no control of the overall type I error rate. Therefore, all p-values presented in these types of analyses should be interpreted with caution and considered as exploratory.*

Table 15: Subgroup Analysis: Time to Cessation of Otorrhea by Age Group (CITT)

Trial 02	**CIPRO+FLUO (N=112)**	**CIPRO (N=109)**	**FLUO (N=110)**
Patients < 3 years old	**N = 66**	**N = 63**	**N = 62**
Number (%) with cessation of otorrhea	46 (69.7%)	38 (60.3%)	27 (43.5%)
Median Days to cessation (95% CI)	4.1 (3.0, 7.5)	8.4 (4.8, NE)	NE (7.6, NE)
Log rank test p-value[1]		0.105	< 0.001
Wilcoxon test p-value[2]		0.052	< 0.001
Patients ≥ 3 years old	**N = 46**	**N = 46**	**N = 48**
Number (%) with cessation of otorrhea	42 (91.3%)	35 (76.1%)	26 (54.2%)
Median Days to cessation (95% CI)	3.4 (2.6, 4.2)	6.7 (4.4, 10.3)	13.3 (4.0, NE)
Log rank test p-value[1]		0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	0.008
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Patients < 3 years old	**N=66**	**N=65**	**N=63**
Number (%) with cessation of otorrhea	50 (75.8%)	42 (64.6%)	27 (42.9%)
Median Days to cessation (95% CI)	5.0 (3.7, 6.8)	6.9 (5.5, 18.7)	NE (12.9, NE)
Log rank test p-value[1]		0.067	< 0.001
Wilcoxon test p-value[2]		0.041	< 0.001
Patients ≥ 3 years old	**N=45**	**N=47**	**N=45**

Number (%) with cessation of otorrhea	37 (82.2%)	35 (74.5%)	20 (44.4%)
Median Days to cessation (95% CI)	4.6 (3.1, 5.5)	6.2 (3.7, 7.6)	NE (5.6, NE)
Log rank test p-value[1]		0.213	< 0.001
Wilcoxon test p-value[2]		0.234	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the unstratified log-rank test

[2]Pairwise comparisons versus CIPRO+FLUO using the unstratified Wilcoxon test

In **Table 16**, a subgroup analysis is performed by gender (male patients vs. female patients). **Table 16** does not show large differences between males and females with respect to time to cessation of otorrhea. Comparisons of CIPRO+FLUO vs. FLUO alone strongly favored CIPRO+FLUO using the log rank test regardless of the subgroup or study considered. In Trial 02, comparisons of CIPRO+FLUO vs. CIPRO alone slightly favored CIPRO alone among males and slightly favored CIPRO+FLUO among females. In Trial 04, comparisons of CIPRO+FLUO vs. CIPRO alone marginally favored CIPRO+FLUO among males and more strongly favored CIPRO+FLUO among females.

Table 16: Subgroup Analysis: Time to Cessation of Otorrhea by Gender (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
Male	**N=64**	**N=66**	**N=68**
Number (%) with cessation of otorrhea	47 (69.7)	46 (73.4)	33 (48.5)
Median Days to cessation (95% CI)	6.8 (4.3, 10.3)	4.3 (3.2, 7.6)	NE (6.8, NE)
Log rank test p-value[1]		0.260	0.005
Wilcoxon test p-value[2]		0.276	0.013
Female	**N=48**	**N=43**	**N=42**
Number (%)with cessation of otorrhea	41 (64.1)	27 (62.8)	20 (47.6)
Median Days to cessation (95% CI)	3.2 (2.5, 3.9)	8.4 (4.8, NE)	NE (7.1, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Male	**N=65**	**N=69**	**N=59**
Number (%)with cessation of otorrhea	50 (76.9)	49 (71.0)	31 (52.5)
Median Days to cessation (95% CI)	4.9 (4.1, 6.0)	6.7 (4.8, 9.0)	18.0 (6.8, NE)
Log rank test p-value[1]		0.189	0.002
Wilcoxon test p-value[2]		0.140	0.003
Female	**N=46**	**N=43**	**N=49**
Number (%)with cessation of otorrhea	37 (80.4)	28 (65.1)	16 (32.7)
Median Days to cessation (95% CI)	4.4 (3.1, 6.6)	7.0 (4.4, 11.8)	NE (NE, NE)
Log rank test p-value[1]		0.069	< 0.001
Wilcoxon test p-value[2]		0.057	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the Wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Table 17 contains the results of a subgroup analysis performed by race (white vs. non-white). In both trials, the CIPRO+FLUO arm had substantially shorter times to cessation of otorrhea than the CIPRO alone and FLUO alone arms among patients who were white. Among non-white patients, comparisons were limited by small numbers, however, shorter times to cessation in the CIPRO+FLUO arm could be observed in Trial 02.

