CLINICAL REVIEW

Application Type	NDA
Application Number	208251
Priority or Standard	Standard
Submit Date	June 30, 2015
Received Date	June 30, 2015
PDUFA Goal Date	April 30, 2016
Division / Office	Division of Anti-Infective Products (DAIP)
Reviewer Name	Mayurika Ghosh, MD
Review Completion Date	February 16, 2016
Established Name	Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution
Proposed Trade Name	Otovel
Therapeutic Class	Fluoroquinolone/Corticosteroid
Applicant	SALVAT
Formulation	Otic drops
Dosing Regimen	0.25 mL instilled into the affected ear canal twice daily for 7 days
Indication	Acute Otitis Media with Tympanostomy Tubes(AOMT)
Intended Population	Patients aged 6 months and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on clinical efficacy and safety data submitted by the Applicant from two randomized, double blind, active controlled clinical trials, there is adequate evidence to recommend the approval of Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution in the treatment of acute otitis media in pediatric patients (aged 6 months and older) with tympanostomy tubes (AOMT).

1.2 Risk Benefit Assessment

Findings from trials provided adequate evidence of safety and efficacy for Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution in the twice daily dosing regimen for the treatment of AOMT. Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution demonstrated therapeutic superiority over Ciprofloxacin 0.3% otic solution and over Fluocinolone Acetonide 0.025% otic solution for the primary endpoint of time to cessation of otorrhea. Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution also demonstrated superiority over individual components with respect to sustained microbiological cure. Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution was found to be safe and well tolerated. Adverse events reported more frequently in the CIPRO+FLUO group were pyrexia, otitis media, rhinorrhea, cough, upper respiratory tract infection and otorrhoea.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

The 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.

Figure 1 Structure of Ciprofloxacin Hydrochloride (C17H18FN3O3·HCl·H2O; MW 385.82)

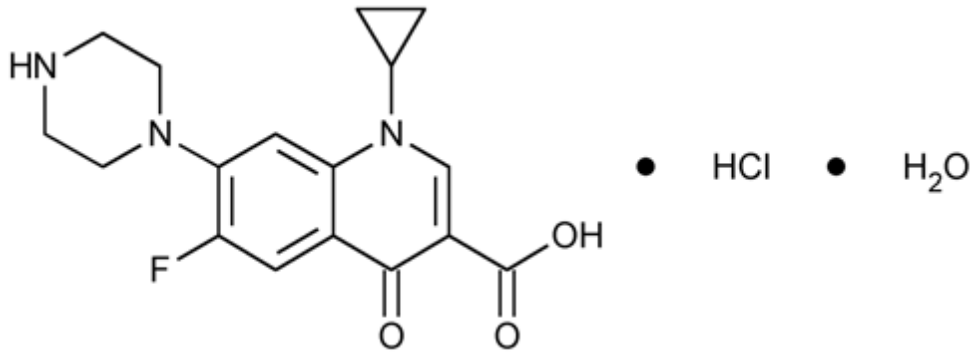
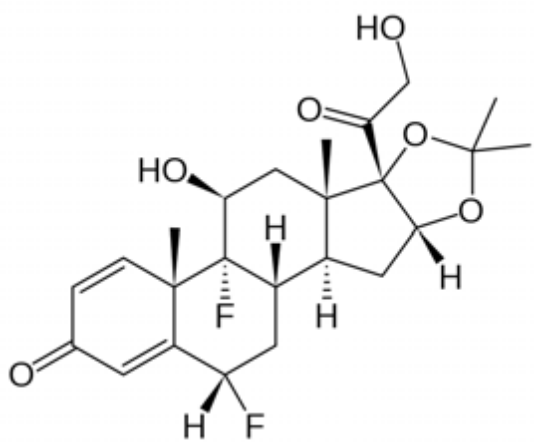


Figure 2 Structure of Fluocinolone Acetonide (C24H30F2O6; MW 452.50)



Source: Page 5 of applicant's nonclinical overview

Generic Name: Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution

Proposed Trade Name: (b) (4) submitted October14, 2015 which was denied by the Agency. The Applicant submitted alternate proposed trade name Otovel

Drug Class: Topical fluoroquinolone and corticosteroid combination

Proposed indication, age group: Acute Otitis Media with Tympanostomy Tubes (AOMT) in 6 months and older

2.2 Currently Available Treatments for Proposed Indications

The following treatments are FDA approved and available for the treatment of AOMT:

- Ofloxacin otic solution
- CIPRODEX (ciprofloxacin 0.3% with dexamethasone 0.1%) otic suspension in children aged 6 months and older

Systemic antibacterials (oral or parenteral) are prescribed for AOMT with systemic infection and severe symptoms, to immunocompromised children and in AOMT associated with occlusion of the auditory canal.

2.3 Availability of Proposed Active Ingredient in the United States

Ciprofloxacin 0.2% otic solution (Cetraxal SALVAT, NDA 21-918, approved on May 1, 2009) is currently marketed for the treatment of acute otitis externa (AOE). Cipro HC and Ciprodex are two otic formulations containing ciprofloxacin in combination with a corticosteroid which are approved and marketed for AOE in both the pediatric and adult populations. Ciprodex is approved and marketed for AOMT in children 6 months or older.

SYNALAR® (fluocinolone acetonide) Topical Solution, 0.01% is approved for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% (Cetraxal Plus) has marketing approval in several countries for AOE. It was first approved in Spain on March 25, 2002.

2.4 Important Safety Issues With Consideration to Related Drugs

Ciprofloxacin 0.2% otic solution
The most common adverse reactions reported in 2-3% of patients treated with CETRAXAL were application site pain, ear pruritis, fungal ear superinfection, and headache.
Ciprodex
In clinical trials with AOMT patients, the treatment emergent adverse events which occurred in 0.5% or more of the patients with non- intact tympanic membranes include ear discomfort, pain, ear precipitate (residue), irritability and taste perversion. In a single patient, tympanostomy tube blockage, ear prurtis, tinnitus, oral moniliasis, crying dizziness and erythema were reported. (b) (4) , treatment emergent adverse events of ear pruritis, debris, congestion, pain, erythema, superimposed infection occurred in more than 0.4% of patients. Ear discomfort, tingling and decreased hearing occurred in a single patient.
CiproHC
The most commonly reported drug related events in the clinical trials were headache and unspecified “ear disorder” occurring in only 1-2% of patients.

Oral or parenteral ciprofloxacin- hypersensitivity reactions including anaphylaxis and reports of tendon inflammation and/or rupture have occurred with systemic fluoroquinolone therapy. Exposure following otic administration is substantially lower than with systemic therapy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The presubmission regulatory history and milestones related to the current NDA submission are summarized as follows:

AOMT (b) (4)

- In 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 indicated 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 for ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution (IND 107809) was submitted.
- March 17, 2011: A Special Protocol Assessment (SPA), conducted in February 2011 was resubmitted after the Agency's input. The Agency recommended superiority for a meaningful clinical endpoint (e.g., time to cessation of otorrhea) be demonstrated for both components in the same population (i.e., ITT) and that sustained microbiological eradication rate in each of the ciprofloxacin-containing arms compared to the fluocinolone arm at the end of treatment (EOT) and test of cure (TOC) visit would be important as a secondary endpoint. Guidance was provided from the *Draft Guidance for Industry, Acute Bacterial Otitis Media: Developing Drugs for Treatment.*
- May 2, 2011: SPA agreement reached.
- July 2011: The applicant initiated twin phase III, multicenter, randomized, double-blind clinical trials (CIFLOTIII/10IA02 and CIFLOTIII/10IA04) to assess the efficacy and safety of ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution in the treatment of AOMT in pediatric subjects. Those studies enrolled 662 subjects in total, with a primary objective to demonstrate increased efficacy of the combination against ciprofloxacin or fluocinolone alone.
- September 3, 2013: The applicant committed to maintaining the CIFLOTIII/10IA04 study blinded until study CIFLOTIII/10IA02 was completed and to limit the number of subjects enrolled from shared sites. Fewer sites was to be transferred into study CIFLOTIII/10IA02 such that enrollment by investigators who participate in CIFLOTIII/10IA02 study accounted for maximum 24% of enrollment in the CIFLOTIII/10IA04 study.
- December 15, 2014: A pre NDA meeting was conducted between the applicant and the Agency.

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

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format. The clinical case summaries were comprehensive. Approximately 10% random sample (69 for CIFLOTIII-0001, 34 for CIFLOTIII-10IA02, 25 for CIFLOTIII-10IA04) case report forms (CRFs) were submitted.

The review of CRFs and datasets prompted information requests including, but not limited to the following:

- The applicant was asked to submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population/practice of medicine.
- The EPOCH variable for the Adverse event domain for studies CIFLOT III -101A 02, CIFLOT III -101A 04 and CIFLOT III -0001 was missing and the applicant was requested to submit updated datasets.

The applicant provided the responses in a timely fashion without delaying the review.

3.2 Compliance with Good Clinical Practices

The Clinical trials in this program were conducted in adherence with the principles of Good Clinical Practices (GCP), including directions set forth in relevant regulatory guidance (for example, ICH E6) and in keeping with study-subject protection as outlined in the Declaration of Helsinki (1964).

A request for site inspections was submitted to the Division of Scientific Investigations for the following U. S. sites due to high subject enrollments:
Study CIFLOTIII/10IA02, Site 010
Study CIFLOTIII/10IA02, Site 079
Study CIFLOTIII/10IA04, Site 247

The site inspections are ongoing at the time of this review.

3.3 Financial Disclosures

The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators had no reportable financial disclosures in the CIFLOTIII/10IA02, CIFLOTIII/10IA04 (b) (4) trials as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f). See Appendix 9.4 for detailed review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The proposed drug product is a sterile, preservative-free otic solution of Ciprofloxacin hydrochloride equivalent to Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025%, supplied in single-use vials. Ciprofloxacin hydrochloride is (b) (4) designed to have a broad spectrum antibacterial

activity. Fluocinolone acetonide is a synthetic corticosteroid primarily used in dermatology to reduce skin inflammation and relieve itching. Refer to Chemistry Manufacturing and Controls review for details.

4.2 Clinical Microbiology

Refer to the Clinical Microbiology review for details.

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology Toxicology review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ciprofloxacin is a fluoroquinolone antibacterial which inhibits the bacterial DNA gyrase and topoisomerase IV enzymes, which are essential for bacterial DNA replication, transcription, repair, and recombination. Fluoroquinolones form complexes of these enzymes with DNA that block movement of the DNA-replication fork, inhibiting DNA replication. Damage to DNA and the generation of DNA strand breaks leads to destabilization of the supercoiling structure and degradation of chromosomal DNA by exonucleases and eventual cell death. Topical application of 0.3% ciprofloxacin drops will result in high local antibacterial concentrations that will be active against the bacterial pathogens associated with AOMT.

Fluocinolone acetonide is a synthetic fluorinated corticosteroid with anti-inflammatory, antipruritic and vasoconstrictive properties. Early anti-inflammatory effects of topical corticosteroids include the inhibition of macrophage and leukocyte movement and activity in the inflamed area by reversing vascular dilation and permeability. Later inflammatory processes such as capillary production, collagen deposition, and keloid (scar) formation are also inhibited by corticosteroids. Clinically, these actions correspond to decreased edema, erythema, pruritus, plaque formation, and scaling of the affected skin.

The most common complications after tube insertion include otorrhea, formation of granulation tissue around the tube, and cholesteatoma. The addition of a corticosteroid to otic antibacterial preparations will aid in the resolution of the inflammatory response that accompanies bacterial infections.

4.4.2 Pharmacodynamics

Microbiology data are summarized in section 4.2. The two active drug substances in the proposed combination are both currently marketed for otic use although they are not marketed as a fixed combination. No specific in vivo pharmacology preclinical studies were performed.

4.4.3 Pharmacokinetics

No specific nonclinical pharmacokinetic or toxicokinetic studies have been performed with Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution in animals because of the low expected systemic exposure after otic application. The applicant refers to published information related to the development of ciprofloxacin and fluocinolone acetonide and their product labeling. The applicant also refers to the studies conducted with Ciprodex in human pediatric patients with tympanostomy tubes which demonstrated that absorption of ciprofloxacin occurred following otic administration; however, the plasma levels were negligible. It is anticipated that the systemic exposure of fluocinolone acetonide will also be negligible, due to the low dose administered and previously reported literature data after topical administration of the product.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table summarizes the phase 3 trials conducted (b) (4)

Table 1 Phase 3 clinical trials for AOMT (b) (4)

Study ID Locations (no. sites)	**Study dates Total enrollment**	**Study design**	**Patient population Duration of follow-up**	**Study and reference drugs Dose, route and regimen (Duration of treatment)**	**Study Objective /endpoints**	**Age of subjects**

CIFLOTIII/10IA02 46 sites (33 in the US, 6 in South Africa, 3 in Spain, 1 in the Czech Republic, 1 in Denmark, 1 in Finland, and 1 in Sweden)	15 July 2011– 23 June 2014 331 enrolled.	Multicenter, randomized, double blind, active controlled, parallel group; 1:1:1 ratio stratified by age into patients younger than 3 years old and patients 3 years and older.	Pediatric patients with AOMT, patent and open tympanostomy tube in the ear that was to be treated, otorrhea for 3 weeks or less, moderate or severe purulent otorrhea; 22 days	Study drug: Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution Reference drugs: Ciprofloxacin 0.3% otic solution Fluocinolone Acetonide 0.025% otic solution twice daily for 7 days	-Efficacy and Safety -Measure systemic absorption of Ciprofloxacin and/or Fluocinolone Acetonide in a subgroup of 30 patients Primary endpoint: Superiority for time to cessation of otorrhea over ciprofloxacin and over fluocinolone acetonide otic solution Secondary endpoint: Superiority of ciprofloxacin and fluocinolone otic solution over fluocinolone alone as well as to demonstrate superiority of ciprofloxacin alone over fluocinolone alone with respect to sustained microbiological cure	6 months to 12 years

CIFLOTIII/10IA04 49 sites (35 in the US, 6 in South Africa, 5 in Spain, 2 in Canada, and 1 in Finland)	19 August 2011 - 29 May 2013 331 enrolled	Multicenter, randomized, double blind, active controlled, parallel group; 1:1:1 ratio stratified by age into patients younger than 3 years old and patients 3 years and older.	Pediatric patients with AOMT, patent and open tympanostomy tube in the ear that was to be treated, otorrhea for 3 weeks or less, moderate or severe purulent otorrhea; 22 days	Study drug: Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution Reference drugs: - Ciprofloxacin 0.3% otic solution -Fluocinolone Acetonide 0.025% otic solution twice daily for 7 days	-Efficacy and Safety -Measure systemic absorption of Ciprofloxacin and/or Fluocinolone Acetonide in a subgroup of 30 patients Primary endpoint: Superiority for time to cessation of otorrhea over ciprofloxacin and over fluocinolone acetonide otic solution Secondary endpoint: Superiority of ciprofloxacin and fluocinolone otic solution over fluocinolone alone as well as to demonstrate superiority of ciprofloxacin alone over fluocinolone alone with respect to sustained microbiological cure	6 months to 12 years

(b) (4)

5.2 Review Strategy

Detailed reviews of the efficacy and safety data are presented by indication. Two new phase 3 clinical trials CIFLOTIII/10IA02 and CIFLOTIII/10IA04 were conducted by the applicant to evaluate the safety and efficacy of Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic Solution in AOMT [redacted] (b) (4) The Clinical Review is divided into two general parts: the review of efficacy and the review of safety. Both are conducted by the Medical Reviewer. Statistical analysis of efficacy is conducted by the statistical reviewer.

[redacted] (b) (4) The safety review was therefore conducted by pooling the CIFLOTIII/10IA02 and CIFLOTIII/10IA04 trials [redacted] (b) (4)

5.3 Discussion of Individual Studies/Clinical Trials

This submission contains data [redacted] (b) (4) Phase 3 trials. The applicant performed two identical clinical trials to support the AOMT indication (CIFLOTIII/10IA02 and CIFLOTIII/10IA04) [redacted] (b) (4) For detailed description of these trials, see section 6.1.1

6 Review of Efficacy

Efficacy Summary

The Applicant performed two Phase 3 randomized, double-blind clinical trials CIFLOTIII/10IA02 and CIFLOTIII/10IA04 to demonstrate efficacy in the treatment of acute otitis media in pediatric patients (aged 6 months and older) with tympanostomy tubes (AOMT). The primary efficacy endpoint was to demonstrate therapeutic superiority of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution over Ciprofloxacin 0.3% otic solution and over Fluocinolone Acetonide 0.025% otic solution for time to cessation of otorrhea. The principal secondary endpoint was to demonstrate therapeutic superiority of the product over each individual component with respect to sustained microbiological cure. The primary analysis of efficacy included analysis of each trial

individually in the CITT and CPP population and repeated separately for each of the 2 age strata (patients younger than 3 years old, patients 3 years and older).

Conclusions that can be drawn from the efficacy analysis are:

- Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution demonstrated therapeutic superiority over Ciprofloxacin and over Fluocinolone for the primary endpoint of time to cessation of otorrhea
- Median time to cessation of otorrhea was shorter for CIPRO+FLUO than for either of the treatments alone: median time to cessation was 2.9 days for CIPRO+FLUO, 4.4 days for CIPRO, and 3.6 days for the FLUO group in the CITT population in trial CIFLOTIII/10IA02
- Median time to cessation of otorrhea was 3.7 days for the CIPRO+FLUO group, 4.6 days for the CIPRO group, and 5.4 days for the FLUO group in the CITT population in trial CIFLOTIII/10IA04
- For study CIFLOTIII/10IA02, the sustained microbiological cure was observed in 47 of 61 patients (77.0%) in the CIPRO+FLUO group, 41 of 65 patients (63.1%) in the CIPRO group, and 23 of 54 patients (42.6%) in the FLUO group in the mITT population. For study CIFLOTIII/10IA04, the sustained microbiological cure was observed in 47 of 57 patients (82.5%) in the CIPRO+FLUO group, 43 of 61 patients (70.5%) in the CIPRO group, and 18 of 57 patients (31.6%) in the FLUO group in the mITT population.
- For study CIFLOTIII/10IA02, the sustained microbiological cure was observed in 41 of 48 (85.4%) in the CIPRO+FLUO group, 35 of 50 (70%) in the CIPRO group and 18 of 44 patients (40.9%) in the FLUO group in the MPP population. For study CIFLOTIII/10IA04, the sustained microbiological cure was observed in 32 of 39 patients (82.1%) in the CIPRO+FLUO group, 37 of 54 patients (68.5%) in the CIPRO group, and 14 of 44 patients (31.8%) in the FLUO group in the MPP population.
- Mean age was 3.5 years

6.1 Indication

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.*

6.1.1 Methods

AOMT

Randomization, stratification, blinding

Patients were randomly assigned in a 1:1:1 ratio to receive treatment with the investigational medication, Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution, or the comparator treatments, Ciprofloxacin 0.3% otic solution or Fluocinolone Acetonide 0.025% otic solution. Patients were stratified at enrollment by age and classified into 2 groups: patients younger than 3 years old and patients 3 years and older. It was planned that the total number of patients in the study would be divided approximately evenly between the 2 age groups. The applicant states that every attempt was made to maintain the blind throughout the study.

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 the patient's legally authorized representative; also, if the patient was capable of providing assent, signed assent from the patient

Key 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. Use of topical or otic steroids within 3 days of enrollment or systemic steroids within 7 days of enrollment
14. Use of intranasal or inhaled steroids within 3 days of enrollment
15. Any infection requiring systemic antimicrobial therapy

Each study consisted of 4 visits:
● Visit 1 at Day 1: Screening, Randomization/enrollment; start of treatment; predose blood samples were collected, if applicable. An audiometric evaluation (behavioral audiogram) was performed before onset of treatment in subjects capable of following the procedure. Middle ear exudate was collected with a syringe or cannula for microbiological culture before onset of treatment. Caregivers completed a quality of life (QoL) questionnaire.
● Visit 2 at Day 3-5: During treatment (signs and symptoms of AOMT assessed by otoscopy; decision to continue or discontinue and record as treatment failure).
● Visit 3 at Day 8-10: End of Treatment (EOT); middle ear exudate collected if present; postdose blood samples collected, if applicable. Caregivers completed a QoL questionnaire.
● Visit 4 at Day 18-22: Post-treatment/Follow-up, Test of Cure (TOC); middle ear exudate, collected if present. Audiometric evaluation performed in subjects who underwent that procedure at Visit 1. Caregivers completed a QoL questionnaire.

Dose selection
With the proposed combination of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025%, the planned exposure to the active ingredient would be approximately 1.5 mg of Ciprofloxacin and 0.125 mg of Fluocinolone Acetonide per day (approximately 10.5 mg of Ciprofloxacin and 0.875 mg of Fluocinolone Acetonide over a 7-day period). This quantity would be doubled in the case of

bilateral disease. Study medication was instilled in the affected ear(s) twice daily (morning and evening), preferably 12 hours apart but no less than 8 hours apart, for 7 continuous days.

Concomitant medications
The following 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.

The use of ibuprofen or medications containing codeine was also permitted to treat otalgia if it was not combined with a non-steroidal anti-inflammatory drug and was recommended by the treating physician.

Study schedule

Table 2 Schedule of observations and assessments

Evaluation	**Visit 1 Screening/ Study Entry**	**Visit 2**	**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[a]	X	X	X	X
Signs and symptoms of otitis[b]	X	X	X	X

Evaluation	**Visit 1 Screening/ Study Entry**	**Visit 2**	**Visit 3 End of Treatment**	**Visit 4 Post-Treatment Follow-Up**
Study Day	**1**	**3-5**	**8-10**	**18-22**
Audiometric evaluation[c]	X			X
Clinical response		X	X	X
Pharmacokinetic sample collection[d]	X		X	
Microbiological culture of ear discharge[e]	X		X	X
Randomization through IWRS	X			
Dispense study medication and explain its use	X	X[f]		
Collect used and unused study medication containers			X[g]	
Dispense diary card and explain its use	X			
Collect diary cards				X
Quality-of-life questionnaire (OM-6)	X		X	X
Concomitant medications	X	X	X	X
Adverse events	X	X	X	X

Abbreviations: IWRS, interactive web response system.

[a] Physical examination included temperature, blood pressure, and pulse rate.

b Signs and symptoms of otitis included otoscopy (volume of otorrhea, type/color of otorrhea, eardrum edema, granulation tissue, eczema of the external auditory canal, tube status) and otalgia.

[c] Behavioral audiogram was performed in patients whenever possible. At Visit 1, the behavioral audiogram was to be performed before the first dose.

[d] At select study sites, blood samples were taken in a subgroup of patients at Visit 1 (before dosing) and at Visit 3 to determinate the plasma levels of Ciprofloxacin and/or Fluocinolone Acetonide.

[e] If no exudate was present, no attempt to culture was made.

[f] If a patient had unilateral acute otitis media with tympanostomy (AOMT) at Visit 1 but bilateral at Visit 2, the investigator obtained a second kit number (with the same medication delivered at Visit 1) through the IWRS.

[g] If patients forgot to bring in containers at Visit 3, they were to bring the containers in no later than Visit 4.
Source: Page 49 of applicant's Clinical Study Report for study CIFLOTIII/10IA02

For patients who had bilateral otitis media with tympanostomy tubes, the most affected ear was considered the evaluable ear. The non-evaluable ear received the same treatment as the evaluable ear, as assigned by the IWRS.

Discontinuation of study drug
Adverse event(s) (AE), lack of efficacy, at the discretion of the investigator, violation of eligibility criteria, deviation from the treatment plan specified in the protocol (e.g., incorrect administration of study medication, failure to attend study visits).

Efficacy assessments

Endpoints

Primary endpoint: **Time to cessation of otorrhea-** The primary efficacy endpoint was to demonstrate therapeutic superiority of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution over Ciprofloxacin 0.3% otic solution and over Fluocinolone Acetonide 0.025% otic solution 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.

Secondary endpoint: **Sustained microbiological cure-** The principal secondary endpoint was to demonstrate therapeutic superiority of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution over Fluocinolone Acetonide 0.025% otic solution 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 was defined as Eradication or Presumed Eradication in the bacteriologic response at both Visit 3 (EOT) and Visit 4 (TOC).

Microbiological cultures of middle ear were collected at Visits 1, 3 and 4 (except when no exudate was present at Visit 3 or 4). The content of the middle ear was obtained by aspirating through the tympanostomy tube using a syringe or cannula after cleaning the external auditory canal. The following species were most likely to be pathogens: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *P. aeruginosa*.

For any patient with a culture positive for a pathogen at Visit 1, bacteriologic response at Visit 3 was classified as follows:

- Eradication if the culture did not show growth of any pathogen
-Presumed Eradication if there was no material to culture and the clinical response was Clinical Cure
-Persistence if any pathogen cultured at Visit 1 was still present
-Superinfection if a pathogen not present at Visit 1 was now present (presence of a non-pathogenic organism was not considered superinfection)
-Indeterminate if none of the above definitions were met and the bacteriologic response could not be determined

Clinical Efficacy

- Clinical Response:

The clinical response was assessed at visits 2, 3 and 4.
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 therapy or development of complications of AOMT, unchanged clinical signs or symptoms or improved clinical signs or symptoms without complete resolution as compared with baseline.

- Volume of otorrhea: assessed at Visits 1, 2, 3, and 4 by the same investigator. Otorrhea was resolved if level was 0.

Severe (3): copious discharge that prevented visualization of the tube.
Moderate (2): the anterior sulcus was full and the fluid came up to the edge of the tube; the tube or part of it still visible.
Mild (1): little fluid accumulating in the anterior tympanomeatal sulcus but the tube still clearly visible.
Absent (0)

- Granulation Tissue: assessed at Visits 1, 2, 3, and 4 by the same investigator.

Severe (3): obstructed tube lumen, extended beyond the eardrum and touched the ear canal > 1 mm.

Moderate (2): may have been in the lumen but not obstructing the lumen, may have extended beyond the eardrum or touched the ear canal skin < 1 mm.
Mild (1): limited to the eardrum adjacent to the tube, not in the tube lumen, not touching the ear canal.
Absent (0)

- Type/Color of Otorrhea: assessed at Visits 1, 2, 3, and 4 by the same investigator whether serous, mucoid or purulent.

- Eardrum Edema: assessed at Visits 1, 2, 3, and 4 by the same investigator.

