CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208251Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
ADDENDUM

NDA: 208251 (SDN1-17, 25, 26) Date Review Completed: 04-29-2016

Date Submitted:	06/30/2015; 09/18/2015; 10/23/2015, 11/13/2015, 12/01/2015, 1/29/2016, 4/25/2016, 4/27/2016
Clinical Microbiology Reviewer:	Kalavati Suvarna, Ph.D
NDA:	208251 SDN1-17, 25, 26
Applicant Name:	Laboratorios SALVAT S.A. (SALVAT) Gall, 30-36 08950 Esplgues de Llobregat Barcelona, Spain
Drug Names:	OTOVEL (Ciprofloxacin 0.3% and Fluocinolone Acetonide 0.025% otic solution)
Dosage Forms (Route of Administration):	Sterile, preservative-free, aqueous-based solution for otic administration.
Dosage Strength:	0.3% ciprofloxacin, 0.025% fluocinolone acetonide

SUMMARY:

This is an addendum to the clinical microbiology review dated 3-16-2016 for NDA 208251 to include change to the reference listed drug for this application. The reference listed drug is Cipro HC (NDA 020805). The applicant has relied on the agency's finding of safety and efficacy for Cipro HC as reflected in the approved labeling for preclinical microbiology information. There are no changes to the recommendations and microbiology section of the labeling. The NDA is recommended for approval.

SIGNATURES:

Kalavati Suvarna, Ph.D. {See appended signature}
Clinical Microbiology Reviewer Signature/Date

Avery Goodwin, Ph.D. {See appended signature}
Clinical Microbiology Peer Reviewer Signature/Date

CC:
Original NDA
DAIP CSO/DeBellas, Carmen
DAIP CDTL/Iarikov, Dmitri
DAIP MO/ Ghosh, Mayurika

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

/s/

KALAVATI C SUVARNA
04/29/2016

AVERY C GOODWIN
04/29/2016

NDA 208251/0001 (SDN1-17)
OTOVEL (Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution)
Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

Division of Anti-Infective Products
Clinical Microbiology Review

NDA: 208251 (Original)

Date Submitted: 06/30/2015; 09/18/2015; 10/23/2015, 11/13/2015, 12/01/2015, 1/29/2016
Date Received: 06/30/2015; 09/18/2015; 10/23/2015, 11/13/2015, 12/01/2015, 1/29/2016
Date Assigned: 07/02/2015; 09/18/2015; 10/23/2015, 11/13/2015, 12/02/2015, 1/29/2016
Date Completed: 03/16/2016
Reviewer: Kalavati Suvarna Ph.D.

NAME AND ADDRESS OF APPLICANT:

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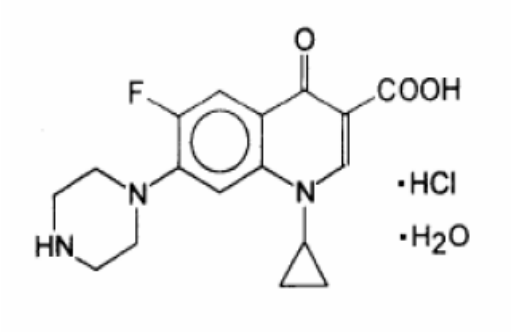
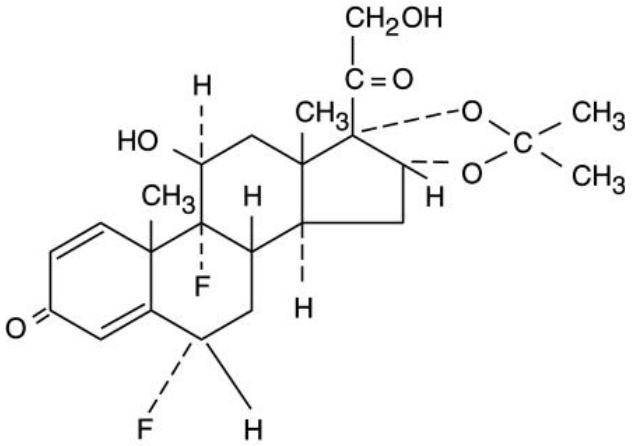
1500 Market Street, STE 3500 West, Philadelphia, PA 19102.
215.282.5500 or 215.292.5502 [direct]

DRUG PRODUCT NAMES:
Proprietary Name: OTOVEL (proposed)
Established Name: Ciprofloxacin
Chemical Name: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid
Molecular formula: $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$
Molecular weight: 385.82
Structural formula:



NDA 208251/0001 (SDN1-17)
OTOVEL (Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution)
Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

Established Name: fluocinolone acetonide
Chemical Name: (6α,11ß,16α)-6,9-difluoro-11,21-dihydroxy-16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione,cyclic 16,17 acetal with acetone
Molecular formula: C24H30F2O6
Molecular weight: 452.50
Structural formula:



DRUG CATEGORY: Antibacterial plus Corticosteroid

PROPOSED DOSAGE FORM AND STRENGTH:
Dosage form: sterile, preservative-free, aqueous-based solution
Strength: 0.3% ciprofloxacin, 0.025% fluocinolone acetonide

ROUTE OF ADMINISTRATION:
Route of administration: Ear instillation (ear drops)

DOSAGE AND DURATION OF TREATMENT:
One (b) (4) vial (containing 0.25 mL deliverable volume) instilled into affected ear, twice daily for 7 days

DISPENSED: Rx

PROPOSED INDICATION: Indicated for

- Acute otitis media (AOMT) in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*
- (b)(4)

NDA 208251/0001 (SDN1-17)
OTOVEL (Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution)
Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

RELATED DOCUMENTS:

NDA 021918 (approved May 1, 2009); Cetraxal (ciprofloxacin hydrochloride 0.2%) Labeled: "CETRAXAL is a fluoroquinolone antimicrobial indicated for the treatment of acute otitis externa due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus*."

NDA 020805 (Alcon, Inc., approved Feb 10, 1998); Cipro HC OTIC [ciprofloxacin 0.2% with hydrocortisone 1%, for treatment of AOE in adult and pediatric patients, one year and older, due to susceptible strains of *P. aeruginosa*, *S. aureus*, and *P. mirabilis*]

NDA 021537 (Alcon, Inc., approved July 18, 2003); Ciprodex [ciprofloxacin 0.3% with dexamethasone 0.1%, for treatment of AOE in pediatric, adult, and elderly patients due to *S. aureus* and *P. aeruginosa*, and AOM in pediatric, adult, and elderly patients due to *S. aureus* and *P. aeruginosa*] (Reference Listed Drug).