Table 17: Subgroup Analysis: Time to Cessation of Otorrhea by Race (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
White	**N=81**	**N=79**	**N=87**
Number (%) with cessation of otorrhea	63 (77.8)	51 (64.6)	41 (47.1)
Median Days to cessation (95% CI)	3.6 (2.9, 4.5)	6.7 (4.4, 9.4)	NE (7.4, NE)
Log rank test p-value[1]		0.015	< 0.001
Wilcoxon test p-value[2]		0.024	< 0.001
Non-white	**N=31**	**N=30**	**N=23**
Number (%)with cessation of otorrhea	25 (79.6)	22 (73.3)	12 (52.2)
Median Days to cessation (95% CI)	3.9 (2.8, 6.1)	10.1 (4.7, 19.4)	7.6 (2.9, NE)
Log rank test p-value[1]		0.048	0.048
Wilcoxon test p-value[2]		0.13	0.106
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
White	**N=86**	**N=89**	**N=89**
Number (%)with cessation of otorrhea	70 (81.4)	60 (67.4)	37 (39.6)
Median Days to cessation (95% CI)	4.2 (3.2, 5.0)	6.8 (5.0, 8.8)	NE (18.0, NE)
Log rank test p-value[1]		0.005	< 0.001
Wilcoxon test p-value[2]		0.002	< 0.001
Non-white	**N=25**	**N=23**	**N=19**
Number (%)with cessation of otorrhea	17 (68.0)	17 (73.9)	10 (52.6)
Median Days to cessation (95% CI)	6.8 (5.2, NE)	6.9 (3.1, 9.0)	13.9 (4.9, NE)
Log rank test p-value[1]		0.606	0.340
Wilcoxon test p-value[2]		0.548	0.466

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the Wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

In **Table 18**, a subgroup analysis performed by geographic region (US vs. non-US) is reported. In both trials the CIPRO+FLUO arm had substantially shorter times to cessation of otorrhea than the FLUO alone arms when considering US and non-US patients. Comparisons of CIPRO+FLUO vs. CIPRO alone also tended to favor CIPRO+FLUO. The p-values shown below were significant among US patients in both trials but not significant among non-US patients in either trial. However, comparisons among non-US patients comparisons were limited by small numbers.

Table 18: Subgroup Analysis: Time to Cessation of Otorrhea by Geographic Region (CITT)

Trial 02	CIPRO+FLUO (N = 112)	CIPRO (N = 109)	FLUO (N = 110)
US	**N=87**	**N=75**	**N=81**
Number (%) with cessation of otorrhea	68 (78.2)	47 (62.7)	37 (45.7)
Median Days to cessation (95% CI)	3.6 (2.8, 4.3)	7.3 (4.6, 9.4)	NE (7.6, NE)
Log rank test p-value[1]		0.003	< 0.001
Wilcoxon test p-value[2]		0.006	< 0.001
Non-US	**N=25**	**N=34**	**N=29**
Number (%)with cessation of otorrhea	20 (80.0)	26 (76.5)	16 (55.2)
Median Days to cessation (95% CI)	4.7 (2.8, 7.8)	7.0 (5.0, 11.8)	9.5 (5.3. NE)
Log rank test p-value[1]		0.153	0.099
Wilcoxon test p-value[2]		0.088	0.196
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
US	**N=82**	**N=72**	**N=75**
Number (%)with cessation of otorrhea	63 (76.8)	46 (63.9)	31 (41.3)
Median Days to cessation (95% CI)	4.7 (3.6, 5.3)	7.1 (4.8, 15.9)	NE (9.8, NE)
Log rank test p-value[1]		0.024	< 0.001
Wilcoxon test p-value[2]		0.014	< 0.001
Non-US	**N=29**	**N=40**	**N=33**
Number (%)with cessation of otorrhea	24 (82.8)	31 (77.5)	16 (48.5)
Median Days to cessation (95% CI)	5.5 (3.1, 7.1)	6.2 (4.4, 7.2)	NE (7.2, NE)
Log rank test p-value[1]		0.609	0.003
Wilcoxon test p-value[2]		0.786	0.009

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the Wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