Severe (3): total loss of landmarks with bulling/fullness
Moderate (2): opacification (loss of transparency) but the malleus handle was still discernible
Mild (1): mild erythema only with well-visualized landmarks
Absent (0)

- Pain (Otalgia): assessed at Visits 1, 2, 3, and 4 by the same investigator

Severe (3): interfered with activities of daily living
Moderate (2): caused discomfort but did not interfere with activities of daily living
Mild (1): awareness of pain but not much discomfort
Absent (0): total absence of pain
Unable to assess: rating could not be given

- Eczema of the External Auditory Canal: assessed at Visits 1, 2, 3, and 4 by the same investigator

Severe (3): moderate to severe edema with stenosis of the ear canal, exudation, lichenification with or without papillary changes
Moderate (2): desquamation, minimal edema (no exudation, stenosis)
Mild (1): erythema only (no edema or desquamation of skin)
Absent (0)

- Presence of Tympanostomy Tubes: presence or absence of tubes; open or closed at visits 1, 2, 3, 4
- Quality-of-Life Questionnaire OM-6: at visits 1, 3, 4 by caregiver. It was composed of 6 domain scores each addressed by a single question (physical suffering, hearing loss, speech impairment, emotional distress, activity limitation and caregivers concerns). Answers were given on a 7-point categorical scale (varying from 0 to 6, with 6 being the most severe score).

- AOM-SOS Questionnaire: completed by caregivers twice daily during the whole study. The questionnaire was composed of 7 domain scores each addressed by a single question (ear rubbing, excessive crying, irritability, restless sleep, less playful or active, poor appetite, and fever). Answers were given on a 3-point categorical scale (varying from 0 to 2; 2 was the most severe score).

Analysis populations

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.

Efficacy analyses were conducted on the CITT and CPP populations (clinical endpoints) and on MITT and MPP populations (microbiological endpoints). Only assessments from the evaluable ear were used for the efficacy analyses.

Sensitivity analysis

Sensitivity Analyses of the Primary Endpoint:

4 sensitivity analyses were conducted:

● To explore the impact of missing data, the primary analysis was repeated for the CITT Population censoring all discontinued subjects at Day 1, regardless of the reason for discontinuation.
● 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 primary analysis was repeated of the primary endpoint for subjects with only bacterial pathogens identified at Visit 1.
● The same analysis was repeated for subjects with both bacterial and viral pathogens identified at Visit 1.

Secondary analyses of the primary endpoint were performed for the CPP Population, for each of the 2 age strata (subjects <3 years versus ≥3 years old) on the CITT and CPP Populations, for subjects in the CITT and CPP Populations that did not take potentially 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 subjects with 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.

For the principal secondary endpoint, the frequency of subjects (n,%) with sustained microbiological cure was summarized and compared between CIPRO+FLUO and FLUO alone and between CIPRO alone and FLUO alone by using a Cochran-Mantel-Haenszel (CMH) test stratified by age (<3 years versus ≥3 years). Additionally, exploratory comparisons between CIPRO+FLUO over CIPRO were performed.

For the other secondary efficacy endpoints, comparisons of the treatment groups were made by using the chi-squared or CMH test, as appropriate.

Statistical analysis plan:

The null hypothesis was that there was no difference in time to cessation of otorrhea between the combination and the components alone. The alternative hypothesis was that there was a difference in time to cessation of otorrhea between the combination and the components alone. The comparison of the treatment groups to be made by using the log-rank test stratified on age (6 months to younger than 3 years old versus 3 years and older), and a difference claimed if the null hypothesis can be rejected at the two-sided 0.05 level.

The following analyses in the tables below are reviewer generated unless specified as Applicant's Tables.

6.1.2 Demographics

The Table below shows the demographics of the safety population of the pooled CIFLOTIII/10IA02 and CIFLOTIII/10IA04 trials.

Table 3 Demographics (Safety population) - pooled CIFLOTIII/10IA02 and CIFLOTIII/10IA04 trials

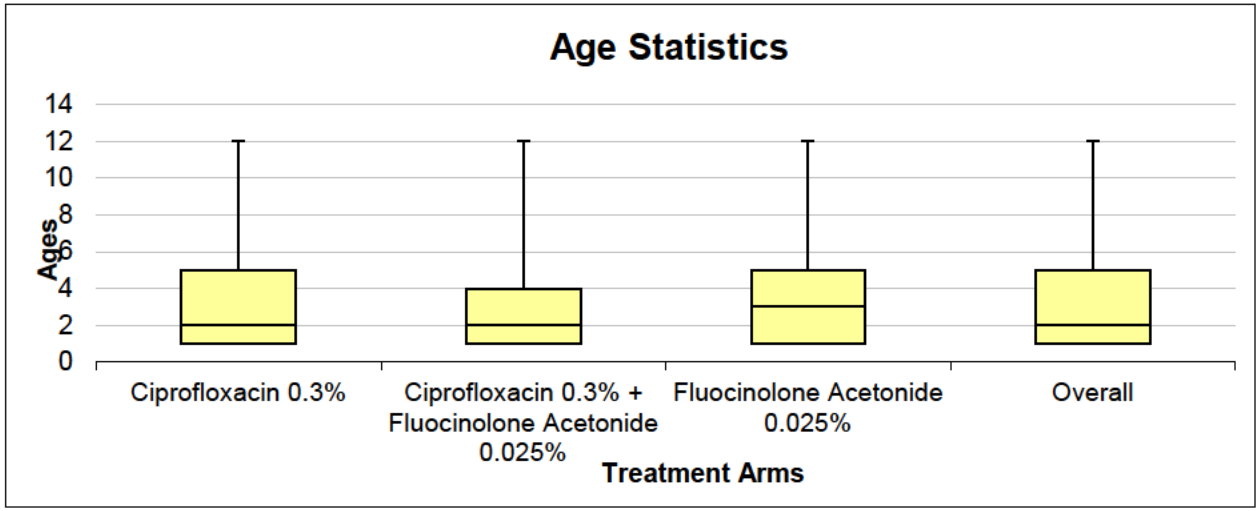
Baseline characteristics		Ciprofloxacin 0.3%	Ciprofloxacin 0.3% + Fluocinolone Acetonide 0.025%	Fluocinolone Acetonide 0.025%	Overall
		N=220	N=224	N=213	N=657
Age	Mean (SE)	3.6 (2.9)	3.3 (2.7)	3.7 (3.0)	3.5 (2.9)
Age Group n(%)	Age under 3 years	111 (50.5)	117 (52.2)	106 (49.8)	334 (50.8)
	Age 3 and over	109 (49.5)	107 (47.8)	107 (50.2)	323 (49.2)
Sex n(%)	F	86 (39.1)	94 (42)	88 (41.3)	268 (40.8)
	M	134 (60.9)	130 (58)	125 (58.7)	389 (59.2)
Race n(%)	American Indian Or Alaska Native	2 (0.9)	1 (0.4)	0 (0)	3 (0.5)
	Asian	8 (3.6)	5 (2.2)	4 (1.9)	17 (2.6)
	Black Or African American	32 (14.5)	33 (14.7)	23 (10.8)	88 (13.4)
	Native Hawaiian Or Other Pacific Islander	1 (0.5)	0 (0)	1 (0.5)	2 (0.3)
	White	167 (75.9)	168 (75)	171 (80.3)	506 (77)

	Other	10 (4.5)	17 (7.6)	14 (6.6)	41 (6.2)
Ethnicity n(%)	Hispanic Or Latino	29 (13.2)	30 (13.4)	28 (13.1)	87 (13.2)
	Not Hispanic Or Latino	191 (86.8)	194 (86.6)	185 (86.9)	570 (86.8)
Country n(%)	CAN	1 (0.5)	0 (0)	1 (0.5)	2 (0.3)
	CZE	1 (0.5)	0 (0)	0 (0)	1 (0.2)
	DNK	3 (1.4)	2 (0.9)	5 (2.3)	10 (1.5)
	ESP	34 (15.5)	24 (10.7)	28 (13.1)	86 (13.1)
	FIN	2 (0.9)	0 (0)	0 (0)	2 (0.3)
	SWE	0 (0)	0 (0)	1 (0.5)	1 (0.2)
	USA	146 (66.4)	170 (75.9)	151 (70.9)	467 (71.1)
	ZAF	33 (15)	28 (12.5)	27 (12.7)	88 (13.4)

MO Comment: The treatment groups were similar with respect to demographic and baseline disease characteristics in both CIFLOTIII/10IA02 and CIFLOTIII/10IA04 trials. Approximately 60% of subjects in each group were males.

The following figure represents the age distribution of the subjects in the AOMT trials.

Figure 3 Age distribution of the pooled CIFLOTIII/10IA02 and CIFLOTIII/10IA04 trial safety population



MO Comment: The mean age was 3.5 years overall and 50.8% of children were under 3 years of age. Majority of the subjects were from the US (71%) and Caucasian (77%).

6.1.3 Subject Disposition

The following table depicts the number of subjects in the pre specified analysis populations.

Table 4 Number of Subjects in the prespecified analysis populations in CIFLOTIII/10IA02 and CIFLOTIII/10IA04

	CIFLOTIII/10IA02			**CIFLOTIII/10IA04**		
Category	CIPRO+FLUO N=112 n	CIPRO N=109 n	FLUO N=110 n	CIPRO+FLUO N=111 n	CIPRO N=112 n	FLUO N=108 n
CITT	112	109	110	111	112	108
CPP	83	80	82	77	89	73

MicroITT	65	70	60	60	65	62
MPP	49	54	45	40	56	46
Safety population	113	108	106	111	112	107

Source: Adapted from Table 10-1 of CSR for CIFLOTIII/10IA02 and CIFLOTIII/10IA04

A total of 662 subjects were randomized in the CIFLOTIII/10IA02 and CIFLOTIII/10IA04 studies. There were a total of 657 subjects in the Safety Population. Five subjects did not take study medication and were excluded from the Safety Population. One subject (Subject CIFLOTIII-10IA02-033-018) was dispensed an incorrect kit by the site. This patient was included in the CITT population under the treatment assigned (FLUO) and included in the safety population under the treatment actually received (CIPRO+FLUO).

The following Table shows the disposition of the subjects in the AOMT trials.

Table 5 Disposition of subjects in the AOMT trials (all randomized subjects)

	Study CIFLOTIII/10IA02			**Study CIFLOTIII/10IA04**		
	CIPRO N=109	CIPRO+FLUO N=112	FLUO N=110	CIPRO N=112	CIPRO+FLUO N=111	FLUO N=108
Major protocol deviations	N=37	N=31	N=30	N=26	N=40	N=45
Concomitant medications	8 (7.3%)	11 (9.8%)	12(10.9%)	15 (13.4%)	15 (13.5%)	14(13.0%)
Dosing	6 (5.5%)	2 (1.8%)	4 (3.6%)	0 (0.0%)	4 (3.6%)	4 (3.7%)
Enrollment criteria	4 (3.7%)	4 (3.6%)	1 (0.9%)	2 (1.8%)	8 (7.2%)	4 (3.7%)
Non-compliance	2 (1.8%)	1 (0.9%)	1 (0.9%)	3 (2.7%)	5 (4.5%)	4 (3.7%)
Other	6 (5.5%)	3 (2.7%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	4 (3.7%)
Visit schedule	8 (7.3%)	9 (8.0%)	8 (7.3%)	3 (2.7%)	1 (0.9%)	9 (8.3%)
Visit/procedure requirement	3 (2.8%)	1 (0.9%)	2 (1.8%)	2 (1.8%)	7 (6.3%)	6 (5.6%)
Reason for Study Med Discontinuation	N=14	N=11	N=24	N=12	N=8	N=20
Adverse event	4 (3.7%)	3 (2.7%)	6 (5.5%)	3 (2.7%)	0	4 (3.7%)

At the discretion of the Investigator	0	0	2 (1.8%)	1 (0.9%)	0	2 (1.9%)
Deviation from the treatment plan specified in the protocol (e.g., incorrect administration of study medication)	0	0	1 (0.9%)	1 (0.9%)	0	2 (1.9%)
Lack of efficacy and/or rescue medication use	4 (3.7%)	3 (2.7%)	11(10.0%)	5 (4.5%)	3 (2.7%)	10 (9.3%)
Other	6 (5.5%)	4 (3.6%)	3 (2.7%)	0	2 (1.8%)	1 (0.9%)
Violation of eligibility criteria	0	1	0	0	2 (1.8%)	0
Withdrew consent	0	0	1 (0.9%)	2 (1.8%)	0	0
Lost to follow-up				0	1 (0.9%)	1 (0.9%)
Reason for Study Withdrawal	N=10	N=8	N=19	N=8	N=5	N=19
Adverse event	3 (2.8%)	3 (2.7%)	4 (3.6%)	2 (1.8%)	0 (0.0%)	3 (2.8%)
At the discretion of the Investigator	0 (0.0%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Lack of efficacy and/or rescue medication use	4 (3.7%)	1 (0.9%)	7 (6.4%)	4 (3.6%)	0 (0.0%)	10 (9.3%)
Lost to follow-up	1 (0.9%)	2 (1.8%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	4 (3.7%)
Other	0 (0.0%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Violation of eligibility criteria	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.8%)	0 (0.0%)
Withdrew consent	1 (0.9%)	1 (0.9%)	3 (2.7%)	2 (1.8%)	0 (0.0%)	1 (0.9%)

MO Comment: In study CIFLOTIII/10IA02, 88.8% subjects completed the study, 11.2% discontinued from the study including 8 patients in the CIPRO+FLUO group, 10 patients in the CIPRO group, and 19 patients in the FLUO group. In study CIFLOTIII/10IA04, 90.3% subjects completed the study, and 9.7% discontinued from the study, including 5 patients in the CIPRO+FLUO group. The most common reason for study discontinuation in both trials was lack of efficacy and/or rescue medication use.

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis of the primary endpoint was conducted in the CITT and CPP population and repeated separately for each of the 2 age strata (patients younger than 3 years old, patients 3 years and older), using a non-stratified log-rank test and a Wilcoxon test.

The following patients were censored at the maximum evaluation (i.e., Day 22):
-Patients who did not discontinue prematurely from the study and for whom the otorrhea still persisted at the end of the study
-Patients who discontinued for any reason
-Patients who discontinued for lack of efficacy or who took rescue medication
-Lost to follow up patients
-Randomized and non-dosed patients

To determine the time to cessation of otorrhea without confounding variables the primary analysis of the primary endpoint was repeated for
1) Patients who did not take out-of-specification study medication in the safety, CITT, and CPP populations.
2) Patients who used or did not use titanium tubes on both the CITT and CPP populations (to remove possible confounding effect of antibacterial or antiseptic properties of titanium tubes).

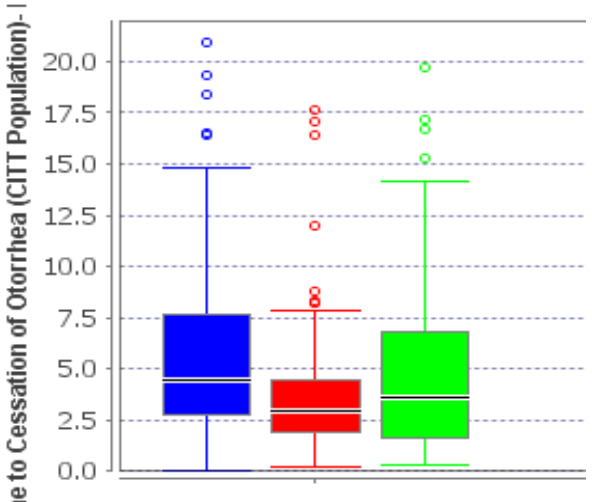
The following Table and Figure shows the primary endpoint analysis of time to cessation of otorrhoea in the CITT population of trial CIFLOTIII/10IA02 using uncensored data.

Table 6 Time to cessation of otorrhoea (CITT population, uncensored data) - trial CIFLOTIII/10IA02

Time to cessation of otorrhea (Days)	CIPRO N=109	CIPRO+FLUO N=112	FLUO N=110
Uncensored patients [a]	n=73	n=88	n=53
Mean	5.76	3.9	4.95
Std Dev	4.6	3.36	4.61
Min	0	0.21	0.27
Max	20.97	17.68	19.74

Time to cessation of otorrhea (Days)	CIPRO N=109	CIPRO+FLUO N=112	FLUO N=110
[a] Patients with known time to cessation of otorrhea and not censored for other reasons.			

Figure 4 Time to cessation of otorrhoea (CITT population) - trial CIFLOTIII/10IA02



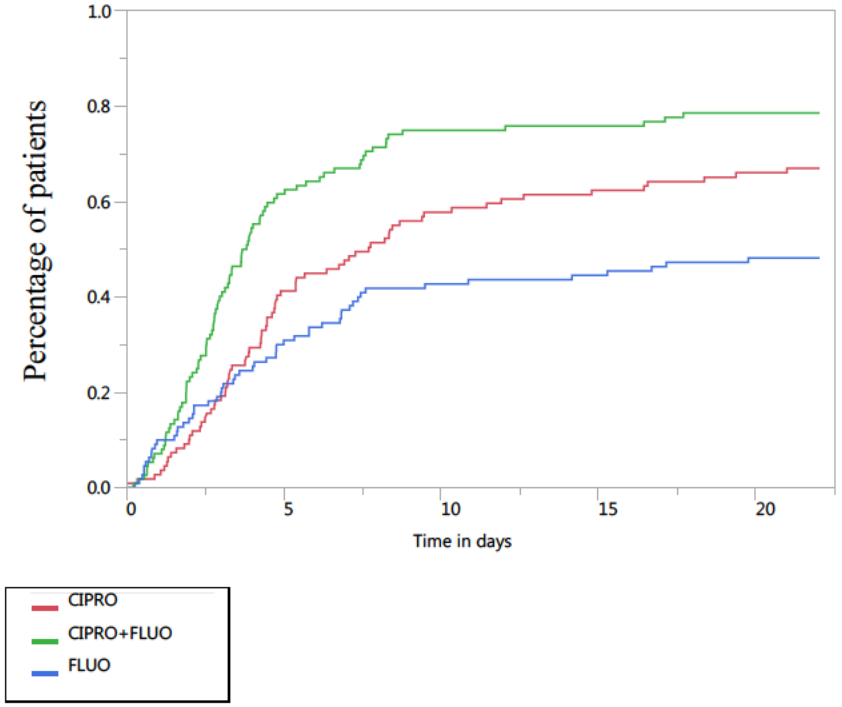
	CIPRO	CIPRO+FLUO	FLUO
Mean	5.76	3.92	4.95
Median	4.43	2.94	3.59
Q1	2.79	1.90	1.62
Q3	7.69	4.43	6.82
N	73	88	53

MO Comment: The mean time to cessation of otorrhea was shorter in the Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% group than Ciprofloxacin and Fluocinolone alone. The median time to cessation of otorrhea was shorter for CIPRO+FLUO than for

either of the treatments alone: median time to cessation was 2.9 days for CIPRO+FLUO, 4.4 days for CIPRO, and 3.6 days for the FLUO group.

The following survival cumulative analysis using the censoring rules and Kaplan-Meier estimates stratified by age (subjects <3 years versus ≥3 years) shows the cumulative incidence function of the time to cessation of otorrhea.

Figure 5 Time to cessation of otorrhea - cumulative Incidence function with Kaplan-Meier estimates (CITT Population) - trial CIFLOTIII/10IA02



Time to event: AVAL= Analysis Value, Censored by CNSR, Censor Code 1, Grouped by Planned Treatment (TRTP).

The Table below shows the pairwise comparisons using the log-rank test and Wilcoxon test, stratified by age (subjects <3 years versus ≥3 years) demonstrating a statistically significant difference in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group (P<0.001) and compared with the FLUO group (P<0.001).

Table 7 Time to cessation of otorrhea (CITT population) - trial CIFLOTIII/10IA02

Group	Number uncensored [a]	Number censored	Mean	Std Error
CIPRO	73	36	10.7794	0.77833
CIPRO+FLUO	88	24	6.86492	0.60604
FLUO	53	57	12.616	0.77411
Combined	214	117	10.5142	0.46437

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	7.6875	4.7778	11.437	3.3486	.
CIPRO+FLUO	3.7486	3.0361	4.3938	2.2538	10.396
FLUO	.	7.4306	.	4.0111	.
Combined	6.8167	4.9958	8.2028	2.8771	.

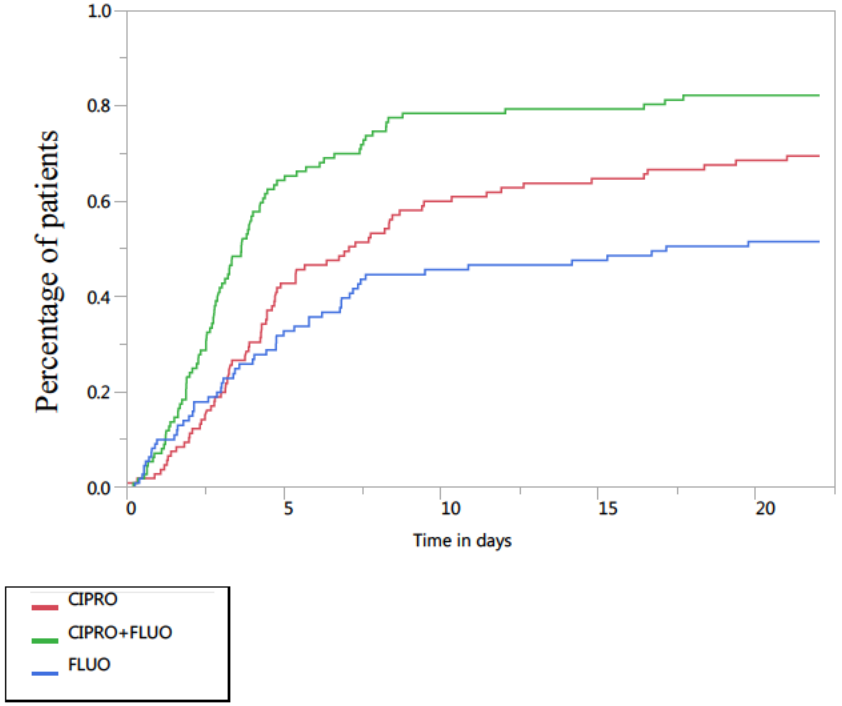
Test between groups	ChiSquare	DF	Prob>ChiSq
Log-Rank	27.2839	2	<.0001
Wilcoxon	25.5017	2	<.0001

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study).

The applicant conducted four sensitivity analyses of the primary endpoint.

● Sensitivity analysis of the primary endpoint censoring all discontinued subjects at Day 1, regardless of the reason for discontinuation. The Figure and Table below represent the Kaplan-Meier estimates of the median time to cessation of otorrhea for this sensitivity analysis.

Figure 6 Kaplan-Meier estimates of the median time to cessation of otorrhea censoring patients who discontinued study drug at Day 1,- trial CIFLOTIII/10IA02



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	73	36	10.4021	Biased	0.78259
CIPRO+FLUO	88	24	6.38037	Biased	0.59039
FLUO	53	57	12.1572	Biased	0.80118
Combined	214	117	9.9845	Biased	0.46816

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	7.0618	4.7535	9.4479	3.3021	.
CIPRO+FLUO	3.6458	2.9313	4.2576	2.2257	8.2403
FLUO	17.142	7.0868	.	3.5882	.
Combined	5.8	4.7118	7.4306	2.8056	.

Tests Between Groups

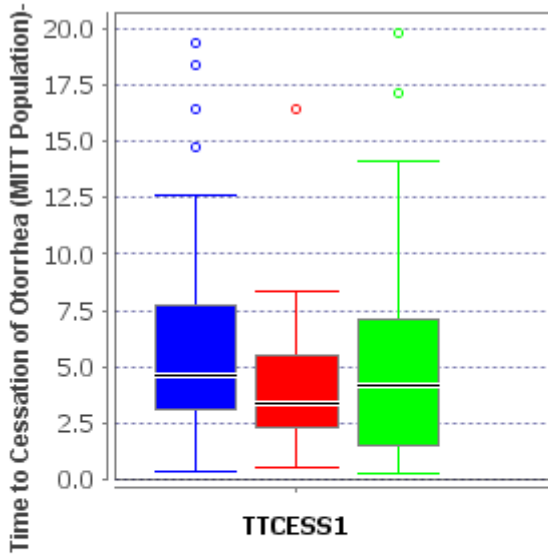
Test	Chi Square	DF	Prob>ChiSq
Log-Rank	27.9916	2	<.0001
Wilcoxon	24.9400	2	<.0001

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO Comment: In analysis censoring patients who discontinued study drug at Day 1, the median time to cessation of otorrhea were 3.6 days (95% CI, 2.9-4.3) for the CIPRO+FLUO group (N = 112), 7.1 days (95% CI, 4.8-9.4) for the CIPRO group (N = 109), and 17.1 days (95% CI, 7.1-not estimable for the FLUO group (N = 110). The pairwise comparisons using the log-rank test and Wilcoxon test, stratified by age (subjects <3 years versus ≥3 years) showed a statistically significant difference in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group (P<0.001) and compared with the FLUO group (P<0.001).

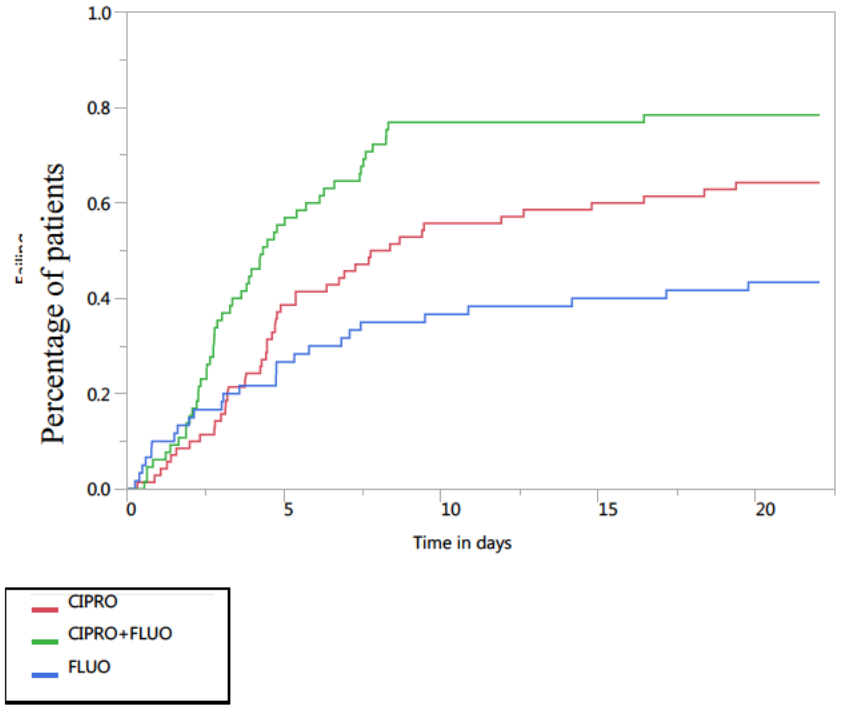
● Sensitivity analysis of the primary endpoint for the MITT Population. The following figures and tables show the primary endpoint analysis of time to cessation of otorrhoea in the MITT population of trial CIFLOTIII/10IA02.