NDA 019452; (Hill Dermac, approved February 3, 1988); DermOtic [fluocinolone acetonide 0.01%, for atopic dermatitis]

IND 107809: Ciprofloxacin 0.3% plus Fluocinolone acetonide Otic solution
DMF (b)(4): Ciprofloxacin hydrochloride; DMF (b)(4) Fluocinolone acetonide

TYPE OF SUBMISSION:

Original NDA

PURPOSE OF SUBMISSION:

The applicant has submitted a 505(b)(2) NDA submission for OTOVEL (ciprofloxacin HCl 0.3% (as base)/fluocinolone acetonide 0.025%) Otic Solution for the indications listed above. The reference listed drug is CIPRODEX® (NDA 021537).

NDA 208251/0001 (SDN1-17)
OTOVEL (Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution)
Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

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OTOVEL (Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution)
Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

EXECUTIVE SUMMARY AND RECOMMENDATIONS:

This is a 505(b)(2) NDA for Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution for the treatment of pediatric patients with Acute Otitis Media with Typanostomy tubes (AOMT) due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa*; (b)(4) The active ingredients in the proposed product are Ciprofloxacin and Fluocinolone Acetonide, both of which are approved and marketed individually but not in combination. The applicant has conducted two Phase III multicenter, randomized, double-blind clinical trials using a 3 arm study design to assess the efficacy and safety of CIPRO+FLUO Otic Solution in the treatment of AOMT in pediatric patients (b)(4) 4)

Ciprofloxacin is a fluoroquinolone antimicrobial that interferes with the DNA gyrase enzyme required for synthesis of bacterial DNA. Fluocinolone Acetonide is a synthetic (b) (4) corticosteroid with anti-inflammatory properties.

In the clinical studies, ciprofloxacin was active against the microorganisms (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus aureus* and *Pseudomonas aeruginosa*) that cause AOMT. In the pooled studies, favorable microbiological response was observed in AOMT patients treated with ciprofloxacin (0.3%) plus fluocinolone acetonide (0.025%) with baseline *P. aeruginosa* (95.0%), *S. aureus* (84.2%), *M. catarrhalis* (92.3%), *H. influenzae* (78.6%), and *S. pneumoniae* (72.7%) isolates. Sustained microbiological response was observed in 84.1% (74/88) patients treated with ciprofloxacin (0.3%) plus fluocinolone acetonide (0.025%) in the microbiological evaluable population compared to 69.2% (72/104) patients treated with ciprofloxacin and 36.0% (31/86) patients treated with fluocinolone acetonide.

The systemic exposure to ciprofloxacin after otic administration of the proposed product is low. In clinical and surveillance studies, the ciprofloxacin MIC_{90} for methicillin-sensitive *S. aureus* (MSSA) and *P. aeruginosa* was 16 µg/mL while that for methicillin-resistant *S. aureus* (MRSA) was 256 µg/mL. The ciprofloxacin MIC_{90} values for *S. pneumonia, H. influenzae* (β-lactamase positive and negative) and *M. catarrhalis* were ≤ 2 µg/mL. The ciprofloxacin MICs against the target bacteria in clinical and surveillance studies were within the ciprofloxacin concentrations in

the otic solution. *In vitro* susceptibility criteria against the bacteria are not applicable as this is a topical product.

From a clinical microbiology standpoint, the NDA is approvable for the AOMT indication pending acceptance of labeling changes to the MICROBIOLOGY subsection of the Package Insert shown below.

MICROBIOLOGY SUBSECTIONS OF THE PACKAGE INSERT
This Reviewer recommends changes to the Microbiology portion of the Package Insert as follows. Deletions are in red and strikethrough font; additions are in blue Font and double underlined. The proposed changes are to meet current standard format for MICROBIOLOGY subsection

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

(b)(4) Ciprofloxacin, is a fluoroquinolone antibacterial (b)(4) *[see Microbiology (12.4)].*

Fluocinolone acetonide, a corticosteroid, inhibits the local biosynthesis of prostaglandins, which explains part of its anti-inflammatory efficacy. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes and the complement system.

12.4. Microbiology

Mechanism of Action:
The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA.

Resistance:
Bacterial resistance to quinolones can develop through chromosomal or plasmid mediated mechanisms.

(b)(4) *In vitro* studies demonstrated cross-resistance between ciprofloxacin and some fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

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Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

Antimicrobial Activity:

[redacted] (b)(4) Ciprofloxacin has been shown to be active against most isolates of the following bacteria, both in vitro and clinically in ~~clinical~~ otic infection~~s~~ ~~[see Section 1]~~: *[see Indications and Usage (1)].*

Aerobic Bacteria:
Gram-positive Bacteria
Staphylococcus aureus
[redacted] (b)(4)
Streptococcus pneumonia

Gram-negative Bacteria
Pseudomonas aeruginosa
Haemophilus influenzae
Moraxella catarrhalis

[redacted] (b)(4)

INTRODUCTION:

Acute Otitis Media (AOM) is characterized by symptomatic inflammation (e.g., bulging of tympanic membrane) of the middle ear due to fluid build-up in the middle ear space [Mandell 2005][1]. AOM is known to occur after a viral upper respiratory tract infection. Bacteria that colonize the nasopharynx reach the middle ear due to the negative pressure build-up in the Eustachian tube, leading to patients being subsequently infected with bacteria. The most common causes of AOM are S*treptococcus pneumoniae*, *Haemophilus influenza* (non-typeable), and *Moraxella catarrhalis*. When otitis media reoccurs, it is often treated by insertion of tympanostomy tubes which makes the middle ear accessible to topical otic solutions. The most common complications observed after tube insertion is otorrhea, formation of granulation tissue around the tube, and cholesteatoma. In studies that have examined the microbiology of otorrhea associated with tympanostomy, S*treptococcus pneumoniae*, *Haemophilus influenza* (non-typeable), *Moraxella catarrhalis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* have been commonly isolated[2,3,4]. Concomitant viral infection is seen in approximately 70% of

[1] Mandell GL, Bennett JE, et al. Principles and Practice of Infectious Diseases 6th Ed. Elsevier Churchill Livingtone, Philadelphia. 2005.

patients. Epidemiologic data also suggests that the percentage of penicillin-susceptible strains of *S. pneumoniae*, compared to penicillin-resistant strains, has increased[5]. Studies have suggested that isolates of methicillin-resistant *S. aureus* and *Pseudomonas aeruginosa*, collected from "ear cultures", may often be non-susceptible to commonly used otic drops, including ciprofloxacin otic solutions[4,6].

The active ingredients in the proposed product are Ciprofloxacin and Fluocinolone Acetonide, both of which are approved and marketed individually but not in combination. Ciprofloxacin is a fluoroquinolone antimicrobial that interferes with the DNA gyrase enzyme required for synthesis of bacterial DNA. Fluocinolone Acetonide is a synthetic (b) (4) corticosteroid with anti-inflammatory properties. In the US, Ciprofloxacin 0.2% Otic Solution (Cetraxal SALVAT, NDA 21-918, approved on May 1, 2009) is approved for the treatment of acute otitis externa (AOE). In addition, Ciprofloxacin in combination with a corticosteroid have been approved for AOE in both the pediatric and adult populations [Cipro HC (Ciprofloxacin 0.2% with Hydrocortisone 1% Suspension, Alcon, NDA 20-805, approved February 10, 1998); and Ciprodex (Ciprofloxacin 0.3% with Dexamethasone 0.1% Sterile Otic Suspension, Alcon NDA 21-537 approved July 18, 2003)]. Ciprodex is also approved for the topical treatment of acute otitis media with tympanostomy tubes (AOMT) in children ages six months and older.