4.2 Subgroup Analyses by Other Variables

The Reviewer did not consider subgroup analyses by other variables due to sample size limitations in the smaller subgroups for many variables of interest. However, the Reviewer conducted sensitivity analyses in several sub-populations, as discussed in **Section 3.2.4.2** and the **Appendix**.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Findings

There were no major statistical issues in this submission. Some minor issues and findings that were noted included the following:

- In the primary analyses, the median estimate for time to cessation of otorrhea was not estimable due to the majority patients not achieving cessation by the end of the study

on Day 22. Although this made comparisons across treatments more difficult to conceptualize, other comparisons could be still be made such as comparisons based on the lower confidence limit of the median. In addition, statistical comparisons based on the log rank test or rank sum test could still be made and were not affected by the lack of an estimable median in the FLUO arm. These comparisons showed that patients in the FLUO arm had a longer time to cessation of otorrhea in comparison to CIPRO+FLUO and that treatment differences were highly significant ($p < 0.001$ in Trial 02 and $p < 0.001$ in Trial 04).

- Secondary analyses considered only patients in the MITT population with observed values for sustained microbiological cure rates. This is generally problematic as it can introduce potential biases, especially in treatment arms with relative high rates of missing data that are not random. In secondary analyses of Trials 02 and 04, however, the use of only observed case values for microbiological cure rates was likely to be conservative given the relatively low rates of missing data in the CIPRO+FLUO arm.

- Sensitivity analyses showed that the contribution of the FLUO component was substantially weaker than the contribution of the CIPRO component. For example, comparisons of CIPRO+FLUO vs. CIPRO did not show a significant benefit in terms of higher rates of cessation of otorrhea (**Table 7**) or in terms of higher sustained microbiological cure rates (**Table 6**). However, the contribution of the FLUO did appear to be consistently trend towards significance in each of the studies. This suggests FLUO is providing some contribution but it is relatively weak.

- Although Trials 02 and 04 are considered as "independent" there were 15 sites (enrolling 246 patients) which were shared across the trials. Reviewer sensitivity analyses assessed the influence of sharing of study sites on primary analysis findings. From **Table 12**, treatment comparisons did not meaningfully change when excluding all shared sites.

5.2 Collective Evidence

The Reviewer primarily considered Trials 02 and 04 separately. Each of these studies provided evidence of efficacy on its own. However, integrated analyses of safety were performed in **Section 3.3**. For example, these analyses showed that many of the commonly reported AEs tended to be slightly higher in the CIPRO + FLUO group vs. the CIPRO group such as pyrexia (7.1% vs. 5.5%), rhinorrhoea (6.3% vs. 2.7%), otitis media (6.3% vs. 4.1%), cough (4.5% vs. 2.7%), otorrhoea (5.4% vs. 4.1%), vomiting (1.8% vs. 0.5%), nasopharyngitis (1.3% vs. 0.5%) and upper respiratory infection (4.5% vs. 4.1%).

5.3 Conclusions and Recommendations

In summary, there were no major statistical issues identified in this submission. Studies 02 & 04 both met their respective primary objectives of demonstrating the contribution of both the antimicrobial (cipro) and steroid (fluocinolone acetonide) components in Otovel. Both

studies also met their respective secondary objectives of demonstrating the contribution of the CIPRO component. Reviewer sensitivity analyses also found that primary and secondary analysis results were robust across a variety of assumptions. Reviewer analyses did not identify any major efficacy, safety or integrity related issues which could compromise overall findings. The Reviewer considers the overall evidence of efficacy and safety to be acceptable in supporting the use of Otovel in the treatment of pediatric patients with AOMT.

5.4 Labeling Recommendations

Negotiations regarding the product labeling are ongoing. Reviewer/Team Leader recommendations to the Division regarding the CLINICAL STUDIES section of the most recent label have included the following:

- Removing text which stated (b) (4)
- Adding text stating that both studies demonstrated the contribution of the components of OTOVEL.
- Modifying Table 2 of the label to depict the percentage of patients with cessation of otorrhea by Day 22.
- Adding more descriptive headings for the rows in Table 2 of the label. For example, the headings of (b) (4) and (b) (4) were replaced with the headings of 'Number (%) with cessation of otorrhea by Day 22' and 'Median time to cessation (days).'
- Clarifying some of the notation (e.g. changing study numbers from (b) (4) to 1 and 2) and footnotes.
- Other editorial changes.