Figure 7 Time to cessation of otorrhea in the MITT population- trial CIFLOTIII/10IA02



	CIPRO	CIPRO+FLUO	FLUO
Mean	5.96	4.15	5.33
Median	4.62	3.36	4.17
Q1	3.14	2.29	1.52
Q3	7.69	5.55	7.09
N	45	51	26

Figure 8 Kaplan-Meier estimates of the median time to cessation of otorrhea (MITT population) - trial CIFLOTIII/10IA02



Summary

Group	Number uncensored	Number censored	Mean		Std Error
CIPRO	45	25	10.7449	Biased	0.88936
CIPRO+FLUO	51	14	6.79573	Biased	0.70481
FLUO	26	34	13.4958	Biased	1.04027

Group	Number uncensored	Number censored	Mean		Std Error
Combined	122	73	10.563	Biased	0.56191

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	8.059	4.8993	16.434	4.25	.
CIPRO+FLUO	4.3354	3.2833	6.2708	2.5576	8.2486
FLUO	.	9.4792	.	4.7632	.
Combined	7.4479	5.3993	9.4792	3.1625	.

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	18.6195	2	<.0001
Wilcoxon	16.0895	2	0.0003

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO Comment: The Kaplan Meier estimates confirmed a shorter time to cessation of otorrhea in the CIPRO+FLUO group (4.3 days for the CIPRO+FLUO group, 8.1 days for the CIPRO group, and not estimable for the FLUO group) since the number of censored patients (n = 34) was greater than the number of patients with cessation of otorrhea (n = 26).

- Sensitivity analysis of the primary endpoint for the MITT Populations of subjects with only bacterial pathogens identified at Visit 1(N= 139) showed a shorter time to cessation of otorrhea in the CIPRO+FLUO group (median 3.7 days for the CIPRO+FLUO group, 8.5 days for the CIPRO group, and not estimable for the FLUO group).

- Sensitivity analysis of the primary endpoint for the MITT Populations of subjects with both viral and bacterial pathogens identified at Visit 1(N=56) showed a shorter time to cessation of otorrhea in the CIPRO+FLUO group (median 5.7 days for the CIPRO+FLUO group, 6.1 days for the CIPRO group, and not estimable for the FLUO group).

Secondary Analysis of the Primary Endpoint

● Analysis for the primary endpoint was performed for the CPP Population.

Kaplan-Meier estimates showed the median time to cessation of otorrhea was shortest for subjects in the CIPRO+FLUO group (3.7 days for the CIPRO+FLUO group, 8.0 days for the CIPRO group, and not estimable for the FLUO group). The pairwise comparisons using the log-rank test and Wilcoxon test, stratified by age (subjects <3 years versus ≥3 years) showed a statistically significant difference in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group (P<0.001) and compared with the FLUO group (P<0.001).

Figure 9 Time to cessation of otorrhea in the CPP population- trial CIFLOTIII/10IA02

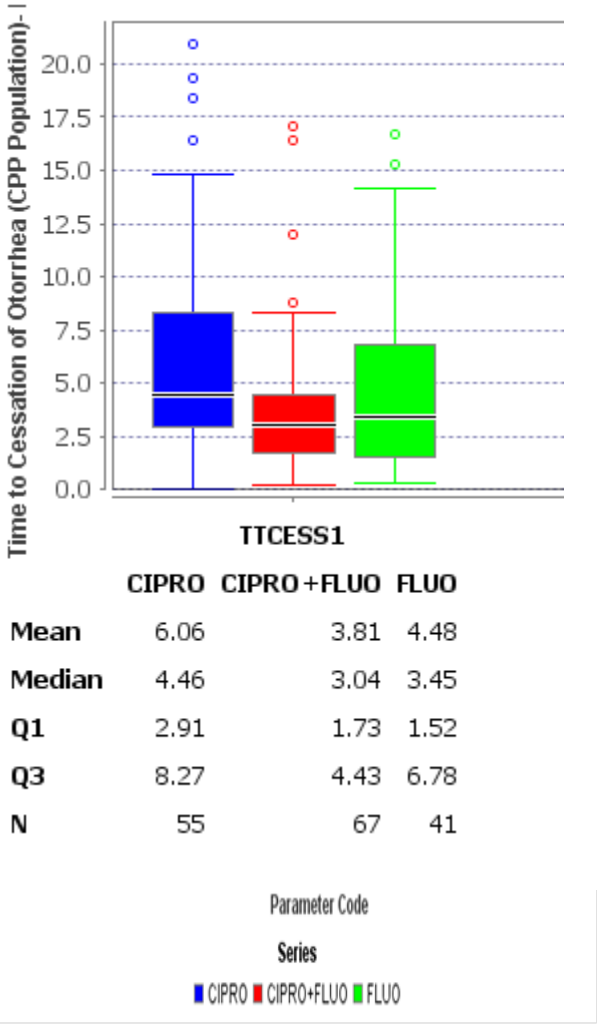
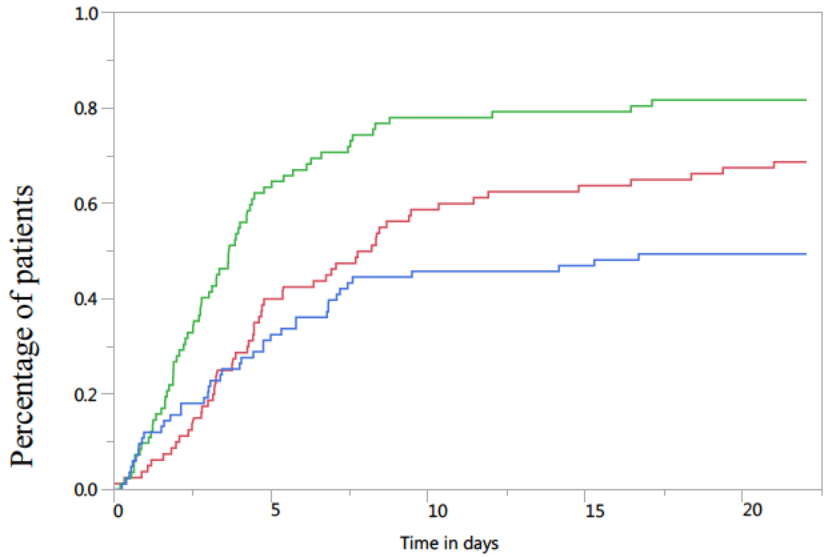


Figure 10 Kaplan-Meier estimates of the median time to cessation of otorrhea (CPP population)- trial CIFLOTIII/10IA02



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	55	25	10.7152	Biased	0.89695
CIPRO+FLUO	67	15	6.24362	Biased	0.65908
FLUO	41	42	10.6513	Biased	0.74316
Combined	163	82	10.1701	Biased	0.5354

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
CIPRO	7.9792	4.7118	11.437	3.5347	.

Group	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
CIPRO+FLUO	3.6712	2.7944	4.3938	1.909	8.2403
FLUO	.	6.8333	.	3.4479	.
Combined	6.5972	4.7625	7.7556	2.8139	.

Tests Between Groups

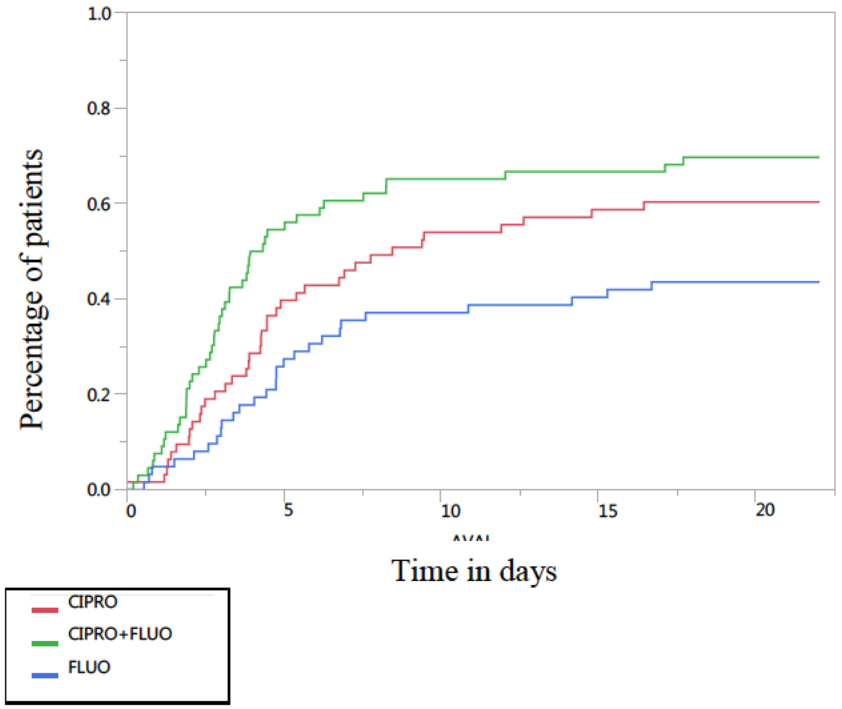
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	23.9506	2	<.0001
Wilcoxon	22.1143	2	<.0001

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO comment: In the reviewer analysis, the number of patients with cessation of otorrhea in the CIPRO+FLUO arm is 67 and 41subjects in the FLUO arm. However the Applicant analysis shows 68 subjects in the CIPRO+FLUO and 40 subjects in the FLUO arm.

● Analyses for the primary endpoint was performed separately for subjects <3 years and for subjects ≥3 years old in both the CITT and CPP Populations.

Figure 11 Kaplan-Meier estimates of the median time to cessation of otorrhea (CITT population, <3 years) - trial CIFLOTIII/10IA02



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	38	25	9.6183	Biased	0.80147
CIPRO+FLUO	46	20	8.11507	Biased	0.87247
FLUO	27	35	11.7901	Biased	0.80259
Combined	111	80	10.1512	Biased	0.51244

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	8.4423	4.7535	.	3.8076	.
CIPRO+FLUO	4.1399	3.0361	7.5208	2.2986	.
FLUO	.	7.5965	.	4.7639	.
Combined	8.2403	5.3993	16.672	3.134	.

Tests Between Groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.6328	1	0.1047
Wilcoxon	3.7758	1	0.0520

Tests Between Groups (CIPRO+FLUO versus FLUO)

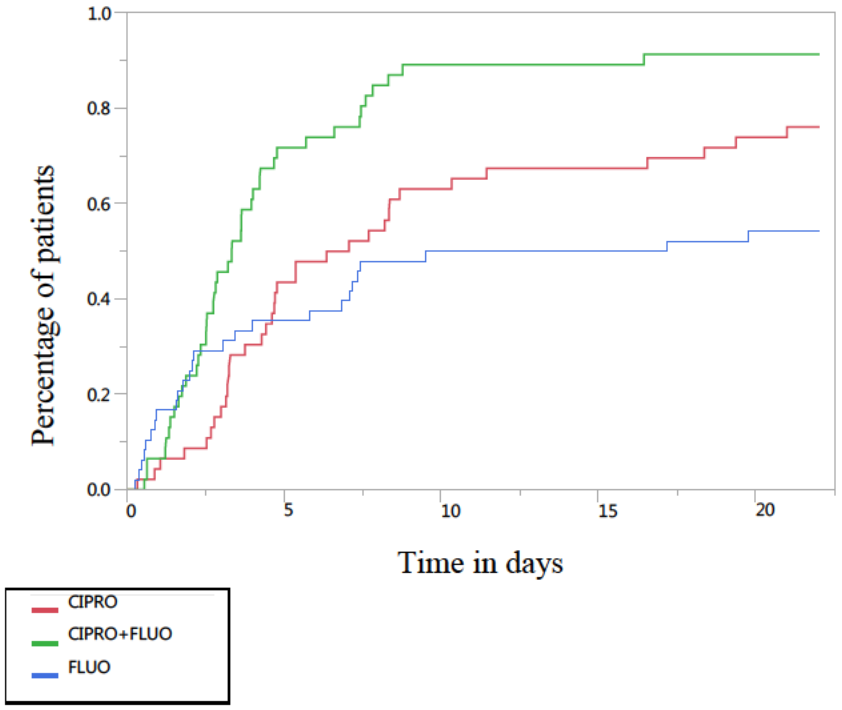
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	11.5523	1	0.0007
Wilcoxon	12.6902	1	0.0004

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO Comment: The time to cessation of otorrhea was shortest for subjects in the CIPRO+FLUO group. For subjects <3 years in the CITT Population, median time to cessation of otorrhea was 4.1 days for the CIPRO+FLUO group, 8.4 days for the CIPRO group, and not estimable for the FLUO group.

Neither the log-rank test nor the Wilcoxon test showed a statistically significant difference in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group (log-rank test P = 0.105, Wilcoxon test P = 0.052); although both tests showed statistically significant differences for the CIPRO+FLUO group compared with the FLUO group (log-rank test P < 0.001, Wilcoxon test P < 0.001).

Figure 12 Kaplan-Meier estimates of the median time to cessation of otorrhea (CITT population, ≥3 years)- trial CIFLOTIII/10IA02



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	35	11	9.90626	Biased	1.14637
CIPRO+FLUO	42	4	4.96241	Biased	0.67441
FLUO	26	22	11.4426	Biased	1.24223
Combined	103	37	9.13048	Biased	0.6845

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	6.7073	4.4264	10.324	3.2604	20.967
CIPRO+FLUO	3.3497	2.5479	4.225	2.2257	6.5972
FLUO	13.311	4.0111	.	2.0417	.
Combined	5.0743	3.9681	7.4063	2.5549	.

Tests Between Groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	10.1702	1	0.0014
Wilcoxon	11.1769	1	0.0008

Tests Between Groups (CIPRO+FLUO versus FLUO)

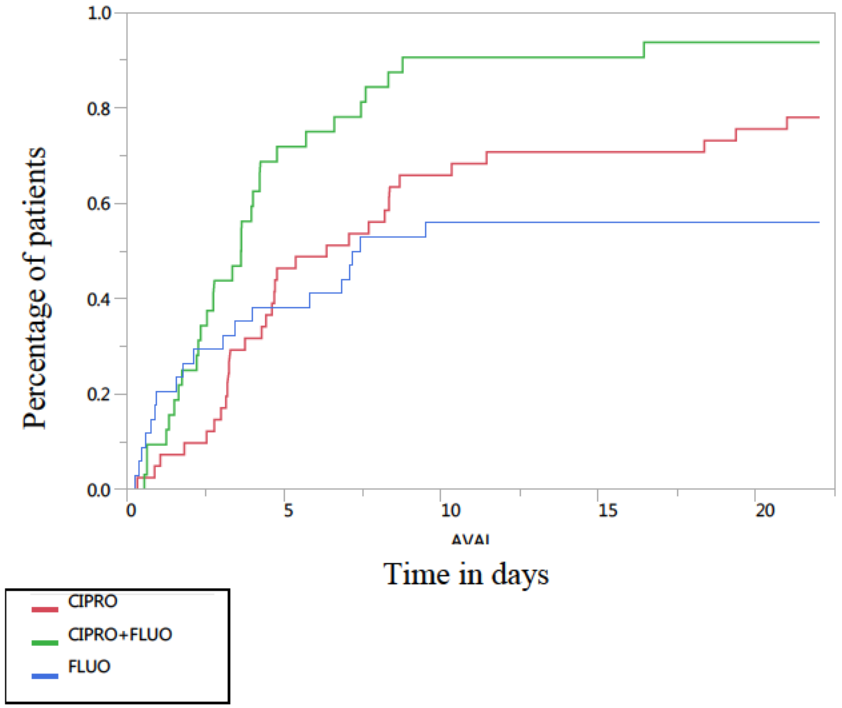
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	13.8992	1	0.0002
Wilcoxon	6.9726	1	0.0083

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO Comment: For subjects aged ≥3 years in the CITT population, the median time to cessation of otorrhea was also the shortest in the CIPRO+FLUO group.

Both the log-rank test and the Wilcoxon test showed statistically significant differences in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group and FLUO group.

Figure 13 Kaplan-Meier estimates of the median time to cessation of otorrhea (CPP population, ≥3 years of age)- trial CIFLOTIII/10IA02



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	32	9	9.49156	Biased	1.19689
CIPRO+FLUO	30	2	4.80141	Biased	0.77806
FLUO	19	15	6.07537	Biased	0.65603
Combined	81	26	8.69863	Biased	0.76278

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	6.3528	4.2951	8.6771	3.2604	19.354
CIPRO+FLUO	3.6399	2.2819	4.2576	1.9965	6.149
FLUO	7.3108	3.0722	.	1.8083	.
Combined	4.7778	3.7674	7.191	2.5576	20.967

Tests Between Groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	8.3952	1	0.0038
Wilcoxon	8.4844	1	0.0036

Tests Between Groups (CIPRO+FLUO versus FLUO)

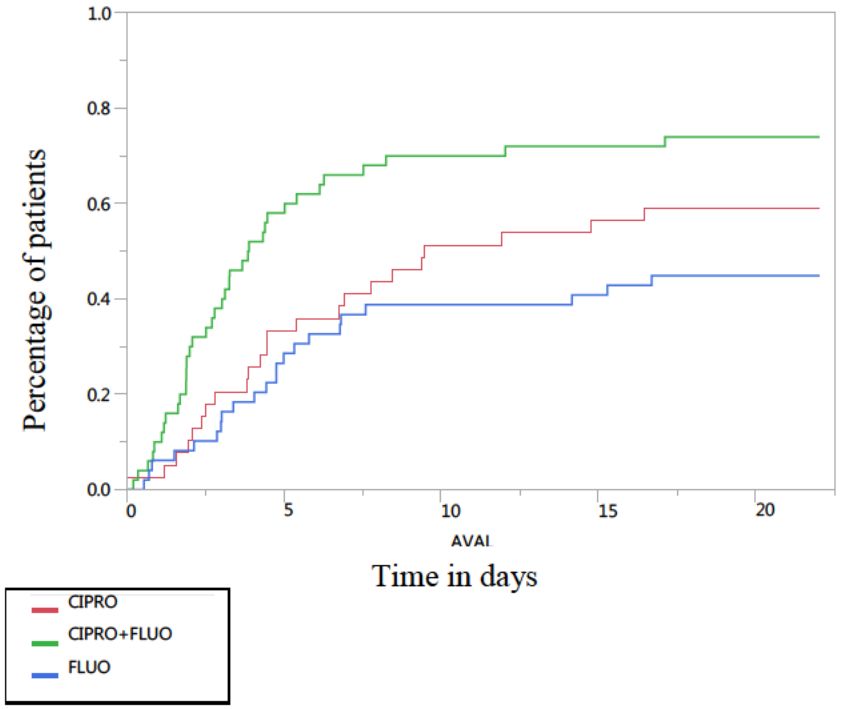
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.1723	1	0.0025
Wilcoxon	4.0500	1	0.0442

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

Kaplan-Meier estimates of median time to cessation of otorrhea were 3.6 days (95% CI, 2.3-4.2) for the CIPRO+FLUO group (N = 33), 6.4 days (95% CI, 4.3-8.7) for the CIPRO group (N = 41), and 7.3 days (95% CI, 3.4-not estimable) for the FLUO group (N = 33). Both the log-rank test and the Wilcoxon test showed statistically significant differences in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group (p=0.003). The log-rank test showed statistically significant differences in time to cessation of otorrhea for the CIPRO+FLUO group compared with the FLUO group (p=0.003) but marginal with the Wilcoxon test (p=0.044).

MO comment: Applicant analysis of Kaplan-Meier estimates of median time to cessation of otorrhea in the CPP population, ≥3 years of age also showed statistically significant differences for the CIPRO+FLUO group compared with the FLUO group (log-rank test P = 0.001, Wilcoxon test P = 0.027).

Figure 14 Kaplan-Meier estimates of the median time to cessation of otorrhea (CPP population, <3 years of age)- trial CIFLOTIII/10IA02



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	23	16	10.142	Biased	1.01203
CIPRO+FLUO	37	13	7.13981	Biased	0.93863
FLUO	22	27	11.6246	Biased	0.92458
Combined	82	56	9.7411	Biased	0.58439

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	9.4479	4.4583	.	3.8854	.
CIPRO+FLUO	3.875	2.7188	6.1319	1.909	.
FLUO	.	6.8167	.	4.7639	.
Combined	7.676	5.3333	16.672	3.0243	.

Tests Between Groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.4028	1	0.0359
Wilcoxon	5.8439	1	0.0156

Tests Between Groups (CIPRO+FLUO versus FLUO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	11.3216	1	0.0008
Wilcoxon	11.9333	1	0.0006

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO Comment: The Kaplan-Meier estimates of the median time to cessation of otorrhea were 3.9 days (95% CI, 2.7-6.1) for the CIPRO+FLUO group (N = 50), 9.4 days (95% CI, 4.5-not estimable) for the CIPRO group (N = 39), and not estimable for the FLUO group (N = 49). The log-rank test and the Wilcoxon test showed statistically significant differences in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group and the FLUO group.

- Secondary analysis of the primary endpoint for patients who did not take out-of-specification study medication and by each batch of study medication.

Stability testing results showed that the Fluocinolone treatment kits from study medication Batch 1 and some from Batch 2 may potentially have been out of specification. In patients who did not take potentially out-of-specification study medication in the safety, CITT and CPP populations, the log-rank test and Wilcoxon test revealed statistically significant differences in the time to cessation of otorrhea between the CIPRO+FLUO and the CIPRO and FLUO groups (log-rank test $P < 0.001$, Wilcoxon test $P < 0.001$).

Analysis of the primary endpoint was also performed for the safety population by each of the 5 batches of study medication used in the study. Time to cessation for otorrhea was shorter for the CIPRO+FLUO group than the FLUO group in all 5 batches of study medication and shorter for the CIPRO+FLUO group than the CIPRO group in study medication Batch 3, Batch 4, and Batch 5. For Batch 1 the median time to cessation of otorrhea were 6.8 days for the CIPRO+FLUO group, 5.6 days for the CIPRO group and not estimable for the FLUO group because the number of censored patients was greater than the number of patients with cessation of otorrhea. For Batch 2 the median time to cessation of otorrhea were 5.1 days for the CIPRO+FLUO group, 4.8 days for the CIPRO group, and not estimable for the FLUO group. The differences in time to cessation of otorrhea in the Batch 1 and 2 subgroups were not statistically significant.

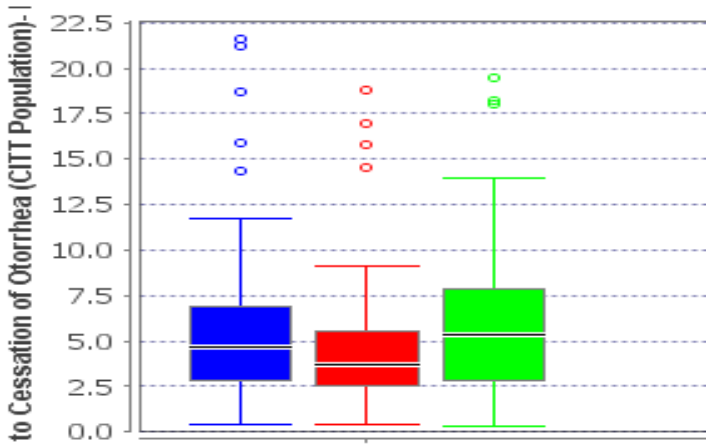
Trial CIFLOTIII/10IA04

Table 8 Time to cessation of otorrhea (CITT population, uncensored data) - trial CIFLOTIII/10IA04

Time to cessation of otorrhea (Days)	**CIPRO (112)**	**CIPRO+FLUO (111)**	**FLUO (108)**
Uncensored patients [a]	77	87	47
ean	5.5	4.5	6.1
Std Dev	4.2	3.3	4.5
Min	0.4	0.4	0.32
Max	21.5	18.8	19.5
[a] Patients with known time to cessation of otorrhea and not censored for other reasons.			

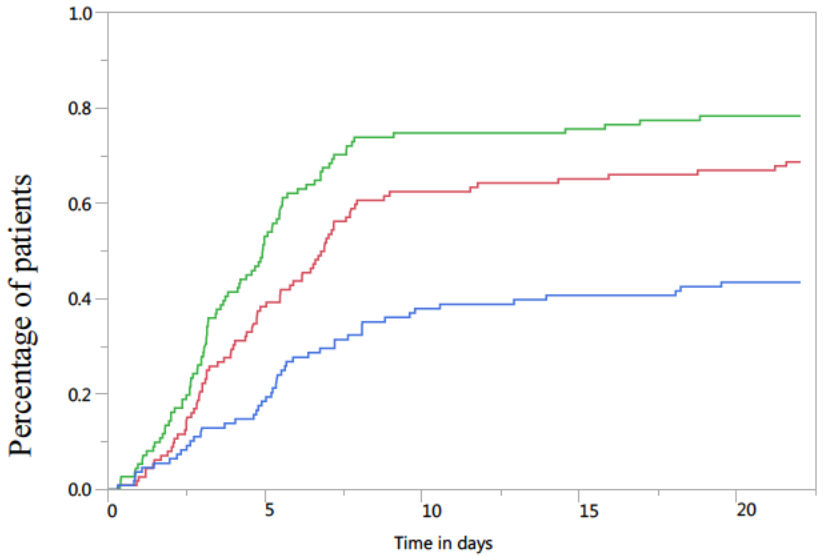
MO Comment: The time to cessation of otorrhea in pediatric subjects with AOMT was shorter in the CIPRO+FLUO group than in the CIPRO and FLUO groups in the CITT population

Figure 15 Time to cessation of otorrhoea (CITT population)- trial CIFLOTIII/10IA04



MO Comment: Analysis of uncensored data showed that the median time to cessation of otorrhea was 3.7 days for the CIPRO+FLUO group (N = 87), 4.6 days for the CIPRO group (N = 77), and 5.4 days for the FLUO group (N = 47).

Figure 16 Kaplan-Meier estimates of the median time to cessation of otorrhea (CITT population) - trial CIFLOTIII/10IA04



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	77	35	10.53	Biased	0.78055
CIPRO+FLUO	87	24	7.57451	Biased	0.62965
FLUO	47	61	13.6727	Biased	0.70501
Combined	211	120	11.143	Biased	0.46661

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	6.8316	5.4854	7.7417	3.1955	.