(b) (4)

(b) (4). The addition of the corticosteroid to otic preparations aids with the resolution of the inflammatory response accompanying the bacterial infection.

The applicant has conducted two Phase III multicenter, randomized, double-blind clinical trials using a 3 arm study design to assess the efficacy and safety of CIPRO+FLUO Otic Solution in the treatment of acute otitis media with tympanostomy tubes in pediatric patients (b)(4) The clinical study design summary is shown in Table 1.

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[2] Shim HJ, Park CH, Kim MG, et al. A pre- and postoperative bacteriological study of chronic suppurative otitis media. J Infect. 2010;38(6):447-452.
[3] Jung H, Lee SK, Cha S-H, et al. Current bacteriology of chronic otitis media with effusion: high rate of nosocomial infection and decreased antibiotic sensitivity. J Infect. 2009; 59(5):308-316.
[4] Saunders JE, Raju RP, Boone J, et al. Current bacteriology of suppurative otitis: resistant patterns and outcomes analysis. Otol Neurotol. 2009; 30(3):339-343.
[5] Lee H, Kim J, Nguyen V. Ear Infections. Otitis externa and Otitis Media. Prim. Care Clin Office Pract. 2013;40:671-686.
[6] MacNeil SD, Westerberg BD, et al. Toward the development of evidence-based guidelines for the management of methicillin-resistant Staphylococcus aureus otitis. J Otolaryngol Head Neck Surg. 2009; 38: 483-94.

Table 1: Overview of Clinical Studies with Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution

Study No.	Study type	Indication	Treatment	Sample size	Duration	Main Endpoint
CIFLOTIII/10IA02	Multicenter, randomized, double blind	AOMT	CIPRO+FLUO CIPRO FLUO	331	22 days 7 days of treatment	Time to cessation of otorrhea
CIFLOTIII/10IA04				331	22 days 7 days of treatment	Time to cessation of otorrhea

(b)(4)

This is a 505(b)(2) NDA for Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% Otic Solution (a sterile and preservative-free otic solution supplied in single use vials) for the treatment of pediatric patients with Acute Otitis Media with Typanostomy tubes (AOMT) due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa*; (b)(4)

(b)(4)

PRE-CLINICAL MICROBIOLOGY:
The applicant relies in part upon FDA's conclusions concerning the safety and efficacy of Ciprofloxacin- and Fluocinolone acetonide-containing products found in reviews for approved NDA products, including Cipro HC, Ciprodex, and DermOtic to provide pre-clinical microbiology information. Besides the package inserts for these products and the (b)(4) EU package insert, the applicant included an *in vitro* study report 14-SVT-01 and a publication describing *in vivo* activity of ciprofloxacin.

MECHANISM OF ACTION:
The 4-quinolones act by inhibiting two bacterial enzymes, DNA gyrase and DNA topoisomerase IV (both categorized as type 2 topoisomerases) necessary for DNA replication, transcription repair and recombination[7, 8, 9]. The bactericidal activity of the 4-quinolones is most likely related

to the release of DNA fragments into the cellular matrix[8]. The Cetraxal, Cipro HC Otic and Ciprodex package inserts were included. No new studies were included in the application.

MECHANISM OF RESISTANCE:

Fluoroquinolone resistance occurs mainly by chromosomal mutations in the genes encoding the principle quinolone targets, DNA gyrase (*gyrA* and *gyrB*) and topoisomerase IV (*parC* and *parE*). However, additional mechanisms of resistance have been identified and include the expression of multidrug efflux pumps with mutation in the MexCD-OprJ efflux pump regulator gene nfxB[10, 11] and transfer of plasmid-borne resistance determinants, including *qnr* genes, aac(6')-IB-cr, and *qepA* [12]. Investigations of pathogens collected from ocular infections have identified frequent mutations in the quinolone resistance determining region (QRDR) in *Staphylococcus epidermidis*[13]. The applicant has not included any information regarding the development of resistance in bacteria commonly associated with ear infections to ciprofloxacin.

ANTIMICROBIAL SPECTRUM:

Study 14-SVT-01[14]: In this study the *in vitro* activity of ciprofloxacin against recent bacterial isolates (year 2012 to 2014) associated with otitis externa and otitis media was tested at JMI Laboratories (North Liberty, Iowa). The cation-adjusted Mueller-Hinton broth (CA-MHB) was used for testing of *S. aureus*, *P. aeruginosa*, and *M. catarrhalis* isolates, CA-MHB supplemented with 2.5-5% lysed horse blood was used for testing *S. pneumoniae* isolates, and Haemophilus Test Medium was used for *H. influenzae*. The minimum inhibitory concentrations were determined using broth microdilution methodology (CLSI document M07-A10, 2015). QC strains tested included (a) *Escherichia coli* ATCC 25922, (b) *Pseudomonas aeruginosa* ATCC 27853, (c) *Staphylococcus aureus* ATCC 29213, (d) *Streptococcus pneumoniae* ATCC 49619,

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[7] Ciprofloxacin Product Information Monograph: Compendium of Preclinical and Clinical Data Marcel Dekker Inc, New York, 1988.

[8] Drlica K and Zhao X, DNA gyrase, topoisomerase IV, and the 4-quinolones, Microbiology and Molecular Biology Reviews: MMBR 1997; 61:377-392.

[9] Hooper DC, Mechanisms of action and resistance of older and newer fluoroquinolones, Clinical Infectious Diseases. 2000; 31:24-28.

[10] Mazzariol AY, Tokue TM, et al. High-level fluoroquinolone-resistant clinical isolates of *Escherichia coli* overproduce multidrug efflux protein acrA. Antimicrob Agents Chemother. 2000; 44: 3441-3443.

[11] Vestergaard M, Paulander W, Marvig RL et al. Antibiotic combination therapy can select for broad-spectrum multidrug resistance in Pseudomonas aeruginosa. Int J Antimicrob Agents. 2016 Jan;47(1):48-55

[12] Ma J, Zheng Z, et al. High Prevalence of Plasmid-Mediated Quinolone Resistance Determinants qnr, aac(6')-Ib-cr and qepA among Ceftiofur-Resistant Enterobacteriaceae Isolates from Companion and Food-Producing Animals. Antimicrob Agents Chemother. 2008

[13] Yamada M, Yoshida J, et al. Mutations in the quinolone resistance determining region in *Staphylococcus epidermidis* recovered from conjunctiva and their association with susceptibility to various fluoroquinolones. Br J Ophthalmol. 2008; 92: 848-51.