The current 'CLINICAL STUDIES' section of the draft label is provided below:

14 CLINICAL STUDIES

(b) (4)

Two phase III multicenter, randomized, double-blind, active-controlled, parallel group studies were conducted in 662 pediatric patients in total (aged 6 months to 12 years old) with AOMT, to assess the efficacy and safety of OTOVEL compared to ciprofloxacin otic solution and to fluocinolone acetonide otic solution ((b) (4) 1 and (b) (4) 2).

In both (b) (4) the OTOVEL treatment arms showed significantly shorter times to cessation of otorrhea in comparison to both the ciprofloxacin and fluocinolone acetonide alone arms demonstrating the contribution of both components of OTOVEL. The results are presented in the table below:

Table 2: Results of the Primary Endpoint: Time to Cessation of Otorrhea ((b) (4) 1 and (b) (4) 2)

	Treatment arm		
(b) (4) 1	**OTOVEL (N=112)**	**Ciprofloxacin (N=109)**	**Fluocinolone acetonide (N=110)**
Number (%) with cessation of otorrhea by Day 22	88 (78.6%)	73 (67.0%)	53 (48.2%)

Median time to cessation* (days)	3.75	7.69	n.e.
p-value vs OTOVEL**		<0.001	<0.001
(b) (4) **2**	**OTOVEL (N=111)**	**Ciprofloxacin (N=112)**	**Fluocinolone acetonide (N=108)**
Number (%) with cessation of otorrhea by Day 22	87 (78.4%)	77 (68.8%)	47 (43.5%)
Median time to cessation* (days)	4.94	6.83	n.e.
p-value vs OTOVEL**		0.028	<0.001

n.e.: not estimable because the number of censored patients was greater than the number of patients with cessation of otorrhea
* Kaplan-Meier median estimate censored all subjects who did not have a cessation of otorrhea at the maximum time point of 22 days.
** Log-rank test stratified by age (patients younger than 3 years versus 3 years and older)

6. REFERENCES

1. Roland PS, Anon JF, Moe RD, Conroy PJ, Wall GM, Dupre SJ et al. Topical ciprofloxacin/dexamethasone is superior to ciproloxacine alone in pediatric patients with acute otitis media and otorrhea with tympanostomy turbes. Laryngoscope. 2003 Dec;113 (12):2116-22

7. APPENDIX

Reviewer Exploratory/Sensitivity Analyses of the Primary Endpoint

Reviewer exploratory/sensitivity analyses of the primary endpoint were conducted in various other subgroups including a per protocol population, patients not taking prior or concomitant antibacterials, patients not using titanium tubes and patients not taking out of specification study medications.

Reviewer Comments: *As with other Reviewer exploratory/sensitivity analyses, caution should be applied in interpreting the observed findings due to the post-hoc nature of the testing and the failure to control the overall type I error rates. It should also be noted that these analyses consider a smaller population than was used in the primary analysis population (i.e. the CITT) and may be limited in terms of power.*

In **Table 19**, time to cessation of otorrhea is analyzed in a per-protocol population which comprised approximately 73% of the CITT population across both trials. In these analyses, per-protocol patients in the CIPRO+FLUO arm had the shortest time to cessation in Trials 02 and 04. Comparisons of CIPRO+FLUO vs. FLUO alone were significant in both trials ($p < 0.001$) while comparisons of CIPRO+FLUO vs. CIPRO alone were significant in Trial 02 ($p < 0.001$) and marginal in Trial 04 ($p = 0.076$).

Table 19: Sensitivity Analysis: Time to Cessation of Otorrhea (Per Protocol Population), Trials 02 & 04

Trial 02	CIPRO+FLUO (N = 82)	CIPRO (N = 80)	FLUO (N = 83)
Number (%) of patients with cessation of otorrhea	67 (81.7)	55 (68.8)	41 (49.4)
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (2.8, 4.4)	8.0 (4.7, 11.4)	NE (6.8, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 77)**	**CIPRO (N = 89)**	**FLUO (N = 73)**
Number of patients with cessation of otorrhea	61 (79.2)	61 (68.5)	28 (38.4)
Time to cessation of otorrhea (days): Median (95% CI)	5.0 (3.7, 5.5)	6.5 (4.8, 7.2)	NE (19.5, NE)
Log rank test p-value[1]		0.076	< 0.001
Wilcoxon test p-value[2]		0.123	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Reviewer Comments: *In Trial 02, the Sponsor reported slightly different findings, identifying 83 rather than 82 patients in the CIPRO+FLUO group and 82 rather than 83 patients in the FLUO group. However, Reviewer calculations of p-values for the log rank and Wilcoxon tests as well as calculations for the median (95% CI) were not altered despite this difference. There was only a slight disparity in findings regarding the number (%) of patients with cessation of otorrhea.*

Table 20 considers patients with prior antibiotic use as well as patients with prior antibiotic use within 48 hours of initiation of study drug. These patients are of primary concern in potentially influencing study outcomes. Since the number of patients with prior antibiotic use within 48 hours was observed to be very small, only one subject per study, prior antibiotic use was not considered to be a factor in the primary analysis and no further analyses were considered.