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO+FLUO	4.9354	3.7431	5.5208	2.8576	14.531
FLUO	.	13.931	.	5.5781	.
Combined	6.9514	5.9028	7.8333	3.2396	.

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

Tests Between Groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.8301	1	0.0280
Wilcoxon	5.4821	1	0.0192

Tests Between Groups (CIPRO+FLUO versus FLUO)

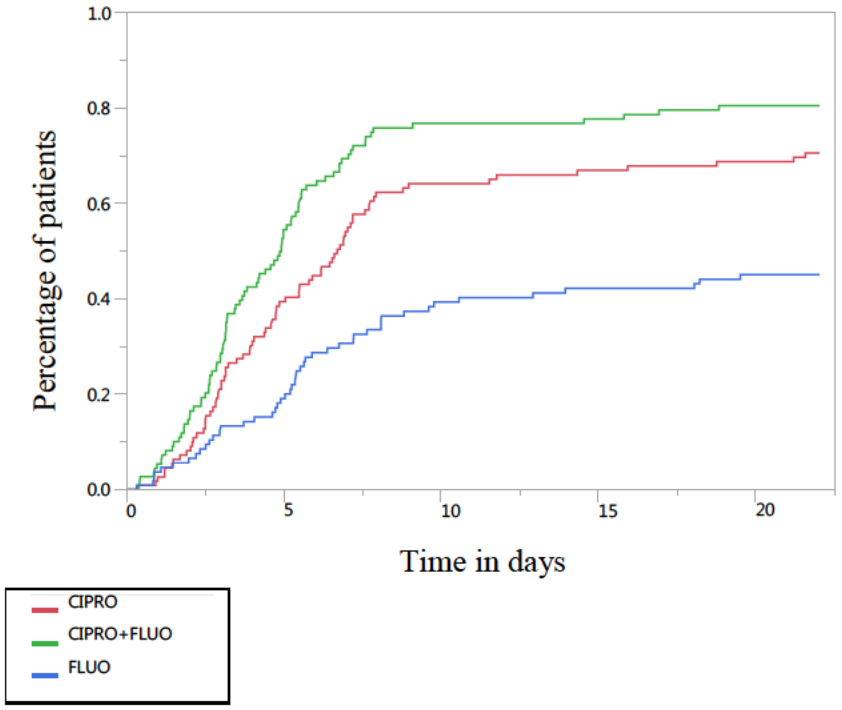
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	35.1912	2	<.0001
Wilcoxon	33.8073	2	<.0001

The Kaplan-Meier estimates for median time to cessation of otorrhea in the CITT population was 4.9 days for the CIPRO+FLUO group, 6.8 days for the CIPRO group, and not estimable for the FLUO group because the number of censored subjects was greater than the number of subjects with cessation of otorrhea. Pairwise comparisons using the log rank test, stratified by age (subjects <3 years versus ≥3 years old), showed a statistically significant difference in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group (P=0.028) and compared with the FLUO group (P<0.001). Pairwise comparisons using the Wilcoxon test stratified by age also showed a statistically significant difference in time to cessation of otorrhea between the CIPRO+FLUO and the CIPRO (P=0.019) and FLUO (P<0.001) groups.

Sensitivity Analysis of the Primary Endpoint.

- Sensitivity analysis of the primary endpoint censoring all discontinued subjects at Day 1 showed a shorter time to cessation of otorrhea in the CIPRO+FLUO group.

Figure 17 Kaplan-Meier estimates of median time to cessation of otorrhea -trial CIFLOTIII/10IA04



Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	77	35	10.2338	Biased	0.78166
CIPRO+FLUO	87	24	7.27283	Biased	0.62042
FLUO	47	61	13.4679	Biased	0.72081
Combined	211	120	10.8317	Biased	0.46941

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	6.691	5.0438	7.7007	3.1514	.

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO+FLUO	4.9167	3.684	5.4583	2.8576	7.8333
FLUO	.	10.553	.	5.5153	.
Combined	6.7639	5.641	7.5986	3.1972	.

Tests Between Groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	5.2442	1	0.0220
Wilcoxon	5.7767	1	0.0162

Tests Between Groups (CIPRO+FLUO versusFLUO)

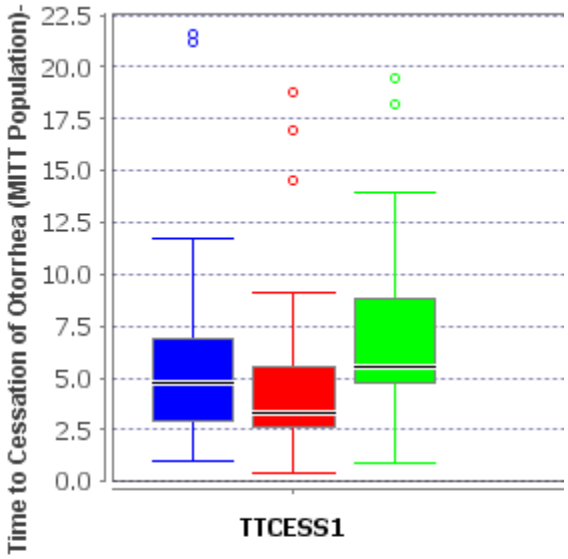
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	35.6444	1	<.0001
Wilcoxon	33.1763	1	<.0001

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO Comment: The Kaplan-Meier estimates of the median time to cessation of otorrhea were 4.9 days (95% CI, 3.7-5.5) for the CIPRO+FLUO group (N=111), 6.7 days (95% CI: 5.0, 7.7) for the CIPRO group (N=112), and not estimable for the FLUO group (N=108).
Pairwise comparisons using the log-rank test, stratified by age (subjects <3 years versus ≥3 years old) revealed a statistically significant difference in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group (P=0.02) and compared with the FLUO group (P<0.0001). The Wilcoxon test confirmed a statistically significant difference in time to cessation of otorrhea between the CIPRO+FLUO group and the CIPRO (P=0.016) and FLUO (P<0.0001) groups.

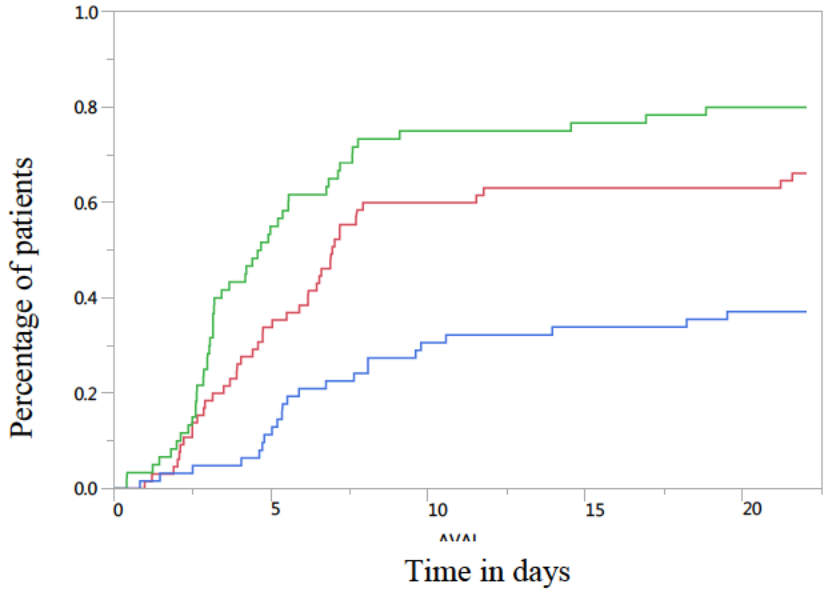
- Sensitivity analysis of the primary endpoint for the MITT Population.

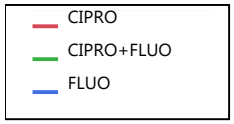
Figure 18 Time to cessation of otorrhoea (MITT population) - trial CIFLOTIII/10IA04



	CIPRO	CIPRO+FLUO	FLUO
Mean	5.74	4.78	7.28
Median	4.75	3.32	5.52
Q1	2.89	2.65	4.76
Q3	6.93	5.56	8.84
N	43	48	23

Figure 19 Kaplan-Meier estimates of median time to cessation of otorrhea (MITT population)-trial CIFLOTIII/10IA04





Summary

Group	Number uncensored [a]	Number censored	Mean		Std Error
CIPRO	43	22	11.0902	Biased	1.03382
CIPRO+FLUO	48	12	7.58995	Biased	0.84944
FLUO	23	39	14.9615	Biased	0.84762
Combined	114	73	11.8566	Biased	0.61862

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25%	75%
CIPRO	6.9514	5.9028	11.75	3.9347	.
CIPRO+FLUO	4.6278	3.166	6.7639	2.9257	11.807
FLUO	.	19.49	.	8.0806	.
Combined	7.6396	6.5958	13.931	4.0486	.

Tests Between Groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.5879	1	0.0322
Wilcoxon	4.9432	1	0.0262

Tests Between Groups (CIPRO+FLUO versus FLUO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	31.1621	1	<.0001
Wilcoxon	31.9248	1	<.0001

[a] Subjects with cessation of otorrhea (assuming none of the subjects had cessation of otorrhea at the beginning of study)

MO Comment: There was a shorter time to cessation of otorrhea in the CIPRO+FLUO group (4.6 days for the CIPRO+FLUO group, 7.0 days for the CIPRO group, and not estimable for the FLUO group).

Pairwise comparisons using the log-rank test, revealed a statistically significant difference in time to cessation of otorrhea for the CIPRO+FLUO group compared with the CIPRO group and compared with the FLUO group .The Wilcoxon test confirmed a statistically significant difference in time to cessation of otorrhea between the CIPRO+FLUO group and the CIPRO and FLUO groups.

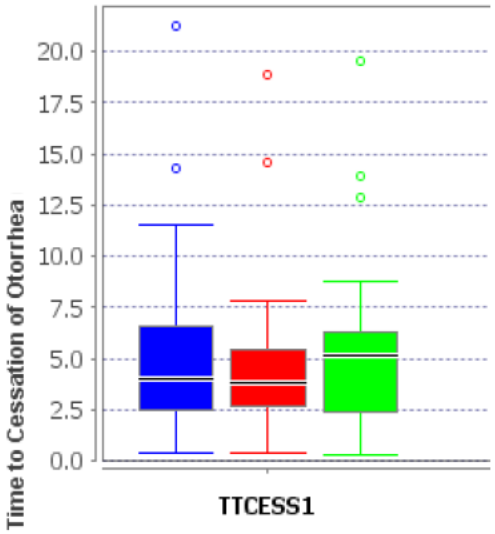
● Sensitivity analysis of the primary endpoint for the MITT Populations of subjects with only bacterial pathogens identified at Visit 1(N=134) showed a shorter time to cessation of otorrhea in the CIPRO+FLUO group (4.6 days for the CIPRO+FLUO group, 7.2 days for the CIPRO group, and not estimable for the FLUO group).

● Sensitivity analysis of the primary endpoint for the MITT Populations of subjects with both viral and bacterial pathogens identified at Visit 1(N=53) also confirmed a shorter time to cessation of otorrhea in the CIPRO+FLUO group (4.6 days for the CIPRO+FLUO group, 6.5 days for the CIPRO group, and not estimable for the FLUO group).

Secondary Analysis of the Primary Endpoint

● Secondary analysis for the primary endpoint was performed for the CPP Population.

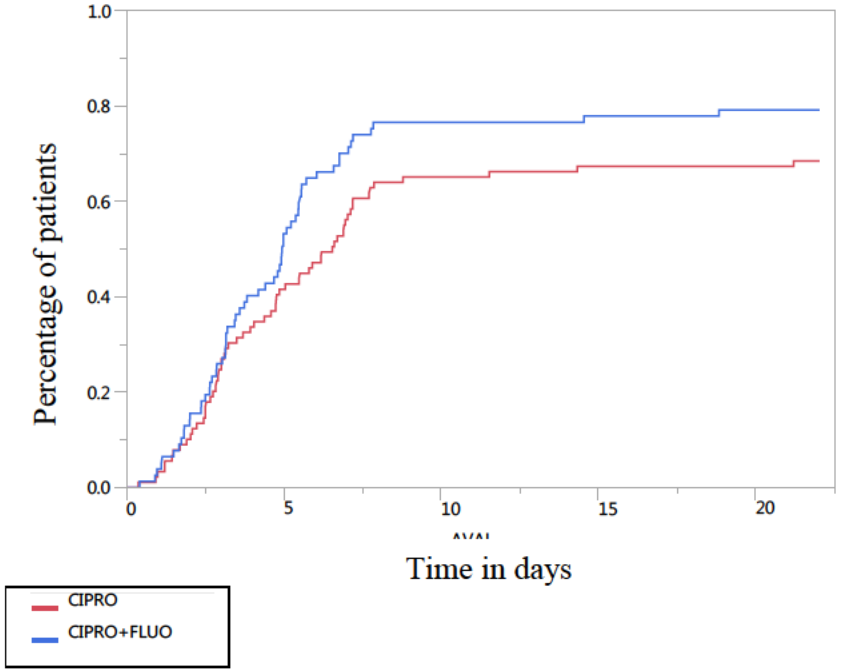
Figure 20 Time to cessation of otorrhea (CPP population) - trial CIFLOTIII/10IA04



	CIPRO	CIPRO+FLUO	FLUO
Mean	4.78	4.40	5.39
Median	4.05	3.83	5.12
Q1	2.53	2.65	2.42
Q3	6.60	5.47	6.32
N	61	61	28

Kaplan-Meier estimates (See figure below) showed the median time to cessation of otorrhea was shortest for subjects in the CIPRO+FLUO group (5.0 days for the CIPRO+FLUO group, 6.5 days for the CIPRO group, and not estimable for the FLUO group).

Figure 21 Kaplan Meier estimates of time to cessation of otorrhea (CPP population, CIPRO+FLUO versus CIPRO) - trial CIFLOTIII/10IA04

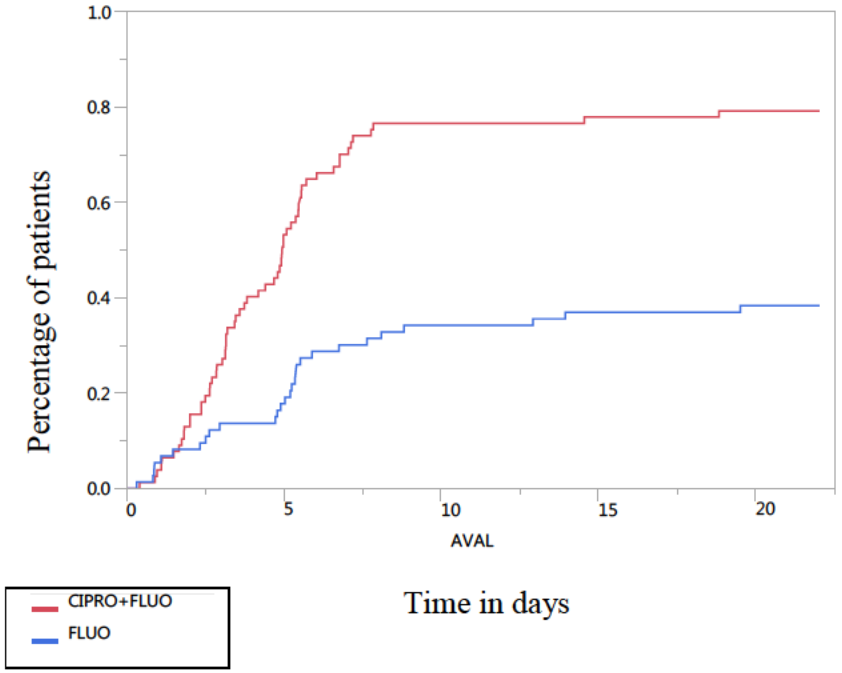


Test between groups (CIPRO+FLUO versus CIPRO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	2.9727	1	0.0847
Wilcoxon	2.3544	1	0.1249

MO Comment: Pairwise comparisons using the log-rank test and Wilcoxon test failed to demonstrate a statistically significant difference when the CIPRO+FLUO group was compared with the FLUO group in the CPP population.

Figure 22 Kaplan Meier estimates of time to cessation of otorrhea (CPP population, CIPRO+FLUO versus FLUO) -trial CIFLOTIII/10IA04



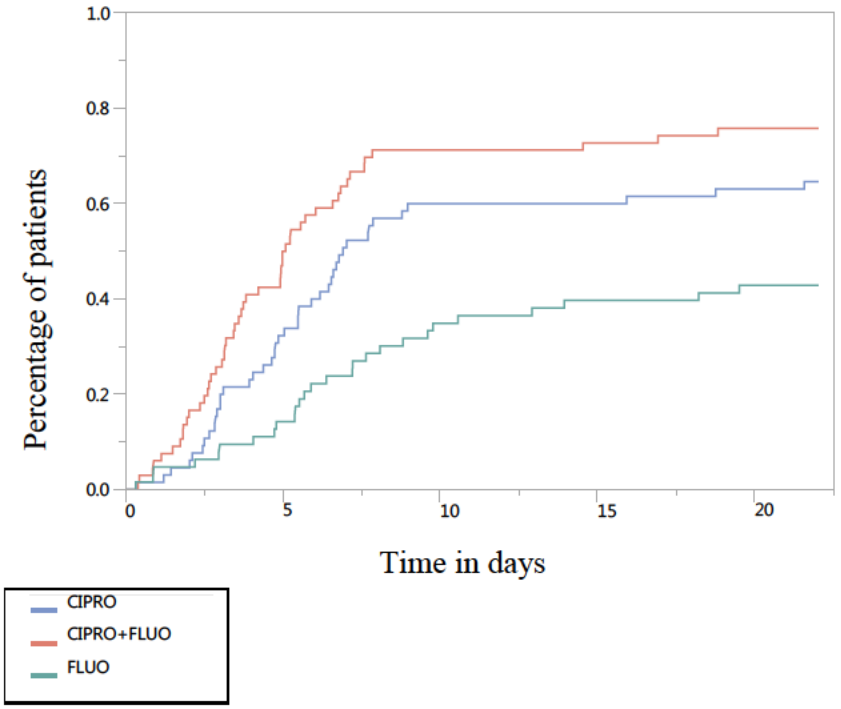
Test between groups (CIPRO+FLUO versus FLUO)

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	27.7408	1	<.0001
Wilcoxon	23.5753	1	<.0001

MO Comment: Pairwise comparisons using the log-rank test and Wilcoxon test stratified by age (<3 years versus ≥3 years old) showed a statistically significant difference when the CIPRO+FLUO group was compared with the FLUO group (P<0.001).

- Secondary analyses for the primary endpoint were performed separately for each of the 2 age strata on both the CITT and CPP Populations. ln each of these analyses, the time to cessation of otorrhea was shortest for subjects in the CIPRO+FLUO group.

Figure 23 Kaplan Meier estimates of median time to cessation of otorrhea in the CITT population (<3 years of age)-trial CIFLOTIII/10IA04

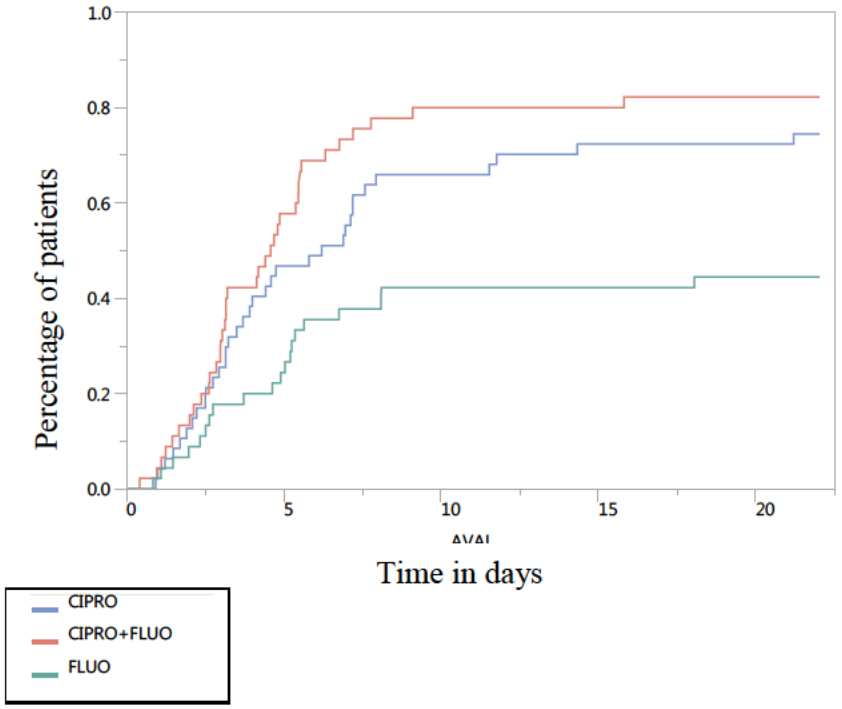


Median time to cessation of otorrhea in the CITT population (<3 years of age)

Group	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
CIPRO	6.9111	5.5035	18.738	4.3813	.
CIPRO+FLUO	5.0351	3.684	6.7639	2.8736	18.813
FLUO	.	12.908	.	7.2083	.
Combined	7.6191	6.5313	13.931	4.0486	.

MO Comment: For subjects <3 years old in the CITT Population, median time to cessation of otorrhea was 5.0 days for the CIPRO+FLUO group, 6.9 days for the CIPRO group, and not estimable for the FLUO group.

Figure 24 Kaplan Meier estimates of median time to cessation of otorrhea in the CITT population (>3 years of age)-trial CIFLOTIII/10IA04



Median time to cessation of otorrhea in the CITT population (≥3 years of age)

Group	Median Time	Lower 95%	Upper 95%	25%	75%s
CIPRO	6.1931	3.7014	7.5764	2.9375	.
CIPRO+FLUO	4.575	3.125	5.4688	2.8576	7.1875
FLUO	.	5.641	.	5.034	.
Combined	5.641	4.8021	7.1903	3.0417	.

MO Comment: For subjects ≥3 years old, the median time to cessation of otorrhea was 4.6 days for the CIPRO+FLUO group, 6.2 days for the CIPRO group, and not estimable for the FLUO group.

Results for the CPP population were similar.

Secondary analysis of the primary endpoint for patients who did not take out-of-specification study medication and by each batch of study medication was also conducted. For all 3 batches of study medication, the time to cessation of otorrhea was shorter in the CIPRO+FLUO group than in the CIPRO group.

6.1.5 Analysis of Secondary Endpoints(s)

The principal secondary endpoint was to demonstrate therapeutic superiority of Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution over Fluocinolone Acetonide 0.025% otic solution 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 was defined as Eradication or Presumed Eradication in the bacteriologic response at both Visit 3 (EOT) and Visit 4 (TOC) conducted on both the MITT and MPP populations.

The frequency of patients (n,%) with sustained microbiological cure was summarized and compared between the combination and Fluocinolone Acetonide 0.025% alone and between Ciprofloxacin 0.3% alone and Fluocinolone Acetonide 0.025% alone by using a Cochran-Mantel-Haenszel (CMH) test stratified by age (younger than 3 years old versus 3 years and older).

Table 9 Sustained microbiological cure in the AOMT trials in the mITT and MPP population

CIFLOTIII/10IA02 Sustained microbiologic cure mITT population				CIFLOTIII/10IA04 Sustained microbiologic cure mITT population			
	CIPRO+FLUO	CIPRO	FLUO		CIPRO + FLUO	CIPRO	FLUO
N	66	70	59	N	60	65	62
Yes n(%)	48 (77.4)	41(65.1)	22 (43.0)	Yes n(%)	47 (82.5)	43(70.5)	18 (31.6)
No n(%)	14 (22.6)	22 (34.9)	29 (56.8)	No n(%)	10 (17.5)	22 (29.5)	39 (68.4)
Total, n (%)	62 (100)	63 (100)	51 (100)	Total, n (%)	57 (100)	61 (100)	57 (100)
Missing	4	7	8	Missing	3	4	5
CIFLOTIII/10IA02 Sustained microbiologic cure MPP population				CIFLOTIII/10IA04 Sustained microbiologic cure MPP population			
	CIPRO+FLUO	CIPRO	FLUO		CIPRO+FLUO	CIPRO	FLUO
N	49	54	45	N	56 (100.0%)	40 (100.0%)	46 (100.0%)
Yes, n(%)	42 (85.7)	35 (70.0)	17 (40.5)	Yes, n(%)	40	56	46
No, n(%)	7 (14.3)	15 (30.0)	25 (59.5)	No, n(%)	32 (82.2)	37 (68.5)	14 (31.8)
Total, n(%)	49 (100)	50 (100)	42 (100)	Total, n(%)	7 (17.9)	15 (31.5)	30 (68.2)
Missing	0	4	3	Missing	1	2	2

If subjects with missing data are excluded, in the mITT population for study CIFLOTIII/10IA02, the sustained microbiological cure was observed in 48 of 62 patients (77.4%) in the CIPRO+FLUO group, 41 of 63 patients (65%) in the CIPRO group, and 22 of 51 patients (43%) in the FLUO group.. For study CIFLOTIII/10IA04, the sustained microbiological cure was observed in 47 of 57 patients (82.5%) in the CIPRO+FLUO group, 43 of 61 patients (70.5%) in the CIPRO group, and 18 of 57 patients (31.6%) in the FLUO group in the mITT population.

MO comment: For study CIFLOTIII/10IA02, the applicant states that the sustained microbiological cure was observed in 23 of 52 patients (44.2%) in the FLUO group in the mITT population which is slightly different that the reviewer results. This difference will likely not impact the study results.

For study CIFLOTIII/10IA02, the sustained microbiological cure was observed in 42 of 49 (85.7%) in the CIPRO+FLUO group, 35 of 50 (70%) in the CIPRO group and 17 of 42 patients (40.5%) in the FLUO group in the MPP population. For study CIFLOTIII/10IA04, the sustained microbiological cure was observed in 32 of 39 patients (82.1%) in the CIPRO+FLUO group, 37 of 54 patients (68.5%) in the CIPRO group, and 14 of 44 patients (31.8%) in the FLUO group.

To determine response without the confounding potential of variables, this analysis was repeated for
-patients who did not take out-of-specification study medication in both the
MITT and MPP populations
-patients in the MITT population who took each batch of study medication
- subgroups of patients who used or did not use titanium tubes, in both the MITT and MPP populations.

The subgroups of patients who used titanium tubes, in both the MITT and MPP populations was small in number. The Table below shows the percentage of sustained microbiological cure in patients who used or did not use titanium tubes, in both the MITT and MPP populations of the AOMT trials.