[14] Report 14-SVT-01. *In vitro* activity of ciprofloxacin tested against contemporary bacteria associated with otitis externa and otitis media, April 2015

and (e) *Haemophilus influenzae* ATCC 49247. A total of 503 US isolates obtained from the following anatomical sites were tested: Ear, nose, throat, middle ear, lower respiratory tract, sinus, upper respiratory tract, eye, blood (Table 2). The MIC results for the QC strains were within the MIC ranges published by CLSI. The ciprofloxacin MIC_{90} for methicillin-sensitive *S. aureus* (MSSA) was 16 µg/mL and for methicillin-resistant *S. aureus* (MRSA) was 256 µg/mL (Table 3). The ciprofloxacin MIC_{90} for *S. pneumonia* were 2 µg/mL. The highest MIC observed with *S. pneumoniae* for ciprofloxacin was 8 µg/mL. The highest ciprofloxacin MIC for *P. aeruginosa* was 256 µg/mL and the MIC_{90} value was 16 µg/mL. For *H. influenzae* (β-lactamase positive and negative), 99% of isolates were inhibited at ciprofloxacin MIC of ≤ 0.12 µg/mL. All 100 isolates of *M. catarrhalis* tested had MIC of ≤0.12 µg/mL. All isolates were inhibited at ciprofloxacin MIC of ≤512 µg/mL and 96% of isolates were inhibited at ciprofloxacin concentration of ≤64 µg/mL.

Table 2: Number of organisms stratified by anatomic site of clinical specimen collection.

	No. of organisms / % from each anatomic site					
Anatomic site	*S. aureus* (101)	*S. pneumoniae* (102)	*P. aeruginosa* (100)	*H. influenzae* (100)	*M. catarrhalis* (100)	All (503)
Ear, nose and throat	25 / 24.8%	16 / 15.7%	36 / 36.0%	26 / 26.0%	24 / 24.0%	127 / 25.3%
Middle ear	3 / 3.0%	64 / 64.7%	3 / 3.0%	26 / 26.0%	8 / 8.0%	104 / 20.7%
Lower respiratory tract	24 / 23.8%	12 / 11.8%	27 / 27.0%	14 / 14.0%	23 / 23.0%	100 / 19.9%
Sinus	15 / 14.9%	5 / 4.9%	10 / 10.0%	14 / 14.0%	20 / 20.0%	64 / 12.7%
Upper respiratory tract	19 / 18.8%	2 / 2.0%	9 / 9.0%	13 / 13.0%	18 / 18.0%	61 / 12.1%
Eye	9 / 8.9%	3 / 2.9%	8 / 8.0%	7 / 7.0%	7 / 7.0%	34 / 6.8%
Blood	6 / 5.9%	0 / 0.0%	7 / 7.0%	0 / 0.0%	0 / 0.0%	13 / 2.6%

Table 3: Summary of ciprofloxacin activity tested against 503 clinical isolates from US medical centers (2012-2014).

Organism	No. of isolates (cumulative %) inhibited at ciprofloxacin MIC (µg/mL) of:													MIC (µg/mL)	
(no. tested)	≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	MIC_{50}	MIC_{90}
S. aureus (101)	1	25	28	3	1	0	13	5	4	7	1	10	3		
	(1.0)	(25.7)	(53.5)	(56.4)	(57.4)	(57.4)	(70.3)	(75.2)	(79.2)	(86.1)	(87.1)	(97.0)	(100.0)	0.5	256
MSSA (51)	1	19	19	3	0	0	2	2	1	1	1	0	2		
	(2.0)	(39.2)	(76.5)	(82.4)	(82.4)	(82.4)	(86.3)	(90.2)	(92.2)	(94.1)	(96.1)	(96.1)	(100.0)	0.5	16
MRSA (50)		6	9	0	1	0	11	3	3	6	0	10	1		
	--	(12.0)	(30.0)	(30.0)	(32.0)	(32.0)	(54.0)	(60.0)	(66.0)	(78.0)	(78.0)	(98.0)	(100.0)	8	256
S. pneumoniae (102)			12	66	15	4	5								
	--	--	(11.8)	(76.5)	(91.2)	(95.1)	(100.0)	--	--	--	--	--	--	1	2
PEN-S (87)			12	54	12	4	5								
	--	--	(13.8)	(75.9)	(89.7)	(94.3)	(100.0)	--	--	--	--	--	--	1	4
PEN-NS (15)				12	3										
	--	--	--	(80.0)	(100.0)	--	--	--	--	--	--	--	--	1	2
P. aeruginosa (100)	53	6	8	4	4	5	2	10	3	2	1	2			
	(53.0)	(59.0)	(67.0)	(71.0)	(75.0)	(80.0)	(82.0)	(92.0)	(95.0)	(97.0)	(98.0)	(100.0)	--	≤0.12	16
CIP-S (71)	53	6	8	4											
	(74.6)	(83.1)	(94.4)	(100.0)	--	--	--	--	--	--	--	--	--	≤0.12	0.5
					4	5	2	10	3	2	1	2			
CIP-NS (29)	--	--	--	--	(13.8)	(31.0)	(37.9)	(72.4)	(82.8)	(89.7)	(93.1)	(100.0)	--	16	128
H. influenzae (100)	99	0	0	0	0	0	1								
	(99.0)	(99.0)	(99.0)	(99.0)	(99.0)	(99.0)	(100.0)	--	--	--	--	--	--	≤0.12	≤0.12
BL- (68)	67	0	0	0	0	0	1								
	(98.5)	(98.5)	(98.5)	(98.5)	(98.5)	(98.5)	(100.0)	--	--	--	--	--	--	≤0.12	≤0.12
BL+ (32)	32														
	(100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.12	≤0.12
M. catarrhalis (100)	100														
	(100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.12	≤0.12

Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; PEN-S = penicillin-susceptible (MIC, ≤2 µg/mL); PEN-NS = penicillin-non-susceptible (MIC, >2 µg/mL); CIP-S = ciprofloxacin-susceptible (MIC, ≤1 µg/mL); CIP-NS = ciprofloxacin-non-susceptible (MIC, >1 µg/mL) BL- = β-lactamase-negative; BL+ = β-lactamase-positive.

The ciprofloxacin minimum inhibitory concentrations for inhibition of MRSA, MSSA, *P. aeruginosa, S. pneumoniae, H. influenza,* and *M. catarrhalis* are much below the concentration of ciprofloxacin in the otic solution (3000 µg/mL)

The USCAST Report USCAST 0001 entitled "Quinolone *in vitro* susceptibility test interpretive criteria evaluations (August 2014)" also provided Ciprofloxacin MIC_{90} values against the target pathogens from surveillance programs (Table 4)[15]. The ciprofloxacin minimum inhibitory concentrations for inhibition of *S. aureus, P. aeruginosa, S. pneumoniae, H. influenza,* and *M. catarrhalis* surveillance isolates are much below the concentration of ciprofloxacin in the otic solution (3000 µg/mL)

Table 4. Ciprofloxacin MIC distributions for the 3 most recent years when testing 11 major pathogen groups [redacted] (b) (4) USA 2011-2013).