Table 20: Number (%) of Patients with Prior Antibiotic Use (CITT)

	CIPRO+FLUO	CIPRO	FLUO	Total
Trial 02	**N=112**	**N=109**	**N=110**	**N=331**
Patients with Prior Antibiotic Use	6 (5.4%)	4 (3.7%)	6 (5.5%)	16 (4.8%)
Patients with Prior Antibiotic Use within 48 hours of initiation of study drug	1 (0.9%)	0	0	1 (0.3%)
Trial 04	**N=111**	**N=112**	**N=108**	**N=331**
Patients with Prior Antibiotic Use	10 (9.0%)	5 (4.5%)	2 (1.9%)	17 (5.1%)
Patients with Prior Antibiotic Use within	0	1 (0.9%)	0	1 (0.3%)

48 hours of initiation of study drug				

Source: Reviewer Table

Tables 21 & 22 explore the potential influence that use of prohibited concomitant antibacterial medications may have on the primary outcome. As shown in **Table 21**, such use was rather limited at 6.0% in Trial 02 and 8.5% in Trial 04.

Table 21: Number (%) of Patients with Use of Prohibited Concomitant Antibacterial Medications (CITT)

	CIPRO+FLUO	CIPRO	FLUO	Total
Trial 02	**N=112**	**N=109**	**N=110**	**N=331**
Patients with use of effective concomitant antibiotic medication	7 (6.3%)	5 (4.6%)	8 (7.3%)	20 (6.0%)
Trial 04	**N=111**	**N=112**	**N=108**	**N=331**
Patients with use of effective concomitant antibiotic medication	8 (7.2%)	9 (8.0%)	11 (10.2%)	28 (8.5%)

Source: Reviewer Table

Reviewer Comments: *The use of prohibited concomitant antibacterial medications can lead to potential confounding of the primary analysis. Note that patients may improve their primary outcome with such antibacterial use. This would tend to reduce the median time to cessation of otorrhea across the treatment arms and make it more difficult to show superiority. However, if large disparities exist across treatment arms with respect to such antibacterial use then this can lead to potential biases.*

*In **Table 22,** a sensitivity analysis is conducted removing all CITT patients using effective concomitant antibacterial medications. Results in this analysis population appeared to be similar to those of the primary analysis indicating that any impact from such concomitant use is likely to be minimal.*

Table 22: Sensitivity Analysis: Time to Cessation of Otorrhea in CITT Patients not Using Prohibited Concomitant Antibacterial Medications (CITT), Trials 02 & 04

Trial 02	**CIPRO+FLUO (N = 105)**	**CIPRO (N = 104)**	**FLUO (N = 102)**
Number (%) of patients with cessation of otorrhea	83 (79.0)	70 (67.3)	51 (50.0)
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (3.0, 4.5)	7.7 (4.9, 11.4)	NE (7.1, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 103)**	**CIPRO (N = 103)**	**FLUO (N = 97)**
Number of patients with cessation of otorrhea	83 (80.6)	72 (69.9)	44 (45.4)
Time to cessation of otorrhea (days):			

Median (95% CI)	5.0 (3.8, 5.6)	6.6 (4.9, 7.6)	NE (9.8, NE)
Log rank test p-value[1]		0.024	< 0.001
Wilcoxon test p-value[2]		0.020	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

In **Table 23**, a sensitivity analysis was conducted in CITT patients not using titanium tubes. The use of titanium tubes can have an antibacterial effect which can confound analyses. These analyses did not indicate that the use of titanium tubes is likely to influence the primary outcome.