Table 10 Sustained microbiological cure in patients who used or did not use titanium tubes, in both the MITT and MPP populations of the AOMT trials

CIFLOTIII/10IA02 Sustained Microbiologic cure with Titanium tubes, mITT population				CIFLOTIII/10IA04 Sustained microbiologic cure with Titanium tubes, mITT population			
Analysis Value	CIPRO	CIPRO+FLUO	FLUO	Analysis Value	CIPRO	CIPRO+FLUO	FLUO
N	7(100.0%)	9 (100.0%)	1 (100.0%)	N	6(100.00%)	2 (100.00%)	4(100.00%)
No	2 (28.6%)	3 (33.3%)	1 (100.0%)	No	0 (0.00%)	0 (0.00%)	3 (75.00%)
Yes	4 (57.1%)	6 (66.7%)	0 (0.0%)	Yes	5 (83.33%)	2 (100.00%)	0 (0.00%)
Total	6 (85.7%)	9 (100.0%)	1 (100.0%)	Total	5 (83.33%)	2 (100.00%)	3 (75.00%)
CIFLOTIII/10IA02 Sustained Microbiologic cure without Titanium tubes, mITT population				CIFLOTIII/10IA04 Sustained microbiologic cure without Titanium tubes, mITT population			
Analysis Value	CIPRO	CIPRO+FLUO	FLUO	Analysis Value	CIPRO	CIPRO+FLUO	FLUO
N	63 (100.00%)	56 (100.00%)	59 (100.00%)	N	59 (100.00%)	58 (100.00%)	58 (100.00%)
No	20 (31.75%)	11 (19.64%)	28 (47.46%)	No	18 (30.51%)	10 (17.24%)	36 (62.07%)
Yes	37 (58.73%)	41 (73.21%)	23 (38.98%)	Yes	38 (64.41%)	45 (77.59%)	18 (31.03%)
Total	57 (90.48%)	52 (92.86%)	51 (86.44%)	Total	56 (94.92%)	55 (94.83%)	54 (93.10%)
CIFLOTIII/10IA02 Sustained Microbiologic cure with Titanium tubes, MPP population				CIFLOTIII/10IA04 Sustained microbiologic cure with Titanium tubes, MPP population			

Analysis Value	CIPRO	CIPRO+FLUO	FLUO	Analysis Value	CIPRO	CIPRO+FLUO	FLUO
N	7 (100.0%)	7 (100.0%)	1 (100.0%)	N	4 (100.00%)	1 (100.00%)	3 (100.00%)
No	2 (28.6%)	2 (28.6%)	1 (100.0%)	No	0 (0.00%)	0 (0.00%)	2 (66.67%)
Yes	4 (57.1%)	5 (71.4%)	0 (0.0%)	Yes	4 (100.00%)	1 (100.00%)	0 (0.00%)
Total	6(85.7%)	7 (100.0%)	1 (100.0%)	Total	4 (100.00%)	1 (100.00%)	2 (66.67%)
CIFLOTIII/10IA02 Sustained Microbiologic cure without Titanium tubes, MPP population				CIFLOTIII/10IA04 Sustained microbiologic cure without Titanium tubes, MPP population			
Analysis Value	CIPRO	CIPRO+FLUO	FLUO	Analysis Value	CIPRO	CIPRO+FLUO	FLUO
N	47 (100.0%)	41 (100.0%)	45 (100.0%)	N	52 (100.00%)	39 (100.00%)	43 (100.00%)
No	13 (27.7%)	5 (12.2%)	24 (53.3%)	No	17 (32.69%)	7 (17.95%)	28 (65.12%)
Yes	31 (66.0%)	36 (87.8%)	18(40.0%)	Yes	33 (63.46%)	31 (79.49%)	14 (32.56%)
Total [a]	44 (93.6%)	41 (100.0%)	42(93.3%)	Total	50 (96.15%)	38 (97.44%)	42 (97.67%)

[a] Total does not include missing subjects

In the CIFLOTIII/10IA02 trial, the MITT population with titanium tubes (N = 17) had sustained microbiological cure in 6 of 9 patients (66.7%) in the CIPRO+FLUO group, 4 of 7 patients (57.1%) in the CIPRO group, and 0 of 1 patient (0%) in the FLUO group. For the MPP population with titanium tubes (N = 15), sustained microbiological cure was observed in 5 of 7 patients (71.4%) in the CIPRO+FLUO group, 4 of 7 patients (57.1%) in the CIPRO group, and 0 of 1 patient (0%) in the FLUO group.

In the CIFLOTIII/10IA04 trial, the MITT population with titanium tubes (N = 12), sustained microbiological cure was observed in 2 of 2 patients (100%) in the CIPRO+FLUO group, 5 of 6 patients (83.3%) in the CIPRO group, and none of the 3 patients in the FLUO group. For the MPP population with titanium tubes (N = 8), sustained microbiological cure was observed in 1 of 1 patient (100%) in the CIPRO+FLUO group, 4 of 4 patients (100%) in the CIPRO group, and neither of the 3 patients in the FLUO group.
Pairwise comparisons of the CMH test, stratified by age (patients younger than 3 years versus 3 years and older) were not statistically significant between the CIPRO+FLUO and FLUO groups or between the CIPRO and FLUO groups in either of the 2 trials.

Other secondary efficacy endpoints were as follows:
- Microbiological outcome at Visit 3 and Visit 4
- Clinical response at Visit 2, Visit 3, and Visit 4
- Volume of otorrhea assessed by the investigator at Visit 2, Visit 3, and Visit 4
- Change in granulation tissue at Visit 2, Visit 3, and Visit 4
- Change in type/color of otorrhea at Visit 2, Visit 3, and Visit 4
- Changes in eardrum edema at Visit 2, Visit 3, and Visit 4
- Change in pain assessed by the investigator at Visit 2, Visit 3, and Visit 4
- Change in eczema of the external auditory canal at Visit 2, Visit 3, and Visit 4
- Presence of tympanostomy tubes at Visit 2, Visit 3, and Visit 4
- Change in scores of the quality-of-life questionnaire OM-6 at Visit 3 and Visit 4

Microbiological outcome at Visit 3 and 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 and FLUO groups and between the CIPRO and FLUO groups using a CMH test at Visit 3 and Visit 4. The microbiological response with imputation of missing data for the MITT population at Visit 3 and Visit 4 is presented in the Table below. The definitions of the microbiological outcome are provided in section 6.1.1.

Presumed eradication was noted in 81.5% patients in the CIPRO+FLUO group compared to 62.9% in the CIPRO and 43.3% in the FLUO group at the end of treatment in trial CIFLOTIII/10IA02. Presumed eradication was noted in 75.4% patients in the CIPRO+FLUO group compared to 61.4% in the CIPRO and 41.7% in the FLUO group at the test of cure visit. The applicant states that with a pairwise comparisons of the CMH test, stratified by age (younger than 3 years old versus 3 years and older) there was a statistically significant difference in microbiological response for the CIPRO+FLUO group compared with the CIPRO group at Visit

3 (P = 0.046) but not at Visit 4 (P = 0.835). At visit 3, a statistically significant difference in microbiological response was noted between the CIPRO+FLUO group compared with the FLUO group (P < 0.001) and for the CIPRO group compared with the FLUO group (P = 0.023). However at visit 4, there were no statistically significant differences in microbiological response between the CIPRO+FLUO group compared with the FLUO group (P =0.057) or between the CIPRO group compared with the FLUO group (P = 0.139).

For trial CIFLOTIII/10IA04, presumed eradication was noted in 83.3% patients in the CIPRO+FLUO group compared to 66.2% in the CIPRO and 35.5% in the FLUO group at the end of treatment. Presumed eradication was noted in 76.7% patients in the CIPRO+FLUO group compared to 63.1% in the CIPRO and 35.5% in the FLUO group at the test of cure visit.

The applicant states that there was a statistically significant difference in microbiological response at visit 3 between the CIPRO+FLUO group compared with the FLUO group ($P <$ 0.001) and for the CIPRO group compared with the FLUO group ($P < 0.001$). There were no statistically significant differences in microbiological response at visit 4 between the CIPRO+FLUO group compared with the FLUO group (P =0.280) or between the CIPRO group compared with the FLUO group (P = 0.310). There was no statistically significant difference in microbiological response for the CIPRO+FLUO group compared with the CIPRO group at Visit 3 or Visit 4.

Table 11 Microbiological outcome at Visit 3 and Visit 4 in the AOMT trials

CIFLOTIII/10IA02				CIFLOTIII/10IA04			
Microbiological outcome in MITT population	CIPRO (N=70)	CIPRO+FLUO (N=65)	FLUO (N=60)	Microbiological outcome in MITT population	CIPRO (N=65)	CIPRO+FLUO (N=60)	FLUO (N=62)
Visit 3 (End of treatment)				**Visit 3**			
Indeterminate	5 (7.14%)	5 (7.69%)	2 (3.33%)	Eradication	4 (6.2%)	0 (0.0%)	0 (0.0%)
Persistence	8 (11.43%)	2 (3.08%)	23 (38.33%)	Indeterminate	4 (6.2%)	4 (6.7%)	3 (4.8%)
Presumed Eradication	44 (62.86%)	53 (81.54%)	26 (43.33%)	Persistence	6 (9.2%)	3 (5.0%)	27(43.5%)
Presumed Persistence	11 (15.71%)	4 (6.15%)	7 (11.67%)	Presumed Eradication	43 (66.2%)	50 (83.3%)	22 (35.5%)
Superinfection	0 (0.00%)	1 (1.54%)	0 (0.00%)	Presumed Persistence	7 (10.8%)	2 (3.3%)	8 (12.9%)
Total	68 (97.14%)	65 (100.00%)	58 (96.67%)	Superinfection	0 (0.0%)	0 (0.0%)	1 (1.6%)
Missing	2	0	2	Total	64(98.5%)	59 (98.3%)	61 (98.4%)
				Missing	1	1	1
Visit 4 (Test of Cure)				**Visit 4**			
Eradication	1 (1.43%)	0 (0.00%)	0 (0.00%)	Eradication	3 (4.6%)	1 (1.7%)	0 (0.0%)
Indeterminate	3 (4.29%)	5 (7.69%)	1 (1.67%)	Indeterminate	1 (1.5%)	2 (3.3%)	2 (3.2%)
Persistence	3 (4.29%)	4 (6.15%)	4 (6.67%)	Persistence	1 (1.5%)	3 (5.0%)	3 (4.8%)
Presumed Eradication	43 (61.43%)	49 (75.38%)	25 (41.67%)	Presumed Eradication	41 (63.1%)	46 (76.7%)	22(35.5%)
Presumed Persistence	0 (0.00%)	0 (0.00%)	2 (3.33%)	Recurrence	3 (4.6%)	1 (1.7%)	3 (4.8%)
Recurrence	1 (1.43%)	1 (1.54%)	3 (5.00%)	Total	49 (75.4%)	53 (88.3%)	30(48.4%)
Total	52 (74.29%)	59 (90.77%)	35 (58.33%)	Missing	16	7	32
Missing	18	6	25				

The microbiological response rates for the MITT population at Visit 3 and Visit 4 are summarized by pathogen for *P. aeruginosa*, *S. aureus*, *M. catarrhalis*, *H. influenzae*, and *S. pneumoniae* for the CIFLOTIII/10IA02 trial and shown in the Table below.

Table 12 Target pathogens in subjects (MITT population) with AOMT and their Visit 3 and Visit 4 microbiological outcomes in trial CIFLOTIII/10IA02

Baseline Isolates Target Pathogen CIFLOTIII/10IA02, MITT population	V3 Patient Microbiological Outcome	CIPRO (N=70)	CIPRO+FLUO (N=65)	FLUO (N=60)	V4 Patient Microbiological Outcome	CIPRO (N=70)	CIPRO+FLUO (N=65)	FLUO (N=60)
Pseudomonas aeruginosa	n*(%)	12 (17.1%)	11 (16.9%)	12 (20.0%)	n(%)	12 (17.1%)	11 (16.9%)	12 (20.0%)
	Indeterminate	1 (1.4%)	0 (0.0%)	0 (0.0%)	Indeterminate	2 (2.8%)	0 (0.0%)	5 (8.4%)
	Persistence	1 (1.4%)	0 (0.0%)	7 (11.8%)	Missing	1 (1.4%)	1 (1.5%)	0 (0.0%)
	Presumed Persistence	3 (4.2%)	1 (1.5%)	2 (3.3%)	Eradication	1 (1.4%)	0 (0.0%)	0 (0.0%)
	Presumed Eradication	6 (8.5%)	10 (15.4%)	2 (3.3%)	Re-infection	1 (1.4%)	0 (0.0%)	0 (0.0%)
	Missing	1 (1.4%)	0 (0.0%)	1 (1.7%)	Presumed Eradication	6 (8.4%)	10 (15.4%)	2 (3.3%)
					Persistence	0 (0.0%)	0 (0.0%)	1 (1.7%)
					Presumed Persistence	1 (1.4%)	0 (0.0%)	4 (6.6%)
Staphylococcus aureus	n(%)	25 (35.7%)	26 (40.0%)	23 (38.3%)	n(%)	25 (35.7%)	26 (40.0%)	23 (38.3%)
	Indeterminate	0 (0.0%)	2 (3.0%)	1 (1.7%)	(missing)	0 (0.0%)	1 (1.5%)	0 (0.0%)
	Presumed Eradication	15 (21.4%)	22 (33.8%)	8(13.4%)	Indeterminate	6 (8.6%)	2 (3.1%)	5 (8.4%)
	Presumed Persistence	4(5.1%)	0 (0.0%)	3 (5%)	Presumed Eradication	15 (21.4%)	18 (27.6%)	7 (11.7%)
	Persistence	4 (5.7%)	2 (3.1%)	8 (13.4%)	Presumed Persistence	1 (1.4%)	1 (1.5%)	5 (8.3%)

	Missing	2 (2.9%)	0 (0.0%)	3 (5.0%)	Missing	3 (4.3%)	1 (1.5%)	3 (5.0%)
					Persistence	0 (0.0%)	1 (1.5%)	1 (1.7%)
					Recurrence	0 (0.0%)	2 (3.1%)	2 (2.4%)
Moraxella catarrhalis	n(%)	7 (10.0%)	6 (9.2%)	1 (1.7%)	n(%)	7 (10.0%)	6 (9.2%)	1 (1.7%)
	Presumed Eradication	4 (5.7%)	6 (9.1%)	1 (1.7%)	Presumed Eradication	6 (8.6%)	5 (7.6%)	1 (1.7%)
	Presumed Persistence	3 (4.3%)	0 (0.0%)	0 (0.0%)	Presumed Persistence	1 (1.4%)	0 (0.0%)	0 (0.0%)
					Missing	0 (0.0%)	1 (1.5%)	0 (0.0%)
Hemophilus influenzae	n(%)	22(31.4%)	18 (27.7%)	16 26.7%)	n(%)	22 (31.4%)	18 (27.7%)	16 (26.7%)
	Indeterminate	3 (4.3%)	3 (4.6%)	1 (1.7%)	Missing	5 (7.1%)	6 (9.2%)	8 (13.3%)
	Presumed Eradication	15(21.4%)	12 (18.3%)	7 (11.6%)	Indeterminate	2 (2.8%)	2 (3.1%)	0 (0.0%)
	Presumed Persistence	4 (5.7%)	2 (3.1%)	1 (1.7%)	Presumed Eradication	15 (21.4%)	9 (13.8%)	8 (13.3%)
	Persistence	0 (0.0%)	0 (0.0%)	6 (10.0%)	Presumed Persistence	0 (0.0%)	0 (0%)	0 (0.0%)
	Super-infection	0 (0.0%)	1 (1.5%)	0 (0.0%)	Recurrence	0 (0.0%)	1 (2.4%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	1 (1.7%)				
Streptococcus pneumonia	n(%)	9 (12.9%)	6 (9.2%)	6 (10.0%)	n(%)	9(12.9%)	6 (9.2%)	6 (10.0%)
	Presumed Eradication	7 (0.0%)	3 (4.5%)	2 (3.3%)	Missing	0 (0.0%)	1 (1.5%)	0 (0.0%)
	Presumed Persistence	1 (1.4%)	3 (4.6%)	1 (1.7%)	Indeterminate	2 (2.7%)	1 (1.5%)	3 (5.1%)
	Persistence	0 (0.0%)	0 (0.0%)	3 (5.0%)	Presumed Eradication	7 (10.0%)	3 (4.6%)	2 (3.3%)

	Indeterminate	1 (1.4%)	0 (0.0%)	0 (0.0%)	Presumed Persistence	0 (0.0%)	1 (1.5%)	0 (0.0%)
					Persistence	0 (0.0%)	0 (0.0%)	1 (1.7%)

*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.

MO Comment: On page 125 of the Clinical study report for trial CIFLOTIII/10IA02, the applicant states that the CIPRO+FLUO group had a higher favorable microbiological response rate than the CIPRO group for P. aeruginosa, S. aureus, M. catarrhalis, and H. influenzae at Visit 3. This reviewer finds that the CIPRO+FLUO group had a higher presumed eradication rate than both the CIPRO and FLUO group for P. aeruginosa, S. aureus and M. catarrhalis at visit 3.

The microbiological response rates for the MITT population at Visit 3 and Visit 4 are summarized by pathogen for *P. aeruginosa*, *S. aureus*, *M. catarrhalis*, *H. influenzae*, and *S. pneumoniae* for the CIFLOTIII/10IA04 trial and shown in the Table below.

Table 13 Target pathogens in subjects (MITT population) with AOMT and their Visit 3 and Visit 4 microbiological outcomes in trial CIFLOTIII/10IA04

Baseline Isolates Target Pathogen CIFLOTIII/10IA04, MITT population	V3 Patient Microbiological Outcome	CIPRO (N=65)	CIPRO+FLUO (N=60)	FLUO (N=62)	V4 Patient Microbiological Outcome	CIPRO (N=65)	CIPRO+FLUO (N=60)	FLUO (N=62)
	n (%)	6 (9.2%)	10 (16.7%)	9 (14.5%)	n (%)	6 (9.2%)	10 16.7%)	9 (14.5%)
Pseudomonas aeruginosa	Presumed Persistence	0 (0.0%)	0 (0.0%)	1 (1.6%)	Indeterminate	1 (1.5%)	0 (1.7%)	6 (9.7%)
	Eradication	1 (1.5%)	0 (0.0%)	0 (0.0%)	Presumed Eradication	5(7.7%)	8 (13.3%)	2 (3.2%)
	Indeterminate	1 (1.5%)	0 (0.0%)	0 (0.0%)	Presumed Persistence	0 (0.0%)	0 (0.0%)	1 (1.6%)
	Persistence	0 (0.0%)	1 (1.7%)	6 (9.7%)	Recurrence	0 (0.0%)	1 (1.7%)	0 (0.0%)
	Presumed Eradication	4 (6.1%)	9 (15.1%)	1 (1.6%)	Missing		1 (1.7%)	
	Missing	0 (0.0%)	0 (0.0%)	1 (1.6%)				
Staphylococcus aureus	n (%)	28 (43.1%)	18 (30.0%)	21 (33.9%)	n (%)	28(43.1%)	18(30.0%)	21 33.9%)
	Presumed Eradication	14 (21.6%)	15 (25.1%)	9 (14.5%)	Presumed Eradication	14(21.5%)	15(25.1%)	8 (12.9%)
	Presumed Persistence	7 (10.7%)	0 (0.0%)	1 (1.6%)	Missing	3 (4.6%)	1 (1.7%)	0 (0.0%)
	Persistence	4 (6.2%)	1 (1.7%)	7 (11.3%)	Indeterminate	10(15.3%)	2 (3.4%)	8 (12.9%)
	Missing	2 (3.0%)	1 (1.7%)	1 (1.6%)	Presumed Persistence	0 (0.0%)	0 (0.0%)	3 (4.8%)
	Indeterminate	1 (1.5%)	1 (1.7%)	3 (4.84%)	Persistence	0 (0.0%)	0 (0.0%)	1 (1.6%)

					Recurrence	1 (1.5%)	0 (0.0%)	1 (1.6%)
Streptococcus pneumonia	n (%)	6 (9.2%)	7 (11.7%)	10 (16.1%)	n (%)	6 (9.2%)	7 (11.7%)	10 (16.1%)
	Presumed Eradication	4 (6.1%)	6 (10.0%)	4 (6.4%)	Presumed Eradication	5 (7.6%)	6 (10.0%)	6 (9.6%)
	Persistence	0 (0.0%)	0 (0.0%)	4 (6.4%)	Indeterminate	0 (0.0%)	0 (0.0%)	4 (6.4%)
	Missing	1 (1.5%)	0 (0.0%)	0 (0.0%)	Eradication	1 (1.5%)	0 (0.0%)	0 (0.0%)
	Eradication	1 (1.5%)	0 (0.0%)	0 (0.0%)	Presumed Persistence	0 (0.0%)	1 (1.7%)	0 (0.0%)
	Presumed Persistence	0 (0.0%)	1 (1.7%)	2 (3.2%)				
Moraxella catarrahalis	n (%)	9 (13.8%)	9 (15.0%)	6 (9.7%)	n (%)	9 (13.8%)	9 (15.0%)	6 (9.7%)
	Missing	0 (0.0%)	0 (0.0%)	1 (1.6%)	Missing	0 (0.0%)	0 (0.0%)	1 (1.6%)
	Eradication	1 (1.5%)	0 (0.0%)	0 (0.0%)	Presumed Eradication	6 (9.1%)	8 (13.3%)	4 (6.4%)
	Persistence	0 (0.0%)	0 (0.0%)	2 (3.2%)	Indeterminate	2 (3.0%)	1 (1.7%)	0 (0.0%)
	Indeterminate	2 (3.1%)	1 (1.7%)	0 (0.0%)	Recurrence	1 (1.5%)	0 (0.0%)	1 (1.6%)
	Presumed Eradication	5 (7.6%)	8 (13.3%)	3 (4.8%)				
	Presumed Persistence	1 (1.5%)	0 (0.0%)	0 (0.0%)				
Hemophillus influenzae	n (%)	19 (29.2%)	15 (25.0%)	25 (40.3%)	n (%)	19(29.2%)	15 (25.0%)	25 (40.3%)
	Eradication	2 (3.0%)	0 (0.0%)	0 (0.0%)	Eradication	2 (3.1%)	1 (1.7%)	0 (0.0%)
	Indeterminate	1 (1.5%)	1 (1.7%)	1 (1.6%)	Indeterminate	0 (0%)	2 (3.3%)	9 (12.9%)
	Persistence	0 (0.0%)	1 (1.7%)	14 (22.5%)	Persistence	0 (0.0%)	1 (1.7%)	1 (1.6%)
	Presumed Persistence	0 (0.0%)	0 (0.0%)	2 (3.2%)	Presumed Eradication	13 (20%)	11 (18.4%)	7 (11.2%)

	Presumed Eradication	14 (21.6%)	10 (16.7%)	7(11.3%)	(missing)	1 (1.54%)	0 (0.0%)	3 (4.8%)
	Missing	2 (3.0%)	3 (5.0%)	1 (1.6%)	Recurrence	1 (1.54%)	0 (0.0%)	3 (4.8%)
					Presumed Persistence	0 (0.0%)	0 (0.0%)	3 (4.8%)

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.

MO Comment: On page 121 of the of the Clinical study report for trial CIFLOTIII/10IA04, the applicant states that the CIPRO+FLUO group had a higher favorable microbiological response rate than the CIPRO and FLUO groups for P. aeruginosa, S. aureus and M. catarrhalis at Visit 3. This reviewer finds that the CIPRO+FLUO group had a higher presumed eradication rate than both the CIPRO and FLUO group for P. aeruginosa, S. aureus, M. catarrhalis and S. pneumoniae at visit 3.

Clinical response at Visit 2, Visit 3, and Visit 4:
The Clinical Response rate is summarized in the Table below.

Table 14 Clinical response at Visit 2, Visit 3, and Visit 4 in the AOMT trials (CITT population)

	CIFLOTIII/10IA02				CIFLOTIII/10IA04		
VISIT	Analysis Value	CIPRO+FLUO (N=112)	CIPRO (N=109)	FLUO (N=110)	CIPRO+FLUO (N=111)	CIPRO (N=112)	FLUO (N=108)
2	(missing)	8	11	15	6	10	16
	CLINICAL SUCCESS	31 (29.8%)	22 (22.4%)	20 (21.1%)	23 (21.9%)	17 (16.7%)	13 (14.1%)
	IMPROVED	70 (67.3%)	69 (70.4%)	69 (72.6%)	78 (74.3%)	68 (66.7%)	60 (65.2%)
	NOT CHANGED	3 (2.9%)	7 (7.1%)	5 (5.3%)	4 (3.8%)	17 (16.7%)	19 (20.7%)
	WORSENED	0	0	1(1.1%)	0	0	0
	TOTAL	104 (100%)	98 (100%)	95(100%)	105	102	92
3	(missing)	3	4	6	1	2	5
	CLINICAL SUCCESS	89 (81.7%)	65 (61.9%)	48 (46.2%)	87 (79.1%)	71 (64.5%)	46 (44.7%)
	IMPROVED	11 (10.1%)	18 (17.1%)	22 (21.2%)	18 (16.4%)	23 (20.9%)	22 (21.4%)
	NOT CHANGED	3 (2.8%)	9 (8.6%)	6 (5.8%)	4 (3.6%)	13 (11.8%)	14 (13.6%)
	WORSENED	6 (5.5%)	13 (12.4%)	28(26.9%)	1 (0.9%)	3 (2.7%)	21 (20.4%)
	TOTAL	109	105	104	110	110	103
4	(missing)	11	25 (21.10%)	36	14	23	47
	CLINICAL	92 (91.1%)	72 (85.7%)	52 (70.3%)%)	87 (89.7%)	75 (84.3)%)	49 (80.3%)

	SUCCESS						
	IMPROVED	3 (3.0%)	5 (6.0%)	4 (5.4%)	5 (5.2%)	2 (2.2%)	5 (8.2%)
	NOT CHANGED	0	2 (2.4%)	5 (6.8%)	1 (1.0%)	5 (5.6%)	4 (6.6%)
	WORSENED	6 (5.9%)	5 (6.0%)	13 (17.6%)	4 (4.1%)	7 (7.9%)	3 (4.9%)

For trial CIFLOTIII/10IA02, using LOCF (Last observation carried forward) values analysis, the clinical response success at Visit 2 in the CIPRO+FLUO, CIPRO, and FLUO groups was achieved by 29.8%, 22.4%, and 21.1% of patients, respectively. By Visit 3, a clinical response of success in the CIPRO+FLUO, CIPRO, and FLUO groups was achieved by 81.7%, 61.9%, and 46.2% of patients, respectively and the clinical response of success at Visit 4 in the CIPRO+FLUO, CIPRO, and FLUO groups was achieved by 91.1%, 85.7%, and 70.3% of patients, respectively.
Comparisons between treatment groups in frequency of patients with clinical response considered as success or failure did not show a statistically significant treatment effect at Visit 2, but all 3 analyses showed a statistically significant treatment effect at Visit 3 ($P <$ 0.001) and Visit 4.
For trial CIFLOTIII/10IA04, using LOCF values analysis, the clinical response success at Visit 2 in the CITT population, in the CIPRO+FLUO, CIPRO, and FLUO groups was achieved by 21.9%, 16.7%, and 14.1% of patients, respectively. By Visit 3, a clinical response of success in the CIPRO+FLUO, CIPRO, and FLUO groups was achieved by 79.1%, 64.5%, and 44.7% of patients respectively and the clinical response of success at Visit 4 in the CIPRO+FLUO, CIPRO, and FLUO groups was achieved by 89.7%, 84.3%, and 80.3% of patients, respectively.
Comparisons between treatment groups in frequency of patients with clinical response considered as success or failure did not show a statistically significant treatment effect at Visit 2, but all 3 analyses showed a statistically significant treatment effect at Visit 3.