[15] Report USCAST 0001. Quinolone *in vitro* susceptibility test interpretive criteria evaluations (August 2014).

Organism/Year (no. tested)	No. (%) at MIC in µg/mL: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4	MIC_{50}	MIC_{90}
Enteric bacilli											
2011 (5206)	3240 (62.2)	413 (7.9)	291 (5.6)	176 (3.4)	91 (1.7)	71 (1.4)	56 (1.1)	61 (1.2)	807 (15.5)	≤0.03	>4
2012 (9034)	5571 (61.7)	651 (7.2)	416 (4.6)	276 (3.1)	203 (2.2)	152 (1.7)	157 (1.7)	119 (1.3)	1489 (16.5)	≤0.03	>4
2013 (8078)	5062 (62.7)	546 (6.8)	344 (4.3)	276 (3.4)	170 (2.1)	146 (1.8)	110 (1.4)	95 (1.2)	1329 (16.5)	≤0.03	>4
All (22318)	13873 (62.2)	1610 (7.2)	1051 (4.7)	728 (3.3)	464 (2.1)	369 (1.7)	323 (1.4)	275 (1.2)	3625 (16.2)	≤0.03	>4
Pseudomonas aeruginosa											
2011 (1127)	25 (2.2)	125 (11.1)	402 (35.7)	108 (9.6)	109 (9.7)	87 (7.7)	56 (5.0)	49 (4.3)	166 (14.7)	0.25	>4
2012 (1978)	42 (2.1)	202 (10.2)	803 (40.6)	212 (10.7)	169 (8.5)	106 (5.4)	99 (5.0)	104 (5.3)	241 (12.2)	0.12	>4
2013 (1732)	32 (1.8)	188 (10.9)	701 (40.5)	174 (10.0)	143 (8.3)	88 (5.1)	90 (5.2)	88 (5.1)	228 (13.2)	0.12	>4
All (4837)	99 (2.0)	515 (10.6)	1906 (39.4)	494 (10.2)	421 (8.7)	281 (5.8)	245 (5.1)	241 (5.0)	635 (13.1)	0.12	>4
Stenotrophomonas maltophilia											
2011 (171)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.1)	29 (17.0)	54 (31.6)	29 (17.0)	52 (30.4)	2	>4
2012 (156)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.2)	29 (18.6)	51 (32.7)	31 (19.9)	40 (25.6)	2	>4
2013 (2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2	-
All (329)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (3.6)	58 (17.6)	106 (32.2)	61 (18.5)	92 (28.0)	2	>4
Acinetobacter spp.											
2011 (209)	3 (1.4)	16 (7.7)	30 (14.4)	30 (14.4)	9 (4.3)	7 (3.3)	0 (0.0)	0 (0.0)	114 (54.5)	>4	>4
2012 (393)	3 (0.8)	15 (3.8)	81 (20.6)	74 (18.8)	15 (3.8)	3 (0.8)	0 (0.0)	1 (0.3)	201 (51.1)	>4	>4
2013 (312)	1 (0.3)	11 (3.5)	56 (17.9)	53 (17.0)	13 (4.2)	4 (1.3)	4 (1.3)	0 (0.0)	170 (54.5)	>4	>4
All (914)	7 (0.8)	42 (4.6)	167 (18.3)	157 (17.2)	37 (4.0)	14 (1.5)	4 (0.4)	1 (0.1)	485 (53.1)	>4	>4
Staphylococcus aureus											
2011 (5858)	7 (0.1)	104 (1.8)	743 (12.7)	1772 (30.2)	699 (11.9)	114 (1.9)	88 (1.5)	60 (1.0)	2271 (38.8)	0.5	>4
2012 (9660)	1 (0.0)	64 (0.7)	639 (6.6)	3319 (34.4)	1373 (14.2)	216 (2.2)	208 (2.2)	95 (1.0)	3745 (38.8)	0.5	>4
2013 (8216)	1 (0.0)	31 (0.4)	510 (6.2)	2984 (36.3)	1129 (13.7)	164 (2.0)	141 (1.7)	76 (0.9)	3180 (38.7)	0.5	>4
All (23734)	9 (0.0)	199 (0.8)	1892 (8.0)	8075 (34.0)	3201 (13.5)	494 (2.1)	437 (1.8)	231 (1.0)	9196 (38.7)	0.5	>4

Organism/Year (no. tested)	No. (%) at MIC in µg/mL: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4	MIC_{50}	MIC_{90}
Coagulase-negative staphylococci											
2011 (899)	5 (0.6)	11 (1.2)	145 (16.1)	257 (28.6)	48 (5.3)	8 (0.9)	6 (0.7)	51 (5.7)	368 (40.9)	0.5	>4
2012 (937)	2 (0.2)	14 (1.5)	132 (14.1)	351 (37.5)	70 (7.5)	11 (1.2)	5 (0.5)	36 (3.8)	316 (33.7)	0.25	>4
2013 (694)	2 (0.3)	10 (1.4)	90 (13.0)	244 (35.2)	56 (8.1)	3 (0.4)	3 (0.4)	35 (5.0)	251 (36.2)	0.5	>4
All (2530)	9 (0.4)	35 (1.4)	367 (14.5)	852 (33.7)	174 (6.9)	22 (0.9)	14 (0.6)	122 (4.8)	935 (37.0)	0.5	>4
Enterococcus spp.											
2011 (1317)	1 (0.1)	0 (0.0)	1 (0.1)	6 (0.5)	167 (12.7)	392 (29.8)	100 (7.6)	19 (1.4)	631 (47.9)	2	>4
2012 (1237)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)	138 (11.2)	459 (37.1)	88 (7.1)	18 (1.5)	528 (42.7)	2	>4
2013 (1050)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.8)	131 (12.5)	386 (36.8)	74 (7.0)	18 (1.7)	433 (41.2)	1	>4
All (3604)	1 (0.0)	0 (0.0)	1 (0.0)	20 (0.6)	436 (12.1)	1237 (34.3)	262 (7.3)	55 (1.5)	1592 (44.2)	2	>4
Streptococcus pneumoniae											
2011 (2156)	2 (0.1)	2 (0.1)	0 (0.0)	11 (0.5)	225 (10.4)	1324 (61.4)	516 (23.9)	44 (2.0)	32 (1.5)	1	2
2012 (2458)	2 (0.1)	0 (0.0)	2 (0.1)	4 (0.2)	233 (9.5)	1462 (59.5)	674 (27.4)	49 (2.0)	32 (1.3)	1	2
2013 (2594)	1 (0.0)	0 (0.0)	4 (0.2)	18 (0.7)	431 (16.6)	1587 (61.2)	481 (18.5)	41 (1.6)	31 (1.2)	1	2
All (7208)	5 (0.1)	2 (0.0)	6 (0.1)	33 (0.5)	889 (12.3)	4373 (60.7)	1671 (23.2)	134 (1.9)	95 (1.3)	1	2
Beta-haemolytic streptococci											
2011 (1072)	3 (0.3)	1 (0.1)	5 (0.5)	101 (9.4)	618 (57.6)	277 (25.8)	58 (5.4)	4 (0.4)	5 (0.5)	0.5	1
2012 (1145)	0 (0.0)	0 (0.0)	3 (0.3)	83 (7.2)	660 (57.6)	344 (30.0)	44 (3.8)	4 (0.3)	7 (0.6)	0.5	1
2013 (1151)	1 (0.1)	0 (0.0)	0 (0.0)	86 (7.5)	715 (62.1)	303 (26.3)	35 (3.0)	3 (0.3)	8 (0.7)	0.5	1
All (3368)	4 (0.1)	1 (0.0)	8 (0.2)	270 (8.0)	1993 (59.2)	924 (27.4)	137 (4.1)	11 (0.3)	20 (0.6)	0.5	1
Viridans group streptococci											
2011 (565)	3 (0.5)	1 (0.2)	3 (0.5)	22 (3.9)	115 (20.4)	172 (30.4)	132 (23.4)	65 (11.5)	52 (9.2)	1	4
2012 (672)	7 (1.0)	1 (0.1)	5 (0.7)	33 (4.9)	153 (22.8)	189 (28.1)	171 (25.4)	66 (9.8)	47 (7.0)	1	4
2013 (499)	0 (0.0)	1 (0.2)	2 (0.4)	28 (5.6)	127 (25.5)	151 (30.3)	115 (23.0)	45 (9.0)	30 (6.0)	1	4
All (1736)	10 (0.6)	3 (0.2)	10 (0.6)	83 (4.8)	395 (22.8)	512 (29.5)	418 (24.1)	176 (10.1)	129 (7.4)	1	4