Table 23: Sensitivity Analysis: Time to Cessation of Otorrhea in CITT Patients not Using Titanium Tubes, Trials 02 & 04

Trial 02	**CIPRO+FLUO (N = 101)**	**CIPRO (N = 100)**	**FLUO (N = 104)**
Number (%) of patients with cessation of otorrhea	79 (78.2)	67 (67.0)	51 (49.0)
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (3.0, 4.7)	7.7 (4.8, 11.4)	NE (7.4, NE)
Log rank test p-value[1]		0.003	< 0.001
Wilcoxon test p-value[2]		0.002	< 0.001
Trial 04	**CIPRO+FLUO (N = 106)**	**CIPRO (N = 100)**	**FLUO (N = 99)**
Number of patients with cessation of otorrhea	82 (77.4)	66 (66.0)	45 (45.5)
Time to cessation of otorrhea (days): Median (95% CI)	5.0 (3.8, 5.6)	6.9 (5.8, 9.0)	NE (10.6, NE)
Log rank test p-value[1]		0.025	< 0.001
Wilcoxon test p-value[2]		0.023	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

In **Table 24**, a sensitivity analysis is performed in CITT patients who took no out of specification study medication in order to investigate possible confounding effects. Sensitivity analyses performed in this patient population showed similar findings to primary analyses performed in the CITT population.

Table 24: Sensitivity Analysis: Time to Cessation of Otorrhea in CITT Patients who Took No Out of Specification Study Medication, Trials 02 & 04

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 93)**
Number (%) of patients with cessation	88 (78.6)	73 (67.0)	47 (50.5)

of otorrhea			
Time to cessation of otorrhea (days): Median (95% CI)	3.8 (3.0, 4.4)	7.7 (4.8, 11.4)	19.7 (7.1, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 84)**
Number of patients with cessation of otorrhea	87 (77.7)	77 (68.8)	38 (45.2)
Time to cessation of otorrhea (days): Median (95% CI)	4.9 (3.7, 5.5)	6.8 (5.5, 7.7)	NE (10.6, NE)
Log rank test p-value[1]		0.028	< 0.001
Wilcoxon test p-value[2]		0.018	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Reviewer Exploratory/Sensitivity Analyses of the Principal Secondary Endpoint

Further exploratory/sensitivity analyses for the principal secondary endpoint were conducted. **Tables 25, 26, 27 and 28** show the microbiological success rates for Visits 3 and 4, both overall and by target pathogen. In **Table 25** (Visit 3) and **Table 26** (Visit 4), the percentage of patients with each microbiological response was summarized at Visit 3 and Visit 4 and compared between the CIPRO+FLUO and CIPRO groups, the CIPRO+FLUO and FLUO groups and the CIPRO and FLUO groups using a CMH test at Visit 3 and Visit 4.

Table 25 shows that for Trials 02 & 04, respectively, microbiological response rates at the end of treatment visit (Visit 3) were highest in the CIPRO+FLUO arm at 81.5% & 84.7%, next highest in the CIPRO arm at 64.7% & 73.4% and lowest in the FLUO arm at 44.8% & 36.1%. Post-hoc comparisons using a CMH test (stratified by age group) were also performed for CIPRO+FLUO vs. FLUO (p-values of < 0.001 & < 0.001), CIPRO vs. FLUO (p-values of 0.023 & < 0.001) and for CIPRO + FLUO vs. CIPRO (p-values of 0.046 & 0.187). However, as these are post-hoc comparisons where the overall type I error rate is not controlled, the interpretation of these findings is extremely limited. However, findings from these sensitivity/exploratory analyses appear to be generally consistent with secondary analyses based on the sustained microbiological cure rate.

Table 25: Microbiological Response at Visit 3 (End of Treatment)

Trial 02	**CIPRO+FLUO (N = 65)**	**CIPRO (N = 70)**	**FLUO (N = 60)**
Favorable	53 (81.5)	44 (64.7)	26 (44.8)
Unfavorable	7 (10.8)	19 (27.9)	30 (51.7)
Indeterminate	5 (7.7)	5 (7.4)	2 (3.4)
Total	65 (100)	68 (100)	58 (100)

Missing	0	2	2
CMH test p-value vs. CIPRO+FLUO		0.046	< 0.001
CMH test p-value vs. CIPRO			0.023
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Favorable	50 (84.7)	47 (73.4)	22 (36.1)
Unfavorable	5 (8.5)	13 (20.3)	36 (59.0)
Indeterminate	4 (6.8)	4 (6.3)	3 (4.9)
Total	59 (100)	64 (100)	61 (100)
Missing	1	1	1
CMH test p-value vs. CIPRO+FLUO		0.187	< 0.001
CMH test p-value vs. CIPRO			< 0.001

[1] Missing data at Visit 4 were imputed as "unfavorable". Missing data after receiving rescue medication are not replaced.