For patients in the MITT and MPP populations of trial CIFLOTIII/10IA02 with a baseline positive culture for *S. pneumonia, H. influenzae, M. catarrhalis, S. aureus, P. aeruginosa,* or any other pathogen identified in 10 or more patients the percentage of patients with a clinical response of success at Visit 3 and Visit 4 was greater in the CIPRO+FLUO group for all of the pathogens except *S. pneumoniae, H. influenzae, and M. catarrhalis.*

For patients in the MITT and MPP populations of trial CIFLOTIII/10IA04 with a baseline positive culture for *S. pneumoniae H. influenzae, M. catarrhalis,S. aureus, P. aeruginosa,* or any other pathogen identified in 10 or more patients the percentage of patients with a clinical response of success at Visit 3 and Visit 4 was greater in the CIPRO+FLUO group for all of the pathogens except *H. influenzae, and S. aureus.*

The following Table represents the number of subjects with clinical response of success or failure at Visit 3 or 4 with baseline positive culture for *S.pneumoniae, H.influenzae, M.catarrhalis, S.aureus,* and *P.aeruginosa* in the MITT population.

Table 15 Clinical response at Visit 3 or 4 with baseline positive culture for target pathogens in the MITT population

CIFLOTIII/10IA02				CIFLOTIII/10IA04			
V3 Clinical Response	CIPRO (N=70)	CIPRO+FLUO (N=65)	FLUO (N=60)	V3 Clinical Response	CIPRO (N=65)	CIPRO+FLUO (N=60)	FLUO (N=62)
Success				**Success**			
Negative culture	16 (22.9%)	19 (29.2%)	5 (8.3%)				
Streptococcus pneumonia	7 (10.0%)	2 (3.1%)	2 (3.3%)	*Streptococcus pneumonia*	4 (1.21%)	6 (1.81%)	2 (0.6%)
Hemophillus influenzae	13 (18.6%)	12 (18.5%)	5 (8.3%)	*Hemophillus influenzae*	14 (4.23%)	13 (3.93%)	5 (1.51%)
Moraxella catarrahalis	3 (4.3%)	4 (6.2%)	1 (1.7%)	*Moraxella catarrahalis*	5 (1.51%)	6 (1.81%)	1 (0.30%)
Staphylococcus aureus	13 (18.6%)	22 (33.8%)	7 (11.7%)	*Staphylococcus aureus*	13 (3.93%)	12 (3.63%)	9 (2.72%)
Pseudomonas aeruginosa	5 (7.1%)	9 (13.8%)	2 (3.3%)	*Pseudomonas aeruginosa*	3 (0.91%)	6 (1.81%)	1 (0.30%)
Failure				**Failure**			
Negative culture	6 (8.6%)	7 (10.8%)	10(16.7%)				
Staphylococcus aureus	11 (15.7%)	3 (4.6%)	15(25.0%)	*Staphylococcus aureus*	14(21.54%)	6 (10.00%)	11 (17.74%)
Pseudomonas aeruginosa	6 (8.6%)	2 (3.1%)	9(15.0%)	*Pseudomonas aeruginosa*	2 (3.08%)	3 (5.00%)	8 (12.90%)
Hemophillus influenzae	7 (10.0%)	5 (7.7%)	10(16.7%)	*Hemophillus influenzae*	4 (6.15%)	2 (3.33%)	19 (30.65%)
Moraxella catarrahalis	4 (5.7%)	2 (3.1%)	0	*Moraxella catarrahalis*	4 (6.15%)	3 (5.00%)	4 (6.45%)
Streptococcus pneumonia	3 (4.3%)	4 (6.2%)	3 (5.0%)	*Streptococcus pneumonia*	2 (3.08%)	1 (1.67%)	8(12.90%)
V4 Clinical Response	CIPRO (N=70)	CIPRO+FLUO (N=65)	FLUO (N=60)	V4 Clinical Response	CIPRO (N=65)	CIPRO+FLUO (N=60)	FLUO (N=62)

Success				**Success**			
NEGATIVE	15 (21.4%)	21 (32.3%)	7 (11.7%)				
Streptococcus pneumonia	8 (11.4%)	3 (4.6%)	2 (3.3%)	*Streptococcus pneumonia*	5 (7.69%)	6 (10.00%)	6 (9.68%)
Hemophillus influenzae	16 (22.9%)	11 (16.9%)	7 (11.7%)	*Hemophillus influenzae*	13(20.00%)	12 (20.00%)	6 (9.68%)
Moraxella catarrahalis	6 (8.6%)	4 (6.2%)	1 (1.7%)	*Moraxella catarrahalis*	6 (9.23%)	8 (13.33%)	3 (4.84%)
Pseudomonas aeruginosa	5 (7.1%)	10 (15.4%)	2 (3.3%)	*Pseudomonas aeruginosa*	5 (7.69%)	6 (10.00%)	2 (3.23%)
Staphylococcus aureus	13 (18.6%)	21 (32.3%)	8 (13.3%)	*Staphylococcus aureus*	15(23.08%)	15 (25.00%)	9 (14.52%)
Failure				**Failure**			
Hemophillus influenzae	0	3 (4.6%)	2 (3.3%)	*Hemophillus influenzae*	4 (6.15%)	2 (3.33%)	6 (9.68%)
Moraxella catarrahalis	0	2 (3.1%)	0	*Moraxella catarrahalis*	0	0	2 (3.23%)
Pseudomonas aeruginosa	3 (4.3%)	1 (1.5%)	2 (3.3%)	*Pseudomonas aeruginosa*	0	2 (3.33%)	0
Staphylococcus aureus	5 (7.1%)	2 (3.1%)	6 (10.0%)	*Staphylococcus aureus*	2 (3.08%)	1 (1.67%)	1 (1.61%)
Streptococcus pneumonia	1 (1.4%)	1 (1.5%)	0	*Streptococcus pneumonia*	1 (1.54%)	0	0

Each patient may have appeared in multiple rows

Volume of otorrhea assessed by the investigator at Visit 2, Visit 3, and Visit 4:
There was a higher percentage of patients in the CIPRO+ FLUO group with resolved otorrhea compared to the CIPRO and FLUO groups in the CITT population at Visit 2, 3 and 4. Comparisons between treatment groups showed a statistically significant treatment effect at Visit 2 (P = 0.013), Visit 3 (P < 0.001), and Visit 4 (P = 0.022) in trial CIFLOTIII/10IA02 and at Visit 2 (P=0.004) and 3 (P<0.001) in trial CIFLOTIII/10IA04.

Change in granulation tissue, type/color of otorrhea, eardrum edema, eczema of the external auditory canal at Visit 2, Visit 3, and Visit 4:

In trial CIFLOTIII/10IA02, at Visit 2, otorrhea type/color was assessed as purulent in 14 patients (12.5% purulent non-sanguinolent and 1.0% purulent sanguinolent) in the CIPRO+FLUO group, 25 patients (1% purulent, 21.2% purulent non-sanguinolent, and 3.0% purulent sanguinolent) in the CIPRO group, and 28 patients (25.0% purulent non-sanguinolent and 4.2% purulent sanguinolent) in the FLUO group. The CMH test, stratified by age (younger than 3 years old versus 3 years and older,) showed a statistically significant treatment effect at Visit 3 (P < 0.001) but not at Visit 2 (P = 0.159) or Visit 4 (P = 0.364). No statistically significant treatment effects were noted for eardrum edema or granulation tissue. At Visit 4, eczema was absent in 100%, 98.8%, and 92.9% of patients in the CIPRO+FLUO, CIPRO, and FLUO groups respectively in the CITT population. A statistically significant treatment effect was noted only at Visit 4.

In trial CIFLOTIII/10IA04, the CMH test, stratified by age (younger than 3 years old versus 3 years and older,) showed a statistically significant treatment effect at Visit 2 (P = 0.024) and Visit 3 (P < 0.001) for otorrhea type/color. A statistically significant treatment effect was noted at Visit 3 (P < 0.001) for eardrum edema and at Visit 2 for eczema. No statistically significant treatment effects were noted for granulation tissue.

Change in pain assessed by the investigator at Visit 2, Visit 3, and Visit 4:

In trial CIFLOTIII/10IA02, otalgia was resolved at Visit 2 in 91.3%, 84.7%, and 78.9% of patients in the CIPRO+FLUO, CIPRO, and FLUO groups, respectively. At Visit 3, otalgia was resolved in 94.6%, 85.8%, and 80.0% of patients respectively, and at Visit 4, otalgia was resolved in 99.0%, 98.8%, and 91.4% of patients, respectively. “Resolved” at Visits 2, 3 and 4 was defined as the combination of “resolved” and “ remain absent” in the table below. Comparison between treatment groups showed a statistically significant treatment effect at Visit 3 (P = 0.006), and Visit 4 (P = 0.011).

In trial CIFLOTIII/10IA04, otalgia was resolved at Visit 2 in 81.6%, 85.0%, and 75.8% of patients in the CIPRO+FLUO, CIPRO, and FLUO groups, respectively. At Visit 3, otalgia was resolved in 97.2%, 91.8%, and 80.6% of patients respectively, and at Visit 4, otalgia was resolved in 97.9%, 97.7%, and 96.6% of patients, respectively. "Resolved" at Visits 2, 3 and 4 was defined as the combination of "resolved" and "remain absent" in the table below. Comparison between treatment groups showed a statistically significant treatment effect at Visit 3 ($P < 0.001$) only.

Table 16 Analysis of otalgia in the CITT population (LOCF values) in the AOMT trials

		CIFLOTIII/10IA02			CIFLOTIII/10IA04		
		CIPRO+FLUO	CIPRO	FLUO	CIPRO+FLUO	CIPRO	FLUO
VISIT	**Analysis value**	**N**	**N**	**N**	**N**	**N**	**N**
Visit 1 (Screening)	All	112	109	110	111	112	108
Visit 2 (During treatment)	RESOLVED	62	48	40	57	50	38
	Missing	1	1	1	2	2	3
	REMAIN ABSENT	32	35	35	27	35	31
	NOT IMPROVED	7	6	10	8	11	16
	IMPROVED	2	9	10	11	4	6
	All	104	99	96	105	102	94
Visit 3 (End of treatment)	RESOLVED	73	52	49	74	62	47
	Missing	0	1	1	0	1	3
	REMAIN ABSENT	32	39	35	32	39	36
	NOT IMPROVED	4	12	17	2	6	17
	IMPROVED	2	3	4	1	3	3
	All	111	107	106	109	111	106
Visit 4 (Test of cure)	RESOLVED	69	48	37	66	52	34
	Missing	11	25	32	13	22	45
	REMAIN	30	31	27	28	32	22

		CIFLOTIII/10IA02			CIFLOTIII/10IA04		
		CIPRO+FLUO	CIPRO	FLUO	CIPRO+FLUO	CIPRO	FLUO
VISIT	**Analysis value**	**N**	**N**	**N**	**N**	**N**	**N**
	ABSENT						
	NOT IMPROVED	1	1	5	1	2	1
	IMPROVED	0	0	1	1	0	1
	All	111	105	102	109	108	103

Presence of tympanostomy tubes at Visit 2, Visit 3, and Visit 4:

Table 17 Presence of tympanostomy tubes in the AOMT trials (CITT population)

		CIFLOTIII/10IA02			CIFLOTIII/10IA04		
VISITN	AVALC	CIPRO (N=109)	CIPRO+FLUO (N=112)	FLUO (N=110)	CIPRO (N=112)	CIPRO+FLUO (N=111)	FLUO (N=108)
1	PRESENT AND CLOSED	5 (4.59%)	9 (8.04%)	6 (5.45%)	6 (5.36%)	8 (7.21%)	7 (6.48%)
	PRESENT AND OPEN	104 (95.41%)	103 (91.96%)	104 (94.55%)	106 (94.64%)	103 (92.79%)	100 (92.59%)
2	ABSENT	1 (0.92%)	1 (0.89%)	1 (0.91%)	1 (0.89%)	1 (0.90%)	2 (1.85%)
	PRESENT AND CLOSED	2 (1.83%)	1 (0.89%)	0 (0.00%)	0 (0.00%)	3 (2.70%)	2 (1.85%)
	PRESENT AND OPEN	96 (88.07%)	102 (91.07%)	95 (86.36%)	101 (90.18%)	101 (90.99%)	88 (81.48%)
3	ABSENT	5 (4.59%)	3 (2.68%)	1 (0.91%)	1 (0.89%)	3 (2.70%)	4 (3.70%)
	PRESENT AND CLOSED	4 (3.67%)	2 (1.79%)	2 (1.82%)	2 (1.79%)	3 (2.70%)	3 (2.78%)
	PRESENT AND OPEN	98 (89.91%)	106 (94.64%)	102 (92.73%)	107 (95.54%)	104 (93.69%)	98 (90.74%)
4	ABSENT	6 (5.50%)	7 (6.25%)	5 (4.55%)	4 (3.57%)	3 (2.70%)	3 (2.78%)

	PRESENT AND CLOSED	3 (2.75%)	3 (2.68%)	1 (0.91%)	1 (0.89%)	3 (2.70%)	1 (0.93%)
	PRESENT AND OPEN	72 (66.06%)	90 (80.36%)	64 (58.18%)	81 (72.32%)	91 (81.98%)	54 (50.00%)

MO Comment: By Visit 4, tympanostomy tubes were present and open in approximately 80% of the subjects in the CIPRO +FLUO group compared to approximately 70% in the CIPRO and approximately 50% in the FLUO groups. A comparison of the treatment effects was not statistically significant at the different visits.

Change in scores of the quality-of-life questionnaire OM-6 at Visit 3 and Visit 4:

A summary of median total scores for each visit is presented in Table below. In trial CIFLOTIII/10IA02, at Visit 4, the median score was 0.00 for the CIPRO+FLUO and CIPRO groups and 0.30 for the FLUO group; the median change from Visit 1 was –1.10 in the CIPRO+FLUO group and –1.20 for the CIPRO and FLUO groups. In trial CIFLOTIII/10IA04, at Visit 4, the median score was lower for all 3 treatment groups. The median change from Visit 1 was greater in the CIPRO+FLUO group (–1.50) than in the CIPRO (–1.40) and FLUO (–1.20) groups.

Table 18 Median total scores of the quality-of-life questionnaire OM-6 for each visit (CITT population)

CIFLOTIII/10IA02		CIPRO		CIPRO+FLUO		FLUO	
AVISIT		**Median**	**N**	**Median**	**N**	**Median**	**N**
Visit 1 (Screening)	AVAL	1.7	108	1.7	112	1.7	108
Visit 3 (End of treatment)	AVAL	0.3	104	0.2	110	0.5	101
Visit 4 (Test of cure)	AVAL	0	101	0	105	0.3	97
All	AVAL	0.7	313	0.5	327	0.8	306

CIFLOTIII/10IA04		CIPRO		CIPRO+FLUO		FLUO	
AVISIT		**Median**	**N**	**Median**	**N**	**Median**	**N**
Visit 1 (Screening)	AVAL	1.8	108	1.7	110	1.5	104
Visit 3 (End of treatment)	AVAL	0.5	107	0.25	108	0.5	101
Visit 4 (Test of cure)	AVAL	0.1	104	0	106	0.2	94
All	AVAL	0.7	319	0.5	324	0.8	299

6.1.6 Other Endpoints

One supportive efficacy

endpoint was the score as calculated in the AOM-SOS Questionnaire. In trial CIFLOTIII/10IA02, the median total score at the test of cure visit in all treatment groups was 0.00 and the median change from Visit 1 was –2.50 for the CIPRO+FLUO group, –3.00 for the CIPRO group, and –3.50 for the FLUO group. In trial CIFLOTIII/10IA04, the median total score at the test of cure visit in all treatment groups was 0.00 and a median change in total score of –3.00.

6.1.7 Subpopulations

A pharmacokinetic analysis of Fluocinolone Acetonide and Ciprofloxacin in plasma samples conducted in a subgroup of 14 patients showed undetectable plasma concentrations of Fluocinolone Acetonide after7 days of treatment. No Ciprofloxacin results were reported.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No evidence of tolerance or withdrawal effects has been detected in the AOMT trials.

6.1.10 Additional Efficacy Issues/Analyses

February 2013: Five investigators initially participating in trial CIFLOTIII/10IA02 were transferred to protocol CIFLOTIII/10IA04 and were inactivated for trial CIFLOTIII/10IA02, as part of the reallocation of sites based on recruitment efforts for faster enrollment in trial CIFLOTIII/10IA04 (communicated to the Agency under IND 107809 in April 2013).

June 2013: The Applicant requested the Agency to permit the majority of sites from trial CIFLOTIII/10IA04 to participate in Study CIFLOTIII/10IA02 due to low enrollment. The plan was to start enrollment after completion of recruitment in trial CIFLOTIII/10IA04.

July 2013: The Agency recommended minimizing site sharing across 2 independent studies to ensure the quality of the data. The Agency also advised that extensive sites sharing across studies could jeopardize data from both studies, especially if there was a

shared site enrolling a large proportion of subjects in both studies where systematic biases or integrity issues were identified. The Agency strongly recommended trial CIFLOTIII/10IA04 should remain blinded until trial CIFLOTIII/10IA02 completed (database locked).

The Applicant stopped the transfer of sites and closed the high-enrolling CIFLOTIII/10IA04 sites that had already been transferred to trial CIFLOTIII/10IA02, but had not yet enrolled subjects. Overall, 15 sites included subjects in both trials.

Both trials were unblinded at the same time. The Applicant also repeated the primary analysis separately for 2 site-sharing groups (sites overlapping Studies CIFLOTIII/10IA02 and CIFLOTIII/10IA04, as well as non-overlapping sites).
The Figure below displays the distribution of subjects by site.

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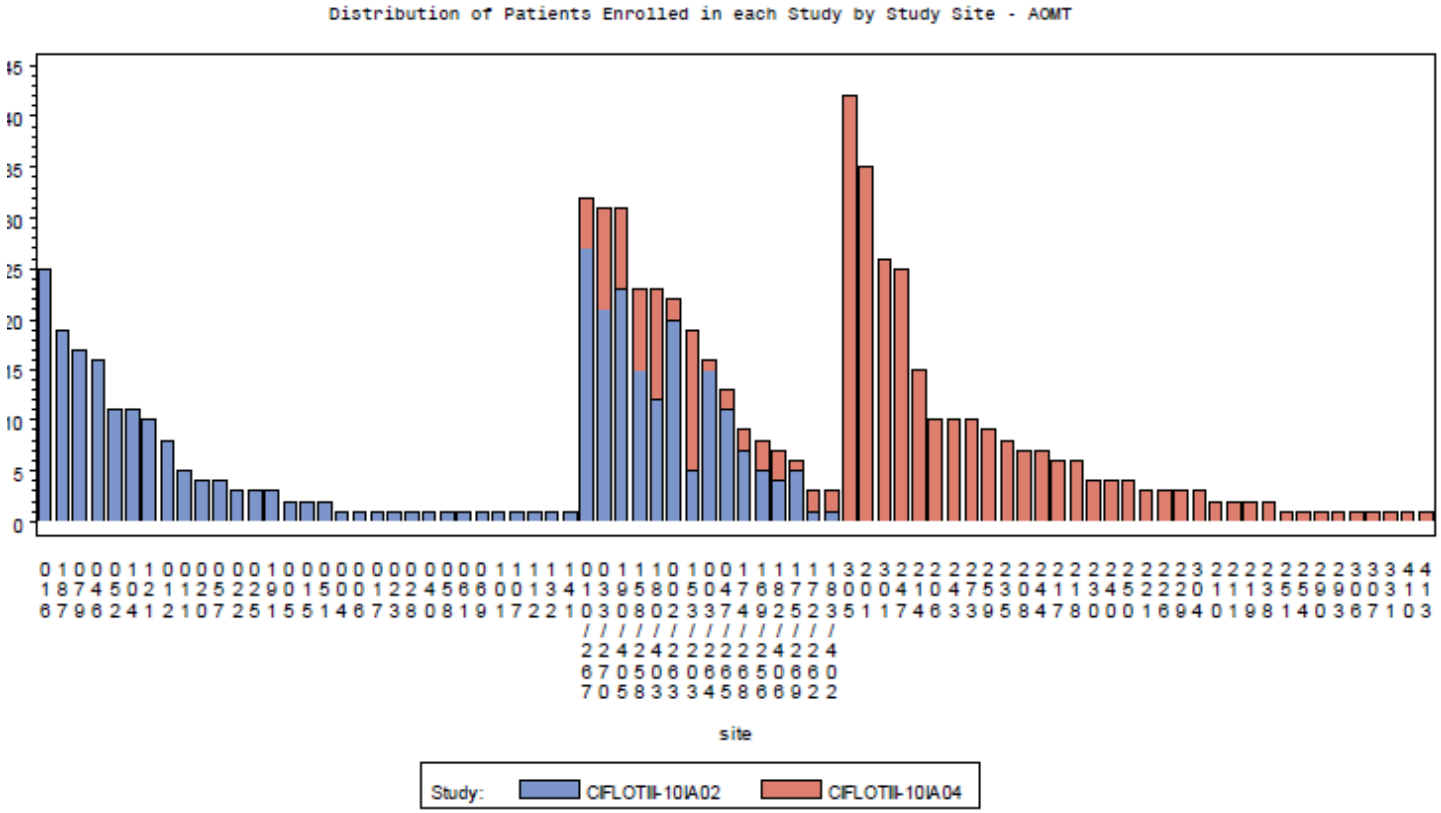
Figure 25 Distribution of subjects by site



Source: Figure 14.2.1.13 of Applicant's submission

7 Review of Safety

Safety Summary

The overall safety database consisted of 224 subjects who received ciprofloxacin and fluocinolone (CIPRO+FLUO), 220 subjects who received ciprofloxacin (CIPRO), and 213 subjects who received fluocinolone (FLUO), for a total of 657 subjects from the two Phase 3 AOMT trials. The mean duration of exposure in the treatment group was 7.5 days. There were no deaths reported. There were 3 serious treatment emergent SAEs found in the SOC of Infections and infestations. Adverse events reported by greater than or equal to 2 % of patients and more frequently in the CIPRO+FLUO group were pyrexia, otitis media, rhinorrhea, cough, upper respiratory tract infection and otorrhoea. It is expected that the safety profile will be limited due to the low absorption of Ciprofloxacin and Fluocinolone acetonide after otic topical administration.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data for this review included two Phase 3 trials CIFLOTIII/10IA02 and CIFLOTIII/10IA04 conducted under IND 107809. (b) (4)

(b) (4)

In the CIFLOTIII/10IA02 and CIFLOTIII/10IA04 studies, 224 subjects received ciprofloxacin and fluocinolone (CIPRO+FLUO), 220 subjects received ciprofloxacin (CIPRO), and 213 subjects received fluocinolone (FLUO), for a total of 657 subjects. All enrolled subjects who took at least 1 dose of study medication were included in the Safety Population. All safety analyses have been conducted in the safety population.

Safety assessments:

Safety was assessed by AE incidence, physical examination (including vital signs), audiometric assessments, and ciprofloxacin and/or fluocinolone acetonide plasma levels.

7.1.2 Categorization of Adverse Events

An AE was defined as any untoward medical occurrence in a patient who had received study medication regardless of its causal relationship to study treatment.

An illness present at entry to the study was considered a preexisting condition and was not considered an AE; however, a preexisting condition that worsened during the study may have been considered an AE.

The intensity of each AE was graded as follows:

- Mild: an AE that did not interfere with usual activities
- Moderate: an AE that interfered with usual activities
- Severe: an AE that was intense or debilitating and interfered with usual activities

A treatment-emergent AE (TEAE) was defined as any AE that occurred after exposure to test medication.

A serious AE (SAE) was defined as any untoward medical occurrence that at any dose:

- Resulted in death
- Was life threatening
- Required or prolongs inpatient hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect

The incidence of TEAEs was summarized based on Medical Dictionary for Regulatory Activities (MedDRA) (Version 13.0) coded terms at the System Organ Class (SOC) and preferred term levels.

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

The safety data was pooled from two trials CIFLOTIII/10IA02 and CIFLOTIII/10IA04. These trials provide safety data for ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution, one vial (0.25 mL) instilled into the affected ear canal twice daily for 7 days.

(b) (4)

(b) (4)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the safety population of 657 subjects, the mean duration of exposure in the treatment group was 7.5 days and comparable across the three groups.

Table 19 Extent of Exposure to Study Medication (Safety Population)

Duration of Exposure (days)	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
Min	1	1	3
Max	38	16	15
Mean	7.38	7.49	7.37
Missing	0	2	3

The extent of exposure was 5 days or greater for 93.3% of patients in the ciprofloxacin and fluocinolone group, 90.5% of patients in the ciprofloxacin group and 87.8% of patients in the fluocinolone group.

Table 20 Extent of Exposure (Safety Population)

Duration of Exposure n(%)	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
Duration of Exposure > 3 days	207 (94.1%)	215 (90.3%)	200 (93.9%)
Duration of Exposure >5 days	199 (90.5%)	209 (93.3%)	187 (87.8%)
Duration of Exposure >7 days	86 (39.1%)	88 (39.3%)	84 (39.4%)

The number of subjects considered to be compliant with study treatment (defined as those subjects who received 80% to 120% of the scheduled study doses) was reported with a similar incidence in the CIPRO+FLUO group (99.3%) and in the CIPRO group (98.5%), but was lower

in the FLUO group (97.7%).