Organism/Year (no. tested)	No. (%) at MIC in µg/mL: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4	MIC_{50}	MIC_{90}
Haemophilus influenzae											
2011 (1129)	1099 (97.3)	15 (1.3)	9 (0.8)	2 (0.2)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	≤0.03	≤0.03
2012 (924)	903 (97.7)	9 (1.0)	5 (0.5)	0 (0.0)	4 (0.4)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	≤0.03	≤0.03
2013 (777)	762 (98.1)	6 (0.8)	4 (0.5)	3 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	≤0.03	≤0.03
All (2830)	2764 (97.7)	30 (1.1)	18 (0.6)	5 (0.2)	7 (0.2)	5 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)	≤0.03	≤0.03

EUCAST proposes use of epidemiological cut-off values (ECOFFs) to indicate susceptibility to topical agents as these would help differentiate isolates as wild type and non-wild type [16]. Epidemiological cut-off values according to EUCAST are as follows:

- *Moraxella catarrhalis* 0.125 µg/mL
- *Haemophilus influenzae* 0.064 µg/mL
- Enterobacteriaceae 0.125 µg/mL
- *Pseudomonas aeruginosa* 0.5 µg/mL
- *Staphylococcus aureus* 1.0 µg/mL
- *Streptococcus pneumoniae* 2.0 µg/mL

IN VIVO ACTIVITY:

The *in vivo* activity of topical Ciprofloxacin hydrochloride was evaluated in an experimental chronic suppurative otitis media Cynomolgus monkey model[17]. The right ear of all monkeys with a non-intact tympanic membrane was inoculated progressively with increasing colony forming units (CFU) (40 to 100,000) of *Pseudomonas aeruginosa* (ATCC 27853) over 2 weeks. Otorrhea persisted for 3 weeks thereafter. The monkeys (n = 10 per group) were then treated twice daily for 4 weeks with saline (negative control), vehicle (potassium sorbate, polysorbate 20, sodium acetate trihydrate, glacial acetic acid, glycerin, methocel A4M and purified water; pH 4.75), Cortisporin otic suspension (positive control; neomycin, polymyxin B sulfate and hydrocortisone), or Ciprofloxacin 0.2%. Baseline assessments of otoscopy, tympanometry, and auditory brainstem response (ABR) test were performed. After 3 weeks of treatment, *Pseudomonas aeruginosa,* was eradicated from all ears (10 of 10) in the Ciprofloxacin and Cortisporin groups, 2 of 10 ears in the saline group, and 9 of 10 ears in the vehicle group. This eradication did not correlate to clearing of drainage.

CLINICAL STUDIES:

Treatment of AOMT:

The applicant conducted two twin phase III, multicenter, randomized(1:1:1), 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 compared to ciprofloxacin alone (0.3% otic solution) and fluocinolone alone (0.025%) in pediatric patients aged 6 months to 12 years. Patients with a patent and open tympanostomy tube in the ear that was to be treated and suffering from otorrhea for 3 weeks or less, with moderate or severe purulent otorrhea were included in the study. Patients with tympanostomy tubes containing antibacterials, those with suspected viral, fungal or mycobacterial ear infections, and those with mastoiditis, and those who used otic steroids within 3 days or systemic steroids within 7 days of enrollment were excluded. Study drug was administered to the affected ear(s) twice daily for 7 days. Patients with bilateral otitis media with tympanostomy tubes were treated in both ears. At screening, vaccination history for *S. pneumoniae* and *H. influenzae* was recorded.

European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website, http://www.eucast.org, last accessed 12 February 2016

[17] Dohar JE, Alper CM, Rose EA, et al, Treatment of chronic suppurative otitis media with topical ciprofloxacin, *Ann Otol Rhinol Laryngol* 107 (1998) 865-871.

The primary endpoint of the study was time to cessation of otorrhea. Caregivers were provided with a patient diary to record the presence of otorrhea and complete an Acute Otitis Media Severity of Symptoms Scale (AOM-SOS) questionnaire. The secondary endpoint was sustained microbiological cure. Sustained microbiological cure was defined as Eradication or Presumed Eradication of bacteria at both Visit 3 [end of therapy (EOT), days 8 to 10], and Visit 4 [test of cure (TOC), days 18 to 22)]. A sample of middle ear exudate was collected using a syringe or cannula for microbiological culture at baseline. Middle ear exudate samples were also collected at EOT and TOC, if present. Signs and symptoms of otitis are also assessed at these visits. Other secondary endpoints such as clinical response, change in granulations, eardrum edema, pain, quality of life questionnaire score, and characteristics of otorrhea (volume, color) were also assessed at visit 2 (days 3-5), visit 3 (EOT) and Visit 4 (TOC). In some sites, blood samples were obtained from a subgroup of patients at Visit 3 (1-2 hours after the last dose) to determine the plasma levels of Ciprofloxacin and/or Fluocinolone Acetonide.