Source: Partially adapted from Sponsor Table 14.2.2.1

Table 26 shows that for Trials 02 & 04, respectively, microbiological response rates at the test of cure visit (Visit 4) were highest in the CIPRO and CIPRO+FLUO arms at 84.6% & 89.8% (CIPRO) and 83.1% & 88.7% (CIPRO+FLUO) and lowest in the FLUO arm at 71.4% and 73.3%. Post-hoc comparisons using a CMH test (stratified by age group) were also performed for CIPRO+FLUO vs. CIPRO, CIPRO vs. FLUO and CIPRO + FLUO vs. CIPRO, however all of the estimated p-values were not significant.

These analyses were limited by the substantial amount of missing data for the test-of-cure visit which was due to patients who did not have a favorable response at Visit 3 being counted as 'Missing' at Visit 4. As a result, missing data occurred much less frequently in the CIPRO+FLUO arm and much more frequently in the FLUO arm. In these analyses, patients who received rescue medication were counted as 'Missing' and patients with no exudate in their ear at Visit 4 were also counted as 'Missing'. However, patients with missing data due to having withdrawn consent were imputed as "Unfavorable."

Reviewer Comments: *The Reviewer considers this methodology for handling missing data as being conservative since the CIPRO+FLUO arm had the least missing data. These analyses show that treatment differences in sustained microbiological cure rates in the principal secondary analyses appear to be driven primarily by the treatment differences observed at the end of treatment visit (Visit 3).*

Table 26: Microbiological Response at Visit 4 (Test of Cure)

Trial 02	**CIPRO+FLUO (N = 65)**	**CIPRO (N = 70)**	**FLUO (N = 60)**
Favorable	49 (83.1)	44 (84.6)	25 (71.4)
Unfavorable	5 (8.5)	5 (9.6)	9 (25.7)
Indeterminate	5 (8.5)	3 (5.8)	1 (2.9)
Total	59 (100)	52 (100)	35 (100)
Missing	6	18	25
CMH test p-value vs. CIPRO+FLUO		0.835	0.057

CMH test p-value vs. CIPRO			0.139
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Favorable	47 (88.7)	44 (89.8)	22 (73.3)
Unfavorable	4 (7.5)	4 (8.2)	6 (20.0)
Indeterminate	2 (3.8)	1 (2.0)	2 (6.7)
Total	53 (100)	49 (100)	30 (100)
Missing	7	16	32
CMH test p-value vs. CIPRO+FLUO		0.876	0.280
CMH test p-value vs. CIPRO			0.310

Source: Partially adapted from Sponsor Table 14.2.2.2.1

Additional analyses were conducted to explore microbiological response rates by pathogen in the MITT population at Visits 3 and 4. Findings in these analyses are shown in **Table 27** (Trial 02) and **Table 28** (Trial 04). However, comparisons by pathogen were generally limited by the small number of isolates presented.

Table 27: Microbiological Response Rates by Pathogen (Visits 3 & 4), Trial 02

Trial 04	**CIPRO+FLUO (N = 65)**		**CIPRO (N = 70)**		**FLUO (N = 60)**	
Pathogen Isolated Response	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**
Pseudomonas aeruginosa, n (%)						
n	11	11	12	12	12	12
Favorable	10 (90.9)	10 (90.9)	6 (50.0)	8 (66.7)	2 (16.7)	2 (16.7)
Unfavorable	1 (9.1)	0	4 (33.3)	0	8 (66.7)	2 (16.7)
Indeterminate	0	0	1 (8.3)	0	1 (11.1)	0
Missing	0	1 (9.1)	1 (8.3)	4 (33.3)	2 (16.7)	8 (66.7)
Staphylococcus aureus, n (%)						
n	26	26	25	25	23	23
Favorable	22 (84.6)	18 (69.2)	15 (60.0)	15 (60.0)	8 (34.8)	7 (30.4)
Unfavorable	2 (7.7)	2 (7.7)	8 (32.0)	0	10 (43.5)	4 (17.4)
Indeterminate	2 (7.7)	2 (7.7)	0	0	2 (8.7)	1 (4.3)
Missing	0	4 (15.4)	2 (8.0)	10 (40.0)	3 (13.0)	11 (47.8)
Moraxella catarrhalis, n (%)						
n	6	6	7	7	1	1
Favorable	6 (100)	5 (83.3)	4 (57.1)	6 (85.7)	1 (100)	1 (100)
Unfavorable	0	0	3 (42.9)	0	0	0
Indeterminate	0	0	0	0	0	0
Missing	0	1 (16.7)	0	1 (14.3)	0	0
Haemophilus influenzae, n (%)						
n	18	18	22	22	16	16
Favorable	13 (72.2)	9 (50.0)	15 (68.2)	15 (68.2)	7 (43.8)	8(50.0)
Unfavorable	2 (11.1)	1 (5.6)	3 (13.6)	0	8 (50.0)	0
Indeterminate	3 (16.7)	2 (11.1)	3 (13.6)	2 (9.1)	1 (6.3)	0
Missing	0	6 (33.3)	1 (4.5)	5 (22.7)	0	8(50.0)
Streptococcus pneumoniae, n (%)						
n	6	6	10	10	6	6
Favorable	3 (50.0)	3 (50.0)	7 (70.0)	8 (80.0)	2 (33.3)	2 (33.3)