Table 21 Compliance to Study Medication During the Overall Treatment Period (Safety population)

Compliant Overall n (%)	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
Y	207 (94.1%)	210 (93.8%)	191 (89.7%)
N	12 (5.5%)	12 (5.4%)	19 (8.9%)
(missing)	1 (0.5%)	2 (0.9%)	3 (1.4%)
Percent Compliance Overall	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
mean	98.54	99.3	97.7
min	50	50	7.1
max	116.7	142.8	233.3

Demographics, including age, gender, ethnicity, race and country are presented for CIFLOTIII/10IA02 and CIFLOTIII/10IA04 using the safety population in Table below.

Table 22 Demographic characteristics in the AOMT trials (safety population)

Demographic Baseline Characteristics	**Ciprofloxacin 0.3%**	**Ciprofloxacin 0.3% + Fluocinolone Acetonide 0.025%**	**Fluocinolone Acetonide 0.025%**	**Overall**
	N=220	**N=224**	**N=213**	**N=657**

Age	Mean (SE)	3.6 (2.9)		3.3 (2.7)		3.7 (3.0)		3.5 (2.9)	
	Min	1		1		1		1	
	Q1	1		1		1		1	
	Median	2		2		3		2	
	Q3	5		4		5		5	
	Max	12		12		12		12	
		Count	%	Count	%	Count	%	Count	%
Age Group	Age under 3 years	111	50.5	117	52.2	106	49.8	334	50.8
	Age 3 and over	109	49.5	107	47.8	107	50.2	323	49.2
Sex	F	86	39.1	94	42.0	88	41.3	268	40.8
	M	134	60.9	130	58.0	125	58.7	389	59.2
Race	American Indian Or Alaska Native	2	0.9	1	0.4	0	0.0	3	0.5
	Asian	8	3.6	5	2.2	4	1.9	17	2.6
	Black Or African American	32	14.5	33	14.7	23	10.8	88	13.4
	Native Hawaiian Or Other Pacific Islander	1	0.5	0	0.0	1	0.5	2	0.3
	White	167	75.9	168	75.0	171	80.3	506	77.0
	Other	10	4.5	17	7.6	14	6.6	41	6.2
Ethnicity	Hispanic Or Latino	29	13.2	30	13.4	28	13.1	87	13.2
	Not Hispanic Or Latino	191	86.8	194	86.6	185	86.9	570	86.8
Country	CAN	1	0.5	0	0.0	1	0.5	2	0.3
	CZE	1	0.5	0	0.0	0	0.0	1	0.2
	DNK	3	1.4	2	0.9	5	2.3	10	1.5
	ESP	34	15.5	24	10.7	28	13.1	86	13.1
	FIN	2	0.9	0	0.0	0	0.0	2	0.3
	SWE	0	0.0	0	0.0	1	0.5	1	0.2
	USA	146	66.4	170	75.9	151	70.9	467	71.1
	ZAF	33	15.0	28	12.5	27	12.7	88	13.4

There were more male subjects included than female subjects with a total of 59.2% male subjects and 40.8% female subjects. The mean age overall was 3.5 years. There were 211 (32%) subjects under 2 years of age and 446 (67.9%) subjects over 2 years of age

overall. With respect to race the majority of subjects were White or Caucasian (77%), and with respect to ethnicity the majority of subjects were Not Hispanic or Latino (86.8%). About 70% of subjects were from the U.S.

MO comment: There appears to be no clinically significant differences among the CIPRO, CIPRO+FLUO and the FLUO groups with respect to demographic characteristics in both CIFLOTIII/10IA02 and CIFLOTIII/10IA04 trials.

The following Table represents the baseline medical history of subjects with incidence of medical conditions greater than 2% in the three treatment arms. About 70% of subjects had ear tube insertion and 33% with acute otitis media at baseline. Baseline incidence of cough (18/224, 8%) and conjunctivitis (17/224, 7.6%) was higher in the ciprofloxacin+fluocinolone group compared to 5% (11/220) in the ciprofloxacin arm and 3%-4% in the fluocinolone arm. There was slightly higher incidence of pyrexia 10/224 (4.5%) compared to 2.3% in the other arms. There were 2% (13/657) subjects with baseline pneumococcal immunization overall.

Table 23 Baseline medical history at screening (Safety population)

Significant medical history at screening	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)	Overall (N=657)
Ear tube insertion	149 (67.7%)	157 (70.1%)	154 (72.3%)	460 (69.5%)
Otitis media	81 (36.8%)	92 (41.1%)	67 (31.5%)	240 (36.3%)
Otitis media chronic	76 (34.5%)	79 (35.3%)	80 (37.6%)	235 (35.5%)
Otitis media acute	73 (33.2%)	75 (33.5%)	70 (32.9%)	218 (32.9%)
Myringotomy	54 (24.5%)	59 (26.3%)	45 (21.1%)	158 (23.9%)
Otorrhoea	55 (25.0%)	42 (18.8%)	57 (26.8%)	154 (23.3%)
Adenoidectomy	49 (22.3%)	59 (26.3%)	44 (20.7%)	152 (23.0%)
Eustachian tube dysfunction	36 (16.4%)	40 (17.9%)	45 (21.1%)	121 (18.3%)
Upper respiratory tract infection	35 (15.9%)	37 (16.5%)	34 (16.0%)	106 (16.0%)
Rhinitis allergic	17 (7.7%)	33 (14.7%)	28 (13.1%)	78 (11.8%)
Conductive deafness	20 (9.1%)	21 (9.4%)	23 (10.8%)	64 (9.7%)
Adenoidal hypertrophy	22 (10.0%)	17 (7.6%)	15 (7.0%)	54 (8.2%)
Asthma	19 (8.6%)	17 (7.6%)	18 (8.5%)	54 (8.2%)
Tonsillectomy	17 (7.7%)	17 (7.6%)	15 (7.0%)	49 (7.4%)

Eczema	11 (5.0%)	16 (7.1%)	12 (5.6%)	39 (5.9%)
Conjunctivitis	11 (5.0%)	17 (7.6%)	8 (3.8%)	36 (5.4%)
Cough	11 (5.0%)	18 (8.0%)	7 (3.3%)	36 (5.4%)
Bronchiolitis	11 (5.0%)	12 (5.4%)	12 (5.6%)	35 (5.3%)
Pharyngitis	14 (6.4%)	9 (4.0%)	12 (5.6%)	35 (5.3%)
Gastrooesophageal reflux disease	12 (5.5%)	10 (4.5%)	12 (5.6%)	34 (5.1%)
Seasonal allergy	12 (5.5%)	13 (5.8%)	9 (4.2%)	34 (5.1%)
Sinusitis	5 (2.3%)	16 (7.1%)	12 (5.6%)	33 (5.0%)
Viral infection	7 (3.2%)	13 (5.8%)	13 (6.1%)	33 (5.0%)
Bronchitis	13 (5.9%)	10 (4.5%)	9 (4.2%)	32 (4.8%)
Tonsillar hypertrophy	11 (5.0%)	10 (4.5%)	10 (4.7%)	31 (4.7%)
Bronchial hyperreactivity	13 (5.9%)	10 (4.5%)	6 (2.8%)	29 (4.4%)
Adenotonsillectomy	9 (4.1%)	8 (3.6%)	9 (4.2%)	26 (3.9%)
Drug hypersensitivity	5 (2.3%)	10 (4.5%)	10 (4.7%)	25 (3.8%)
Cerumen impaction	8 (3.6%)	10 (4.5%)	4 (1.9%)	22 (3.3%)
Rhinitis	4 (1.8%)	12 (5.4%)	6 (2.8%)	22 (3.3%)
Ear infection	6 (2.7%)	7 (3.1%)	8 (3.8%)	21 (3.2%)
Gastroenteritis	6 (2.7%)	9 (4.0%)	6 (2.8%)	21 (3.2%)
Tonsillitis	7 (3.2%)	6 (2.7%)	8 (3.8%)	21 (3.2%)
Dermatitis atopic	7 (3.2%)	9 (4.0%)	4 (1.9%)	20 (3.0%)
Pneumonia	6 (2.7%)	12 (5.4%)	2 (0.9%)	20 (3.0%)
Pyrexia	5 (2.3%)	10 (4.5%)	5 (2.3%)	20 (3.0%)
Rhinorrhoea	13 (5.9%)	7 (3.1%)	0 (0.0%)	20 (3.0%)
Speech disorder developmental	6 (2.7%)	6 (2.7%)	8 (3.8%)	20 (3.0%)
Ear pain	4 (1.8%)	8 (3.6%)	7 (3.3%)	19 (2.9%)
Croup infectious	4 (1.8%)	10 (4.5%)	4 (1.9%)	18 (2.7%)
Respiratory syncytial virus infection	8 (3.6%)	4 (1.8%)	6 (2.8%)	18 (2.7%)
Sleep apnoea syndrome	8 (3.6%)	5 (2.2%)	5 (2.3%)	18 (2.7%)
Acute sinusitis	6 (2.7%)	5 (2.2%)	6 (2.8%)	17 (2.6%)
Constipation	2 (0.9%)	8 (3.6%)	7 (3.3%)	17 (2.6%)
Wheezing	4 (1.8%)	7 (3.1%)	6 (2.8%)	17 (2.6%)
Deafness	8 (3.6%)	2 (0.9%)	6 (2.8%)	16 (2.4%)

Adenoiditis	5 (2.3%)	6 (2.7%)	3 (1.4%)	14 (2.1%)
Pharyngitis streptococcal	3 (1.4%)	5 (2.2%)	6 (2.8%)	14 (2.1%)
Attention deficit/hyperactivity disorder	3 (1.4%)	7 (3.1%)	3 (1.4%)	13 (2.0%)
Chronic sinusitis	3 (1.4%)	4 (1.8%)	6 (2.8%)	13 (2.0%)
Nasal congestion	4 (1.8%)	5 (2.2%)	4 (1.9%)	13 (2.0%)
Nasopharyngitis	4 (1.8%)	6 (2.7%)	3 (1.4%)	13 (2.0%)
Pneumococcal immunisation	3 (1.4%)	5 (2.2%)	5 (2.3%)	13 (2.0%)
Tympanic membrane perforation	1 (0.5%)	9 (4.0%)	3 (1.4%)	13 (2.0%)

MO comment:
There was a lower incidence (18.8%) of otorrhea (42/224) at baseline in the ciprofloxacin and fluocinolone arm compared to ciprofloxacin (55/220, 25.0%) and fluocinolone arms (57/213, 26.8%). However this difference was not statistically significant.

The following Table represents the most common concomitant medications by class in the safety population.

Table 24 Common concomitant medications by class (safety population)

Concomitant medications n (%)	**CIPRO (N=220)**	**CIPRO+FLUO (N=224)**	**FLUO (N=213)**
Antibacterials for systemic use	42 (19.09%)	42 (18.75%)	63 (29.58%)
Analgesics	29 (13.18%)	47 (20.98%)	47 (22.07%)
Ophthalmological and otological preparations	46 (20.91%)	24 (10.71%)	59 (27.70%)
Antiinflammatory and antirheumatic products	21 (9.55%)	27 (12.05%)	42 (19.72%)

Prohibited concomitant medications included any topical otic agents including steroids, antimicrobial, antifungal and anti-inflammatory agents; oral corticosteroids, antibiotics, antifungals, anti-inflammatory, anti-rheumatic, antiemetics, and antinauseants products; drugs for obstructive airway diseases, analgesics, and cough and cold preparations.
Concomitant medications considered rescue medications were defined as any otic or systemic treatment administered for reasons associated with otitis media of the evaluable ear started after Visit 1 but before Visit 4.

A total of 107/657 (16.2%) subjects in the AOMT Safety Population used at least one prohibited medication during the study: 33/224 (14.7%) subjects in the CIPRO+FLUO group, 31/220 (14.1%) subjects in the CIPRO group and 43/213 (20.2%) subjects in the FLUO group. Out of the prohibited medications, 15/224 (6.7%) subjects in the CIPRO+FLUO arm, 19/213 (8.9%) in the FLUO arm and 14/220 (6.4%) in the CIPRO arm received antibacterials for systemic use.

In the safety population, 162/657 (24.7%) of subjects took at least 1 rescue medication. Of the subjects who received rescue medications, 26/224 (11.6%) subjects were in the CIPRO+FLUO group, 51/220 (23.2%) subjects in the CIPRO group, and 85/213 (39.9%) subjects were in the FLUO group.

MO comment: The use of rescue medications was greater in the fluocinolone group (40%) which is expected given that overall cure rates were lower in the fluocinolone group.

The following subjects received antibacterials as concomitant, prohibited and rescue medications in the AOMT trials.

Table 25 Concomitant, prohibited and rescue antibacterials in the AOMT trials.

	Ciprofloxacin + Fluocinolone N=224	Ciprofloxacin N=220	Fluocinolone N=213
Concomitant antibacterials	42 (18.75%)	42 (19.09%)	63 (29.58%)
Prohibited antibacterials	15 (6.7%)	14 (6.4%)	19 (8.9%)
Rescue antibacterials	20 (8.9%)	21 (9.5%)	41 (19.2%)

MO Comment: The above number of subjects were noted to be discrepant since number of subjects who received concomitant antibacterials were greater than the sum of subjects who received prohibited and rescue antibacterials. An information request was sent to the Applicant for clarification. On November 30, 2015, the Applicant responded that several patients started the antibacterial medication the same date that they completed the study (V4, discontinuation date) or after end of study and therefore this antibacterial

medication does not affect the assessment of the patient and was not considered as rescue or prohibited medication. Other patients received topical antibiotic which were administered in the non-study ear or in the eye.
These antibacterials were not considered rescue or prohibited medication. Two patients, one in the CIPRO+FLUO group (259-002) and one in the FLUO group (235-007), took prohibited and rescue medication. There were three patients (259-002 with CIPRO+FLUO and 047-004 and 305-026 with FLUO) who took "other antibacterials and prohibited and/or rescue medication. 9 subjects (4%) in the CIPRO+FLUO arm, 7 subjects (3.2%) in the CIPRO arm and 6 subjects (2.8%) in the FLUO arm, received other antibacterials.
Of note, the efficacy data (excluding diary data) collected after the patient received rescue medication was not included in the efficacy analyses. Patients who received prohibited medication were excluded from the CPP and MPP. Patient who received both, rescue and prohibited, medications were not excluded from the CPP and MPP.

(b) (4)

7.2.2 Explorations for Dose Response

Ciprofloxacin 0.3% + Fluocinolone Acetonide (0.025%) was administered in one dosage regimen. The contents of one single use vial (deliverable volume: 0.25 mL) was instilled into the affected ear canal twice daily for 7 days in each of the AOMT Phase 3 trials. No dose response information was obtained for the indication.

7.2.3 Special Animal and/or In Vitro Testing

Ciprofloxacin (0.3%) and Fluocinolone acetonide (0.025%) for 7 days will result in a total administration of 10.5 mg of Ciprofloxacin and 0.875 mg of Fluocinolone acetonide per ear. Exposure is expected to be the highest at the site of local application and no specific nonclinical pharmacokinetic or toxicokinetic studies have been performed in animals because of the low expected systemic exposure after otic application. The most plausible toxicological concerns are morphological changes and functional changes resulting in hearing changes or loss.

To applicant has conducted the following pivotal nonclinical toxicology studies under Good Laboratory Practice (GLP) conditions (acute dermal irritation, local lymph node assay (LLNA), and subacute ototoxicity studies).

- Primary Dermal Irritation in the Rabbits: to assess the degree of skin irritation caused by the drug product (0.3% Ciprofloxacin + 0.025% Fluocinolone acetonide) when applied with a semi-occlusive patch to shaved rabbit skin for four hours: found to be non irritant

- Evaluation of the acute dermal irritant and/or corrosive effect of Cetraxal Plus after a single dose administration to female New Zealand White rabbits: found to be non-irritant and non-corrosive under the experimental conditions assayed

- Local Lymph Node Assay (LLNA) to assess the skin sensitisation potential following topical application to the dorsal surface of the ear: was considered to be a non-sensitizer under the conditions of the test.

- A subacute toxicology study in Guinea pig was also performed where Cetraxal Plus was administered otically for 28 days. No significant histological changes were observed.

- A second study was performed administering Ciprofloxacin plus Fluocinolone acetonide Otic solution via the intratympanic route drug product. The proposed product did not cause mortality, was without effect on clinical observations at 28 days.

- A skin tolerance study performed with the Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic solution US formulation: found that the proposed product was tolerant.

Observed toxicities of CIPRO+FLUO acetonide after systemic administration include crystalluria, arthropathy or chondrotoxicity in immature animals , CNS effects in the case of Ciprofloxacin and reproductive and developmental toxicity issues and ulcerogenic actions in the case of Fluocinolone acetonide. However, the systemic exposure needed for these toxicities is quite high and it is highly unlikely to occur after topical application.

7.2.4 Routine Clinical Testing

The schedule of clinical observations and assessments in phase 3 trials presented in section 6.1.1 appear adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The absorption, distribution, metabolism, and excretion (ADME) of ciprofloxacin after systemic administration are well known and described in the literature. There are literature reports of the mean maximum concentration (Cmax) after a single dose of ototopically administered Ciprodex (Ciprofloxacin 0.3% and Dexamethasone 0.1%) ranging from 0.54 to 3.45 ng/mL which is approximately 570-fold lower than the mean Cmax of 760 ng/mL after administration of a 250 mg oral dose of ciprofloxacin in adult subjects. The main route of elimination is urinary and the majority of the drug is excreted unchanged.

Most glucocorticoids are rapidly removed from the blood and distributed to muscles, liver, skin, intestines and kidneys. Corticosteroids are metabolized primarily by the liver via CYP3A4 to biologically inactive compounds and excreted by the kidneys. A drug-drug interaction expected for this drug is the alteration of its metabolism by other drugs that have the ability to inhibit this isozyme.

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

The adverse events reported during the development of are consistent with other topical quinolones. The assessment of these adverse events within the clinical trials was adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the conduct of the CIFLOTIII/10IA02 and CIFLOTIII/10IA04 trials. (b) (4)

7.3.2 Nonfatal Serious Adverse Events

The Table below shows the incidence of Treatment emergent SAE by SOCs and PT.
There were 3 treatment emergent SAEs found in the MedDRA system organ class (SOC) of Infections and infestations.

Table 26 Incidence of Treatment emergent SAE by SOC and PT in Pooled AOMT trials

Body System or Organ Class (SOC) PreferredTerm (PT)	CIPRO N=220	CIPRO+FLUO N=224	FLUO N=213
Number of subjects with at least 1 serious TEAE	1 (0.5%)	1 (0.4%)	1 (0.5%)
Infections and infestations			
Abscess	0 (0.0%)	0 (0.0%)	1 (0.5%)
Mastoiditis	1 (0.5%)	0 (0.0%)	0 (0.0%)
Respiratory syncytial virus infection (RSV)	0 (0.0%)	1 (0.4%)	0 (0.0%)

Among, these SAEs, a 14 month old female (subject 247-007) in the CIPRO+ FLUO group developed severe RSV infection 3 days after completion of study treatment preceded by moderate bronchiolitis which subsequently resolved. A 6-year-old male (subject 240-003) in the CIPRO group experienced severe mastoiditis. This patient developed sinusitis 3 days into study treatment with ciprofloxacin otic solution. He was then diagnosed with acute mastoiditis which was treated with intravenous ceftriaxone and oral amoxicillin clavulanate. The mastoiditis and sinusitis resolved. A 2-year-old female subject (Subject 012-002) in the FLUO group experienced a moderate abscess (in the right calf) due to methicillin-resistant *Staphylococcus aureus*. All these cases required hospitalization but was not related to study drug treatment.

7.3.3 Dropouts and/or Discontinuations

Table 27 Reason for withdrawal in the pooled AOMT trials

	Treatment arms		
Reason for withdrawal	**CIPRO N=220**	**CIPRO+FLUO N=224**	**FLUO N=213**
Adverse event	5	3	7
At the discretion of the Investigator	0	0	3
Lack of efficacy and/or rescue medication use	8	1	17
Lost to follow-up	1	4	5

	Treatment arms		
Reason for withdrawal	**CIPRO N=220**	**CIPRO+FLUO N=224**	**FLUO N=213**
Other	0	2	0
Violation of eligibility criteria	1	2	0
Withdrew consent	2	1	2
All	17	13	34

MO Comment: Subject CIFLOTIII-10IA02-033-018 was randomized to receive CIPRO treatment, but began taking CIPRO+FLUO. Thus, 224 subjects received CIPRO+FLUO, 220 subjects received CIPRO, and 213 subjects received FLUO, for a total Safety Population of 657 subjects. The majority of withdrawal of the subjects from the study was due to treatment failure in the steroid arm as expected.

Treatment-emergent AEs that led to discontinuation of study treatment were reported in 5 subjects (2.2%) in the CIPRO+FLUO group, 8 subjects (3.6%) in the CIPRO group, and 17 subjects (8.0%) in the FLUO group.

The Table below shows the SOC and the PTs for the AEs which lead to treatment discontinuation. Most of the AEs were in the Infection and infestation SOC followed by Ear and labyrinth disorders. The events in the Infection and infestation SOC were mostly in the fluocinolone arm and included infections commonly occurring in children (i.e croup, viral gastroenteritis), AEs related to the indication (acute otitis media, and otitis externa) and complications relating to otitis (rhinitis, sinusitis, pharyngitis).

MO comment: AEs like acute otitis media and otitis externa would be expected in the steroid only arm given the lack of antibacterial effect.

Table 28 Adverse Events which led to treatment discontinuation

Body System or Organ Class	Dictionary Derived Term	CIPRO N=8	CIPRO+FLUO N=5	FLUO N=17

BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	0	0	1 (5.9%)
EAR AND LABYRINTH DISORDERS	Ear canal erythema	0	0	1 (5.9%)
	Ear pain	0	0	3 (17.6%)
	Otorrhoea	0	0	1 (5.9%)
EYE DISORDERS	Eyelid odema	0	0	1 (5.9%)
GASTROINTESTINAL DISORDERS	Vomiting	0	0	1 (5.9%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia	2 (25.0%)	2 (40.0%)	2 (11.8%)
INFECTIONS AND INFESTATIONS	Conjunctivitis infective	0	0	1 (5.9%)
	Croup infectious	0	0	1 (5.9%)
	Ear infection fungal	0	0	1 (5.9%)
	External ear cellulitis	0	0	1 (5.9%)
	Gastroenteritis viral	0	0	1 (5.9%)
	Laryngitis	0	0	1 (5.9%)
	Mastoiditis	1 (12.5%)	0	0
	Otitis externa	2 (25.0%)	0	0
	Otitis media	0	1 (20.0%)	1 (5.9%)
	Otitis media acute	2 (25.0%)	1 (20.0%)	0
	Pharyngitis streptococcal	0	1 (20.0%)	1 (5.9%)
	Rhinitis	0	0	1 (5.9%)
	Sinusitis	1 (12.5%)	0	3 (17.6%)
	Upper respiratory tract infection	1 (12.5%)	2 (40.0%)	3 (17.6%)
	Viral upper respiratory tract infection	0	0	1 (5.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Animal bite	0	0	1 (5.9%)
NERVOUS SYSTEM DISORDERS	Headache	0	0	1 (5.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Asthma	0	0	1 (5.9%)
	Cough	0	0	1 (5.9%)

	Nasal congestion	0	0	1 (5.9%)
	Rhinorrhoea	1 (12.5%)	0	1 (5.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dermatitis	1 (12.5%)	0	0
	Rash	2 (25.0%)	0	2 (11.8%)
N – number of subjects; a subject may have more than one adverse event.				

7.3.4 Significant Adverse Events

Serious TEAE are described in sections 7.3.2. The TEAE leading to treatment discontinuation are described in section 7.3.3 of the review. Refer to Section 7.4.1 for Common Adverse Events. No other significant adverse events were identified.

The following Table represents the TEAE probably or possibly related to the study drug.

Table 29 TEAE probably or possibly related to the study drug (safety population)

Dictionary Derived Term	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
PROBABLY RELATED			
Ear infection fungal	0 (0.0%)	0 (0.0%)	1 (0.5%)
Dermatitis	1 (0.5%)	0 (0.0%)	0 (0.0%)
Otitis externa candida	1 (0.5%)	0 (0.0%)	0 (0.0%)
Otitis media	0 (0.0%)	1 (0.4%)	0 (0.0%)
POSSIBLY RELATED			
Otitis media	1 (0.5%)	2 (0.9%)	4 (1.9%)
Otitis media acute	1 (0.5%)	1 (0.4%)	0 (0.0%)
Ear canal erythema	0 (0.0%)	0 (0.0%)	1 (0.5%)
Ear discomfort	1 (0.5%)	0 (0.0%)	0 (0.0%)
Ear haemorrhage	0 (0.0%)	0 (0.0%)	1 (0.5%)
Ear pain	1 (0.5%)	1 (0.4%)	2 (0.9%)
Ear pruritus	1 (0.5%)	1 (0.4%)	0 (0.0%)

Eczema	1 (0.5%)	0 (0.0%)	1 (0.5%)
Excessive granulation tissue	0 (0.0%)	1 (0.4%)	1 (0.5%)
Otitis externa	1 (0.5%)	0 (0.0%)	0 (0.0%)
Otorrhoea	1 (0.5%)	1 (0.4%)	2 (0.9%)
Rash	0 (0.0%)	1 (0.4%)	2 (0.9%)
Auricular swelling	0 (0.0%)	1 (0.4%)	0 (0.0%)
Deafness neurosensory	1 (0.5%)	0 (0.0%)	0 (0.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	1 (0.5%)
Tympanic membrane disorder	0 (0.0%)	1 (0.4%)	0 (0.0%)

Subject CIFLOTIII-101A02-010-021 in the CIPRO+FLUO arm developed severe worsening of otitis media after 7 days of treatment which resolved. Subject CIFLOTIII-101A04-290-001 developed mild neurosensory deafness in the CIPRO arm which did not resolve.

The overall severity of TEAEs, measured as the percentage of patients with mild, moderate, and severe TEAEs is presented for each treatment group in the Table below. Most TEAEs experienced during the study were of mild severity as reported by 54%, 45%, and 68.1% of patients in the CIPRO+FLUO, CIPRO, and FLUO groups, respectively.

Table 30 TEAEs by severity (Safety population)

Severity Intensity	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
MILD	99 (45%)	121 (54%)	145 (68.1%)
MODERATE	39 (17.2%)	37 (16.5%)	65 (30.5%)
SEVERE	6(2.7%)	3 (1.3%)	7 (3.3%)

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported TEAE was pyrexia which is expected as it is a common symptom of acute otitis media. The other TEAEs were also reflective of the signs and symptoms of AOM. There were no clinically significant imbalances in AEs that were considered to be drug related including allergic reactions or other local reactions. Other common TEAEs reported were otitis media, upper respiratory tract infection, nasopharyngitis, rhinorrhoea and cough, ear pain, and otorrhea.