Organisms were identified by the (b) (4) Maldi-TOF (mass spectrometry) or a variety of biochemical tests. Susceptibility tests against ciprofloxacin and comparators were performed against the cultured isolates according to the most recent Clinical Laboratory Standards Institute guidelines. The following organisms were considered to be pathogens: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *P. aeruginosa*. Serotyping was performed on all isolates of *H. influenzae* and *S. pneumoniae*. The specimen was also tested for the presence of respiratory viruses. All staphylococcal isolates were classified as either "methicillin resistant" or "methicillin susceptible." Those isolates identified as methicillin-resistant *S. aureus* were tested for the presence of the Panton-Valentine leucocidin (PVL) genes.

The central laboratories for this study are shown below:

For patients with a culture positive baseline pathogen, bacteriologic response at EOT 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 baseline was still present
Superinfection if a pathogen not present at baseline 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

For patients with a culture positive baseline pathogen, bacteriologic response at TOC 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 baseline and EOT was still present
Recurrence if there was reappearance of the pathogen eradicated or presumably eradicated at TOC
Superinfection if a pathogen not present at baseline and EOT was now present (presence of a non-pathogenic organism was not considered superinfection)
Reinfection if there was isolation of a new pathogen different from the one eradicated or presumably eradicated at EOT
Indeterminate if none of the above definitions were met and the bacteriologic response could not be determined

Sustained microbiological cure was defined as eradication or presumed eradication at both EOT and TOC visits. When more than one pathogen was isolated at baseline, the worst microbiological response among all baseline pathogens was reported.

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

Clinical Failure: Worsened signs and symptoms of otitis media that warranted change in antimicrobial therapy or development of complications of AOMT (e.g., mastoiditis or meningitis) or signs or symptoms remained unchanged compared with baseline or significant improvement without complete resolution in clinical signs or symptoms compared with baseline.

Study CIFLOTIII/10IA02:

The number of patients included in each of the analysis populations is as follows:

1. Clinical intent-to-treat (CITT) population (all patients randomly assigned to a treatment group): 331 patients
2. Clinical per-protocol (CPP) population (all CITT patients who did not have any major protocol deviations leading to exclusion from the CPP population): 245 patients
3. Microbiological intent-to-treat (MITT) population (all CITT patients whose baseline microbiological culture yielded 1 or more pathogens): 195 patients
4. Microbiological per-protocol (MPP) population (all CPP patients whose baseline microbiological culture yielded 1 or more pathogens and who had microbiological results at EOT and TOC unless the patient was deemed a clinical failure at an earlier visit than TOC): 148 patients

The MITT and MPP populations are analyzed in this review using the dataset MBDS.xpt. The applicant performed analysis on the MITT population based on study treatment assigned while analysis of the MPP population was performed based on study treatment received. One patient (Patient 033-018) was dispensed an incorrect kit by the site. This patient was included in the MITT population under the treatment assigned (FLUO) in the applicant's analysis. However, for the purposes of this review, the patients was included in the MITT population based on the treatment actually received (CIPRO+FLUO).

In the MITT population for study CIFLOTIII/10IA02, 195 patients had a baseline pathogen identified. The clinical success and favorable microbiological response (eradication + presumed eradication) by pathogen for all 195 patients in the MITT population and 129 patients in the MITT population with only bacterial pathogen at baseline are shown in Tables 5 and 6. In the MITT population, the Kaplan-Meier estimates of median time to cessation of otorrhea were 4.3 days for the CIPRO+FLUO and 8.1 days for CIPRO groups. This analysis could not be performed for the FLUO group as the number of discontinued patients or those who received rescue medication (n = 34) was greater than number of patients with cessation of otorrhea (n = 26). For patients with only bacterial pathogens at baseline, Kaplan-Meier estimates of median time to cessation of otorrhea were 3.7 days for the CIPRO+FLUO group and 8.5 days for the CIPRO group. For patients with both viral and bacterial pathogens, Kaplan-Meier estimates of median time to cessation of otorrhea were 5.7 days for the CIPRO+FLUO group and 6.1 days for the CIPRO group.

Table 5 Clinical success and favorable microbiological response by pathogen in the MITT population of study CIFLOTIII/10IA02 with baseline bacterial and viral pathogen.

Baseline pathogen*	**CIPRO (n = 70)**	**CIPRO + FLUO (n = 66)**	**FLUO (n =59)**

	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC
Pseudomonas aeruginosa	5/12	6/12	5/12	8/12	9/11	10/11	10/11	10/11	2/12	2/12	2/12	2/12
Staphylococcus aureus	13/25	15/25	13/25	15/25	24/27	23/27	23/27	19/27	6/22	7/22	6/22	6/22
Moraxella catarrhalis	3/7	4/7	6/7	6/7	4/6	6/6	4/6	5/6	1/1	1/1	1/1	1/1
Haemophilus influenzae	14/22	15/22	16/22	15/22	13/18	13/18	11/18	9/18	5/16	7/16	7/16	8/16
Streptococcus pneumonia	7/10	7/10	8/10	8/10	2/6	3/6	3/6	3/6	2/6	2/6	2/6	2/6

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

Table 6 Clinical success and favorable microbiological response by pathogen in the MITT population study CIFLOTIII/10IA02 with baseline bacterial pathogen only.

Baseline pathogen*	**CIPRO (n = 52)**				**CIPRO + FLUO (n = 37)**				**FLUO (n = 40)**			
	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC
Pseudomonas aeruginosa	3/9	4/9	3/9	5/9	7/8	7/8	7/8	7/8	2/10	2/10	2/10	2/10
Staphylococcus aureus	11/20	12/20	11/20	12/20	16/17	16/17	15/17	13/17	5/16	6/16	5/16	4/16
Moraxella catarrhalis	3/6	4/6	6/6	6/6	2/2	2/2	2/2	2/2	0/0	0/0	0/0	0/0
Haemophilus influenzae	10/17	11/17	13/17	11/17	4/5	4/5	4/5	4/5	2/8	4/8	3/8	4/8
Streptococcus pneumonia	5/6	5/6	56	5/6	0/1	0/1	1/1	1/1	2/4	2/4	2/4	2/4

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

A total of 148 patients were included in the MPP population. The clinical success and favorable microbiological response (eradication + presumed eradication) for the 148 patients in the MPP with bacterial and viral pathogens and 96 with bacterial pathogen only are shown in Tables 7 and 8.

Table 7 Clinical success and favorable microbiological response by pathogen in the MPP population of study CIFLOTIII/10IA02 with baseline bacterial and viral pathogen.