Unfavorable	3 (50.0)	0	2 (20.0)	0	1 (16.7)	0
Indeterminate	0	0	1 (10.0)	1 (10.0)	1 (16.7)	0
Missing	0	3 (50.0)	0	1 (10.0)	1 (16.7)	4 (66.7)

Notes: n is the number of patients who had the pathogen alone or in combination with other pathogens at Visit 1 (each patient may have appeared in multiple rows). n (%) is the number (percentage of n) of patients with each microbiological outcome.

Source: Partially adapted from Sponsor Table 14.2.2.5

Table 28: Microbiological Response Rates by Pathogen (Visits 3 & 4), Trial 04

Trial 04	**CIPRO+FLUO (N = 60)**		**CIPRO (N = 65)**		**FLUO (N = 62)**	
Pathogen Isolated Response	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**
Pseudomonas aeruginosa, n (%)						
n	10	10	6	6	9	9
Favorable	9 (90.0)	8 (80.0)	5 (83.3)	5 (83.3)	1 (11.1)	2 (22.2)
Unfavorable	0	1 (10.0)	0	0	7 (77.8)	0
Indeterminate	1 (10.0)	0	0	0	1 (11.1)	0
Missing	0	1 (10.0)	1 (16.7)	1 (16.7)	0	7 (77.8)
Staphylococcus aureus, n (%)						
n	18	18	28	28	21	21
Favorable	15 (83.3)	15 (83.3)	15 (53.6)	14 (50.0)	9 (42.9)	8 (38.1)
Unfavorable	1 (5.6)	0	11 (39.3)	1 (3.6)	8 (38.1)	1 (4.8)
Indeterminate	1 (5.6)	0	1 (3.6)	0	3 (14.3)	1 (4.8)
Missing	1 (5.6)	3 (16.7)	1 (3.6)	13 (46.4)	1 (4.8)	11 (52.4)
Moraxella catarrhalis, n (%)						
n	9	9	9	9	6	6
Favorable	8 (88.9)	8 (88.9)	6 (66.7)	6 (66.7)	4 (66.7)	4 (66.7)
Unfavorable	0	0	1 (11.1)	0	1 (16.7)	1 (16.7)
Indeterminate	1 (11.1)	0	2 (22.2)	0	0	0
Missing	0	1 (11.1)	0	3 (33.3)	1 (16.7)	1 (16.7)
Haemophilus influenzae, n (%)						
n	15	15	19	19	25	25
Favorable	13 (86.7)	12 (80.0)	17 (89.5)	15 (78.9)	7 (28.0)	7 (28.0)
Unfavorable	1 (6.7)	1 (6.7)	0	2 (10.5)	16 (64.0)	3 (12.0)
Indeterminate	1 (6.7)	1 (6.7)	1 (5.3)	0	1 (4.0)	0
Missing	0	1 (6.7)	1 (5.3)	2 (10.5)	1 (4.0)	15 (60.0)
Streptococcus pneumoniae, n (%)						
n	7	7	6	6	10	10
Favorable	6 (85.7)	6 (85.7)	6 (100)	6 (100)	5 (50.0)	6 (60.0)
Unfavorable	1 (14.3)	0	0	0	5 (50.0)	0
Indeterminate	0	0	0	0	0	0
Missing	0	1 (14.3)	0	0	0	4 (40.0)

Notes: n is the number of patients who had the pathogen alone or in combination with other pathogens at Visit 1 (each patient may have appeared in multiple rows). n (%) is the number (percentage of n) of patients with each microbiological outcome.

Source: Partially adapted from Sponsor Table 14.2.2.5

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04/14/2016

KAREN M HIGGINS
04/14/2016
I concur.