Tonsillar disorder occurred in 3 cases (1.3%) in the CIPRO+FLUO group compared to none in the other 2 treatment groups. The incidence of rash was slightly lower in the CIPRO+FLUO group compared to the CIPRO and FLUO groups. Excessive granulation tissue were noted in 3 cases in the CIPRO+FLUO group and 2 cases in the FLUO group compared to none in the CIPRO group, however this was not clinically meaningful given the low incidence of the AE.
Otorrhoea occurred at a frequency of 5.4% (12 subjects) in the CIPRO+FLUO compared to 4.1% (9 subjects) in the ciprofloxacin group and 5.6% (12 subjects) in the FLUO group. Tympanic membrane disorder was noted in 2 subjects in the CIPRO+FLUO group compared to none in the other treatment groups.

Table 31 Adverse Events That Occurred in > 1% of Patients in the Treatment Groups (Safety Population) in the AOMT trials.

Body System or Organ Class	**CIPRO N=220**	**CIPRO+FLUO N=224**	**FLUO N=213**
Preferred Term			
Number of patients with ≥1 TEAE	94	96	110
General disorders and administration site conditions			
Pyrexia	12 (5.5%)	16 (7.1%)	23 (10.8%)
Infections and infestations			
Otitis media	9 (4.1%)	14 (6.3%)	15 (7.0%)

Otitis media acute	6 (2.7%)	6 (2.7%)	5 (2.3%)
Upper respiratory tract infection	9 (4.1%)	10 (4.5%)	8 (3.8%)
Nasopharyngitis	1 (0.5%)	3 (1.3%)	9 (4.2%)
Sinusitis	6 (2.7%)	2 (0.9%)	5 (2.3%)
Bronchitis	3 (1.4%)	2 (0.9%)	1 (0.5%)
Ear infection	3 (1.4%)	2 (0.9%)	1 (0.5%)
Pharyngitis	3 (1.4%)	0 (0.0%)	3 (1.4%)
Tonsillitis	1 (0.5%)	4 (1.8%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	6 (2.7%)	14 (6.3%)	16 (7.5%)
Cough	6 (2.7%)	10 (4.5%)	7 (3.3%)
Nasal congestion	4 (1.8%)	2 (0.9%)	4 (1.9%)
Tonsillar disorder	0 (0.0%)	3 (1.3%)	0 (0.0%)
Ear and labyrinth disorders			
Ear pain	4 (1.8%)	4 (1.8%)	8 (3.8%)
Otorrhoea	9 (4.1%)	12 (5.4%)	12 (5.6%)
Gastrointestinal disorders			
Vomiting	1 (0.5%)	4 (1.8%)	9 (4.2%)
Teething	0 (0.0%)	3 (1.3%)	1 (0.5%)
Diarrhoea	4 (1.8%)	3 (1.3%)	4 (1.9%)
Skin and subcutaneous tissue disorders			
Rash	5 (2.3%)	2 (0.9%)	4 (1.9%)
Excessive granulation tissue	0 (0.0%)	3 (1.3%)	2 (0.9%)
Eczema	3 (1.4%)	0 (0.0%)	3 (1.4%)
Blood and lymphatic system disorders			
Lymphadenopathy	1 (0.5%)	2 (0.9%)	3 (1.4%)
Nervous system disorders			
Headache	0 (0.0%)	1 (0.4%)	4 (1.9%)

MO Comment: Adverse events reported by greater than or equal to 2 % of patients and more frequently in the CIPRO+FLUO group were pyrexia, otitis media, rhinorrhea, cough, upper respiratory tract infection and otorrhoea.

The safety databases for trials CIFLOTIII-10IA02 and CIFLOTIII-10IA04 were explored by conducting standardized MedDRA queries.

This search identified a greater number of subjects with adverse events in the narrow SMQ of Oropharyngeal disorders in the ciprofloxacin+fluocinolone arm (13 subjects compared to 9 subjects in the fluocinolone arm). However these were mostly tonsillitis and one case of hand foot and mouth disease unrelated to the study drug.

There were greater number of subjects with adverse events in the narrow SMQ of Hearing and vestibular disorders in the ciprofloxacin+fluocinolone arm (3 subjects compared to 1 subject in the fluocinolone and ciprofloxacin arms). Two subjects in trial CIFLOTIII-10IA02 (CIFLOTIII-10IA02-003-015 and CIFLOTIII-10IA02-012-001) had moderately inflamed right tympanic membrane and mild left eardrum edema unrelated to study drug which also resolved. One subject (one year old male) in trial CIFLOTIII-10IA04 (CIFLOTIII-10IA04-254-001) had mild eardrum edema possibly related to the study drug which resolved. There was one subject CIFLOTIII-10IA04-247-007 in the ciprofloxacin+fluocinolone arm in the narrow SMQ of interstitial lung disease with moderate acute bronchiolitis which resolved.
There were 13 subjects in the ciprofloxacin+fluocinolone arm versus 8 subjects in the ciprofloxacin arm in the narrow SMQ of oropharyngeal disorders. There were 3 subjects with PT of excessive granulation tissue in the ciprofloxacin+fluocinolone arm compared to none in the ciprofloxacin arm. These were mild AEs and one case possibly related to the study drug.

There were greater number of subjects with AE in the ciprofloxacin+fluocinolone arm compared to the ciprofloxacin arm in the SOC of Respiratory, thoracic and mediastinal disorders (27 vs 18), Ear and labyrinth disorders (19 vs 17), Gastrointestinal disorders (11 vs 6), General disorders and administration site conditions (18 vs 13). The respiratory thoracic and mediastinal disorders mostly included cough, rhinorrhea, wheezing, bronchial hyper reactivity, nasal congestion, pharyngeal erythema, tonsillar disorder.

The analyses of AE by SOC revealed that there were more subjects in the FLUO (n=57) and CIPRO (n=50) arms with SOC of Infections and infestations than in the CIPRO+FLUO arm (n=45).

Twelve subjects were identified in the ciprofloxacin+fluocinolone arm with AE of otorrheoa. All of these subjects recovered except 3 subjects (CIFLOTIII-10IA02-003-004, CIFLOTIII-10IA04-307-002, CIFLOTIII-10IA04-403-001). In one subject CIFLOTIII-10IA02-003-004, otorrheoa was felt to be related to the study drug. Nine subjects were identified in the ciprofloxacin arm with AE of otorrhoea. Five of these subjects recovered, one had severe otorrhoea. Twelve subjects were identified in the fluocinolone arm with otorrhoea. Three of these subjects did not recover and one had severe otorrhoea.

In study: CIFLOTIII-10IA04, AE of otitis media (n=1), respiratory syncytial virus (n=1) in the CIPRO+ FLUO arm, otorrhoea (n=1), acute otitis media (n=1), bronchiolitis (n=1), mastoiditis (n=1) in the CIPRO arm, and cough and sinusitis (n=1) in the FLUO arm were severe in intensity.

In study: CIFLOTIII-10IA02, AE of otitis media (n=1) in the CIPRO+FLUO arm, ear pain (n=1) and acute otitis media (n=1) in the CIPRO arm, ear pain (n=3), otorrhoea (n=1), ear canal erythema (n=1) in the FLUO arm were severe in intensity.

The following Figures show the risk difference per hundred of adverse events by SOC in the AOMT trial safety pool (n=657). Adverse events that were observed more frequently in the CIPRO+FLUO versus CIPRO arm were in the respiratory, thoracic and mediastinal SOC and AE that were observed more frequently in the CIPRO+FLUO versus FLUO arm were in the investigations SOC (pyrexia).

Figure 26 Risk difference per hundred of adverse events by SOC in descending order in the AOMT safety pool (CIPRO+FLUO versus CIPRO)

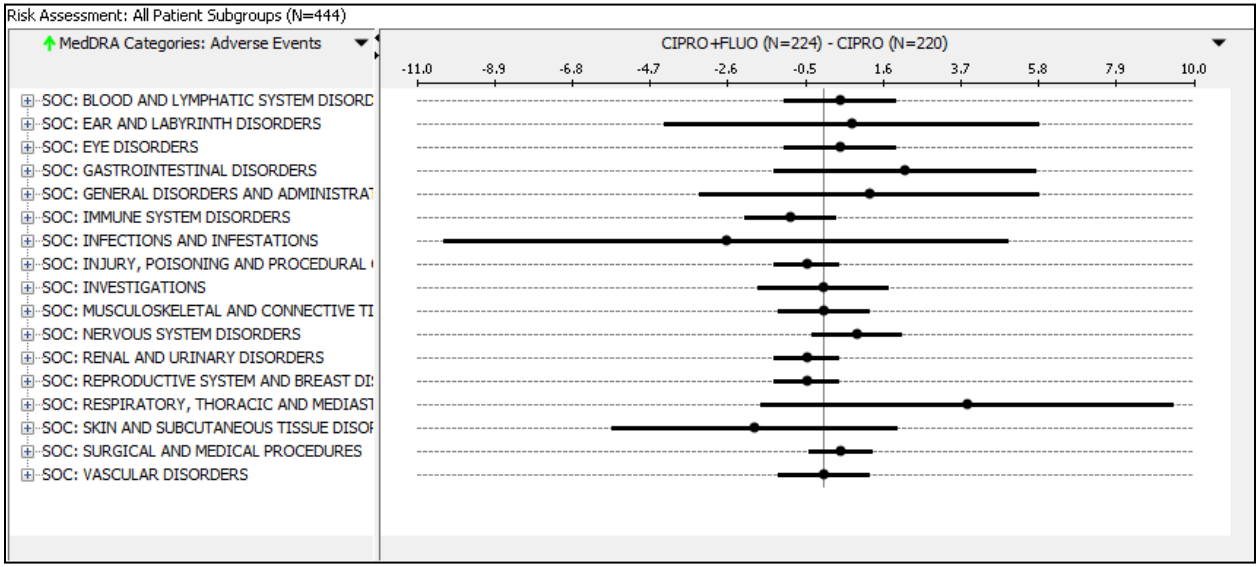
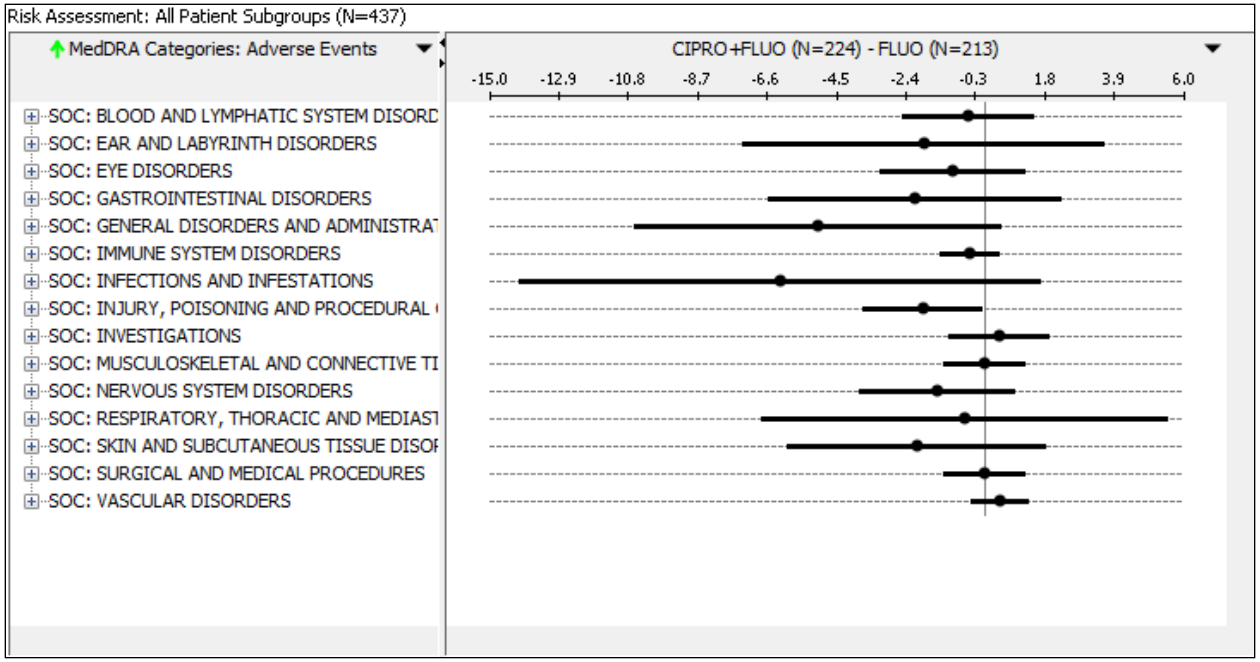


Figure 27 Risk difference per hundred of adverse events by SOC in descending order in the AOMT safety pool (CIPRO+FLUO versus FLUO)



MO comment: There were greater numbers of subjects in the CIPRO+FLUO arm compared with FLUO or CIPRO arms for narrow SMQs of oropharyngeal, hearing and vestibular disorders. Adverse events(AEs) that were observed more frequently in the CIPRO+FLUO versus CIPRO arm were in the respiratory, thoracic and mediastinal SOC and AE that were observed more frequently in the CIPRO+FLUO versus FLUO arm were in the investigations SOC (pyrexia). However, the incidence of AEs was balanced overall.

7.4.2 Laboratory Findings

Safety laboratory assessments were not performed. Microbiological culture of ear discharge for efficacy assessments and pharmacokinetic assessments were conducted.

7.4.3 Vital Signs

Cardiovascular parameters (pulse and blood pressure) were measured for all subjects in the AOMT trials. No changes in pulse rate or blood pressure were assessed as clinically relevant. Physical examinations and audiometric assessments were also performed for all subjects in the trials. Abnormal ear exams were similar at screening among the treatment arms. At the end of treatment visit, only 33% of subjects had abnormal ear exams in the CIPRO+FLUO arm compared to 53% in the CIPRO arm and 61% in the FLUO arm.

Table 32 Abnormal ear exam at the different visits (safety population)

Analysis Visit	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
Visit 1 (Screening)	205 (93.2%)	213 (95.1%)	199 (93.4%)
Visit 2 (During treatment)	155 (70.5%)	143 (63.8%)	145 (68.1%)
Visit 3 (End of treatment)	117 (53.2%)	74 (33.0%)	130 (61.0%)
Visit 4 (Test of cure)	68 (30.9%)	61 (27.2%)	67 (31.5%)

Analysis of audiometric assessments showed little difference between the age subgroups. Improvements were noted in all subjects from abnormal non-clinically significant (NCS) to normal or from abnormal clinically significant (CS) to normal from visit 1 to test of cure visit.

Table 33 Air and bone conduction thresholds in the age groups less than or more than 3 years of age (safety population)

		AIR CONDUCTION THRESHOLDS			
Age Group	Analysis Visit	Analysis Category 1	CIPRO N=220	CIPRO+FLUO N=224	FLUO N=213
< 3 YEARS OLD	Visit 1 (Screening)	ABNORMAL NCS	3 (1.4%)	3 (1.3%)	2 (0.9%)
		NORMAL	3 (1.4%)	3 (1.3%)	2 (0.9%)
		ABNORMAL CS	6 (2.7%)	5 (2.2%)	10 (4.7%)
	Visit 4 (Test of cure)	ABNORMAL CS	0 (0.0%)	2 (0.9%)	1 (0.5%)
		ABNORMAL NCS	0 (0.0%)	1 (0.4%)	0 (0.0%)
		NORMAL	10 (4.5%)	5 (2.2%)	10 (4.7%)
>= 3 YEARS OLD	Visit 1 (Screening)	ABNORMAL NCS	14 (6.4%)	12 (5.4%)	13 (6.1%)
		NORMAL	9 (4.1%)	8 (3.6%)	13 (6.1%)
		ABNORMAL CS	32 (14.5%)	28 (12.5%)	27 (12.7%)
	Visit 4 (Test of cure)	ABNORMAL NCS	9 (4.1%)	7 (3.1%)	9 (4.2%)
		NORMAL	36 (16.4%)	31 (13.8%)	27 (12.7%)
		ABNORMAL CS	6 (2.7%)	4 (1.8%)	7 (3.3%)
		BONE CONDUCTION THRESHOLDS			
< 3 YEARS OLD	Visit 1 (Screening)	ABNORMAL NCS	0 (0.0%)	1 (0.4%)	0 (0.0%)
		ABNORMAL CS	0 (0.0%)	0 (0.0%)	1 (0.5%)
		NORMAL	3 (1.4%)	3 (1.3%)	6 (2.8%)
	Visit 4 (Test of cure)	ABNORMAL CS	0 (0.0%)	0 (0.0%)	1 (0.5%)
		NORMAL	4 (1.8%)	3 (1.3%)	5 (2.3%)
>= 3 YEARS OLD	Visit 1 (Screening)	ABNORMAL NCS	1 (0.5%)	2 (0.9%)	1 (0.5%)
		NORMAL	34 (15.5%)	34 (15.2%)	35 (16.4%)
		ABNORMAL CS	3 (1.4%)	1 (0.4%)	3 (1.4%)
	Visit 4 (Test of cure)	ABNORMAL NCS	1 (0.5%)	1 (0.4%)	0 (0.0%)

		NORMAL	37 (16.8%)	30 (13.4%)	32 (15.0%)
		ABNORMAL CS	1 (0.5%)	0 (0.0%)	1 (0.5%)

CS= clinically significant, NCS=non clinically significant

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in the AOMT trials.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this product.

The following is reviewer generated summary of hypersensitivity reactions grouped by PT. There were 14 events of hypersensitivity in 13 subjects(5.8%) in the CIPRO+FLUO arm, 13 events in 13 subjects (5.9%) in the CIPRO arm and a slightly higher proportion of 7.98% in the FLUO arm (18 events in 17 subjects).

Table 34 Hypersensitivity events by PT in the AOMT trials (Safety population)

PT	**CIPRO+FLUO (N=224)**	**CIPRO (N=220)**	**FLUO (N=213)**
Cough	9	6	7
Rash	2	5	3
Wheezing	1		
Flushing		1	
Chest discomfort		1	
Hypersensitivity			1
Erythema			1
Asthma			2

Wheezing			1
Eyelid edema			1
Pruritus	1		1

MO comment: One subject in the CIPRO+FLUO arm had both rash and cough. One subject in the fluocinolone arm had both eyelid edema and rash.

7.4.6 Immunogenicity

Ciprofloxacin has been reported to alter immune responses via interleukin-2 induction in peripheral blood lymphocytes (PBL), increased transcription of stress response proteins and increased [3H]-thymidine incorporation in phytohemagglutinin-stimulated PBLs.. However immunotoxicity events are expected to be few considering the low doses administered and the expected low absorption.

No relevant information regarding immunotoxicity has been obtained with Fluocinolone acetonide.

Clinical hypersensitivity reactions are discussed in section 7.4.5 of the review.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Ciprofloxacin 0.3% + Fluocinolone Acetonide (0.025%) was administered in one dosage regimen. The contents of one single use vial (deliverable volume: 0.25 mL) was instilled into the affected ear canal twice daily for 7 days in each of the Phase 3 trials. No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

There were no clinically significant differences between age (<2 years, 2 to 5 years and 6 yearsto 12 years), gender and race subgroups for vital signs, physical examination and audiometric assessments. The TEAEs decreased with increasing age as shown in the table below.

Table 35 TEAE in the different age groups in the AOMT trials (Safety population)

Age Group	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
< 2 YEARS OLD	48 (21.82%)	55 (24.55%)	50 (23.47%)
2 to 5 YEARS OLD	40 (18.18%)	34 (15.18%)	45 (21.13%)
6 to 12 YEARS OLD	6 (2.73%)	7 (3.13%)	15 (7.04%)

MO Comment: TEAE analysis in the 6 to 12 years age group shows that TEAE was reported in 2.7% of patients in the ciprofloxacin group, 3.1% of patients in the CIPRO+FLUO group and 7% of patients in the fluocinolone group.

In the younger subgroups (≤5 years old) more TEAEs were reported in in the Infections and infestations SOC, while among the older subjects (6 to 12 years old), more TEAEs were reported in the Ear and labyrinth disorders SOC and Respiratory, thoracic, and mediastinal disorders SOC. The types of TEAEs were similar between the gender groups.

There were fewer subjects with bilateral disease in the CIPRO+FLUO arm (19.2%) versus 25% in the ciprofloxacin arm and 22.5% in the fluocinolone arm.

Table 36 Type of Otitis media in AOMT trials

Otitis Media Type	CIPRO (N=220)	CIPRO+FLUO (N=224)	FLUO (N=213)
Bilateral	55 (25.00%)	43 (19.20%)	48 (22.54%)
Unilateral	165 (75.00%)	181 (80.80%)	165 (77.46%)

There were also fewer subjects with bilateral disease in the CIPRO+FLUO arm in the age group less than 2 years. The number of days since the onset of otorrhea was recorded for subjects in the AOMT studies: the mean (SD) number of days was 4.3 (4.75), and the median was 2.0 across the treatment groups.

7.5.4 Drug-Disease Interactions

There were 18.3% (41/224) concurrent conditions(Asthma being the most common condition in all arms) in the CIPRO+FLUO, 16.4% (35/213) in FLUO and 13.6% (30/220) in the CIPRO arms.
These conditions were expected and no safety signal was identified. A review of adverse events by subpopulations categorized by concomitant diseases also revealed no safety concerns.

7.5.5 Drug-Drug Interactions

Specific drug interaction studies have not been conducted with ciprofloxacin 0.3% plus
fluocinolone acetonide 0.025% otic solution. Given the low systemic concentration following topical otic administration of the product, drug interactions are unlikely to occur.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific carcinogenicity study was conducted with Ciprofloxacin 0.3% plus Fluocinolone acetonide 0.025% Otic solution. The applicant has referred to long-term carcinogenicity studies of Ciprofloxacin in rats and mice which shows no carcinogenic or tumorigenic effects when administered at oral doses up to 250 mg/kg/day (rats) and 750 mg/kg/day (mice) for up to two years (2, 3). Carcinogenicity studies have not been conducted with Fluocinolone acetonide.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant females were excluded from the clinical development program. No adequate and well-controlled studies have been performed in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

The clinical development program did not produce any evidence that the otic administration of CIPRO+FLUO otic solution had any adverse effect on weight bearing joints or the pediatric population generally.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential for abuse with ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution. No reports of overdose were received during the clinical studies with the product.

7.7 Additional Submissions / Safety Issues. (b) (4). None of the AEs were of moderate intensity in the CIPRO+FLUO arm. There was 1 SAE of perichondritis which was not treatment related. A 36 year old man patient started treatment with CIPRO+FLUO , then noted to have perichondritis the same day. The patient was hospitalized.The mild perichondritis was treated with oral ciprofloxacin and methylprednisolone and resolved within 7 days. The subject discontinued from the study.

MO comment: The SAE of perichondritis was likely due to a complication of the diffuse otitis externa rather than an AE from the study drug. The narrative is conflicting as to whether the patient received a full course of the study drug.

Three subjects discontinued from the study due to AEs. The tympanic membrane perforations on the CIPRO+FLUO arm were mild in severity and were not related to study treatment. Among the 5 AEs reported in the CIPRO group, 2 were considered to be related to study treatment (mild eczema and mild dizziness) and 3 were not related (mild dyspepsia,
moderate laryngeal edema, and moderate vertigo).

Table 37 Adverse Events That Occurred in the Treatment Groups (Safety Population N=590) (b) (4).

		SEVERITY		SERIOUS		TREATMENT	
TRTA	AETERM	MILD	MODERATE	N	Y	NOT RELATED	RELATED
CIPRO	DIZZY WHEN PUT DROPS IN THE MORNING	1	0	1	0	0	1
N=294	EDEMA OF GLOTTIS	0	1	1	0	1	0
	PYROSIS	1	0	1	0	1	0
	SKIN ECZEMA EAR	1	0	1	0	0	1
	VERTIGO	0	1	1	0	1	0
CIPRO+FLUO	PERFORATION	1	0	1	0	1	0

		SEVERITY		SERIOUS		TREATMENT	
TRTA	AETERM	MILD	MODERATE	N	Y	NOT RELATED	RELATED
N=296	PERICHONDRITIS	1	0	0	1	1	0
	TYMPANIC PERFORATION	1	0	1	0	1	0

8 Postmarket Experience

The applicant has submitted safety data from summary tabulations of serious reactions from marketing experience, including reports from healthcare professionals, consumers, scientific literature worldwide and from non-interventional studies and other non-interventional solicited sources with a total exposure of (b) (4) patients until January 31, 2015 for Ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution (Cetraxal Plus) which is approved outside the U.S. in some countries.

The following table represents the cumulative numbers of adverse drug reactions by preferred term from post-marketing sources. None of these events were noted as serious.

Table 38 Cumulative Numbers of Adverse Drug Reactions by Preferred Term from Post-Marketing Sources.

System Organ Class Preferred Term	**Total spontaneous including competent authorities (worldwide) and literature**	**Non-interventional post-marketing study and reports from other sources[b]**
	Non-serious	Non-serious
General disorders and administration site conditions	3	3
Administration site pain	1	0

Application site stinging	1	0
Localized edema	0	1
Pain	0	1
Pruritus	1	0
Pyrexia	0	1
Ear and Labyrinth Disorders	5	2
Auricular swelling	0	1
Ear congestion	1	0
Ear pain	2	0
Tinnitus	2	0
Vertigo	0	1
Infections and Infestations	1	0
Mycosis	1	0
Injury, Poisoning and Procedural Complications	2	2
Error medication	1	2
Exposure during pregnancy[c]	1	0
Nervous System Disorders	1	0
Paresthesia	1	0
Skin and Subcutaneous Tissue Disorders	1	0
Urticaria	1	0

Source: Table 24 of Applicant's Summary of Clinical Safety

9 Appendices

9.1 Literature Review/References

1. Riesbeck K, Forsgren A, Henriksson A, and Bredberg A, Ciprofloxacin induces an immunomodulatory stress response in human T lymphocytes, Antimicrob Agents Chemother 42 (1998) 1923-1930.
2. Cipro HC Otic prescribing information (Ciprofloxacin Hydrochloride; Hydrocortisone). NDA 020-805. Alcon Pharms Ltd; Aug. 2011.
3. Cipro prescribing information (Ciprofloxacin Hydrochloride). NDA 020-780. Bayer Healthcare; Jul. 2013.

9.2 Labeling Recommendations

At the time of the review preparation the reviewer had no specific comments on labeling.

9.3 Advisory Committee Meeting

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAYURIKA GHOSH
03/15/2016

DMITRI IARIKOV
03/15/2016