Baseline pathogen*	**CIPRO (n =54)**				**CIPRO + FLUO (n = 49)**				**FLUO (n = 45)**			
	CS	FMR	CS	FMR	CS	FMR	CS	FMR	CS	FMR	CS	FMR

	EOT	EOT	TOC	TOC	EOT	EOT	TOC	TOC	EOT	EOT	TOC	TOC
Pseudomonas aeruginosa	5/11	6/11	5/11	7/11	9/10	10/10	10/10	10/10	2/11	2/11	2/11	2/11
Staphylococcus aureus	11/20	12/20	10/20	12/20	17/20	17/20	16/20	16/20	3/13	4/13	4/13	4/13
Moraxella catarrhalis	2/4	3/4	4/4	4/4	3/4	4/4	3/4	4/4	1/1	1/1	1/1	1/1
Haemophilus influenzae	10/16	12/16	12/16	12/16	10/13	9/13	7/13	8/13	3/13	4/13	5/13	5/13
Streptococcus pneumonia	5/7	6/7	6/7	6/7	2/4	2/4	2/4	2/4	1/5	1/5	1/5	1/5

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

Table 8 Clinical success and favorable microbiological response by pathogen in the MPP population study CIFLOTIII/10IA02 with baseline bacterial pathogen only.

Baseline pathogen*	**CIPRO (n = 41)**				**CIPRO + FLUO (n = 26)**				**FLUO (n = 29)**			
	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC
Pseudomonas aeruginosa	3/8	4/8	3/8	5/8	7/7	7/7	7/7	7/7	2/9	2/9	2/9	2/9
Staphylococcus aureus	9/16	9/16	8/16	9/16	11/12	11/12	10/12	10/12	2/8	3/8	3/8	3/8
Moraxella catarrhalis	3/5	4/5	5/5	5/5	2/2	2/2	2/2	2/2	0/0	0/0	0/0	0/0
Haemophilus influenzae	7/12	9/12	9/12	9/12	4/4	4/4	3/4	3/4	1/6	2/6	2/6	2/6
Streptococcus pneumonia	4/5	4/5	4/5	4/5	0/0	0/0	0/0	0/0	1/3	1/3	1/3	1/3

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

The favorable microbiological response for the CIPRO+FLUO group was slightly better than the CIPRO group for *P. aeruginosa*, *S. aureus*, *M. catarrhalis*, and *H. influenzae* at EOT (Tables 6 and 8). A very small number of patients had recurrences (CIPRO + FLUO, n = 2; CIPRO, n = 0; FLUO, n = 2).

The percentage of sustained microbiological cure in the MITT and MPP populations is presented in Table 9. In the MITT population, sustained microbiological cure (eradication + presumed eradication) was observed in 48 of 62 patients (77.4%) in the CIPRO+FLUO group, 41 of 63 patients (65.1%) in the CIPRO group, and 22 of 51 patients (43%) in the FLUO group. Similar observations were made in the MPP population. Sustained microbiological cure was observed in 42 of 49 patients (85.7%) in the CIPRO+FLUO group, 35 of 50 patients (70.0%) in the CIPRO group, and 17 of 42 patients (40.5%) in the FLUO group.

Table 9: Sustained Microbiological Cure – Without Imputation of Missing Data (MITT and MPP Population) in

study CIFLOTIII/10IA02

Sustained Microbiological Cure	**CIPRO + FLUO**	**CIPRO**	**FLUO**
MITT Population			
N	66	70	59
Yes, n (%)	48 (77.4)	41(65.1)	22 (43.0)
No, n (%)	14 (22.6)	22 (34.9)	29 (56.8)
Total, n (%)	62 (100)	63 (100)	51 (100)
Missing	4	7	8
MPP Population			
N	49	54	45
Yes, n (%)	42 (85.7)	35 (70.0)	17 (40.5)
No, n (%)	7 (14.3)	15 (30.0)	25 (59.5)
Total, n (%)	49 (100)	50 (100)	42 (100)
Missing	0	4	3

Most patients had a history of previous vaccination for *S. pneumoniae* and *H. influenzae*. Most baseline isolates of *H. influenzae* were nontypeable, two isolates belonged to serotype f and one isolate belonged to serotype a, suggesting replacement of type b strains with nontypeable strains. The *S. pneumoniae* baseline isolates belonged to the following serotypes: 15A, 15B, 15C, 16F, 19A, 21, 3, 33F, 35B, and 6C. *S. pneumoniae* serotypes not found in PCV7 or PCV13 vaccines have been recovered from middle ear fluid specimens in the post-vaccination period.

Study CIFLOTIII/10IA04:

In the MITT population for study CIFLOTIII/10IA04, a baseline bacterial pathogen was identified in 187 patients. The clinical success and favorable microbiological response (eradication + presumed eradication) by pathogen for all 187 patients in the MITT with mixed bacterial and viral pathogen at baseline, and 131 patients in the MITT with only bacterial pathogen at baseline, are shown in Tables 10 and 11. The Kaplan-Meier estimates of median time to cessation of otorrhea were 4.6 days for the CIPRO+FLUO and 7.0 days for CIPRO (7.0 days groups. The median time to cessation of otorrhea could not be estimated for the FLUO group because the number of discontinued patients (n = 39) was greater than the number of patients with cessation of otorrhea (n = 23). For patients with only baseline bacterial isolates, the Kaplan-Meier estimates of median time to cessation of otorrhea were 4.6 days for the CIPRO+FLUO group and 7.2 days for the CIPRO group.

Table 10 Clinical success and favorable microbiological response by pathogen in the MITT population of study CIFLOTIII/10IA04 with baseline bacterial and viral pathogen.

Baseline pathogen*	**CIPRO (n = 65)**	**CIPRO + FLUO (n = 60)**	**FLUO (n = 62)**

	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC
Pseudomonas aeruginosa	3/6	5/6	5/6	5/6	7/10	9/10	7/10	8/10	1/9	1/9	2/9	2/9
Staphylococcus. aureus	13/28	15/28	15/28	14/28	12/18	15/18	15/18	15/18	9/21	9/21	9/21	8/21
Moraxella catarrhalis	5/9	6/9	6/9	6/9	6/9	8/9	8/9	8/9	1/6	4/6	3/6	4/6
Haemophilus influenzae	14/19	17/19	13/19	15/19	13/15	13/15	12/15	12/15	5/25	7/25	6/25	7/25
Streptococcus pneumonia	4/6	6/6	5/6	6/6	6/7	6/7	6/7	6/7	2/10	5/10	6/10	6/10

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

Table 11 Clinical success and favorable microbiological response by pathogen in the MITT population of study CIFLOTIII/10IA04 with only baseline bacterial pathogen.

Baseline pathogen*	**CIPRO (n = 46)**				**CIPRO + FLUO (n = 46)**				**FLUO (n = 39)**			
	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC
Pseudomonas aeruginosa	2/4	3/4	3/4	3/4	6/8	8/8	6/8	7/8	1/6	1/6	1/6	1/6
Staphylococcus aureus	9/20	10/20	11/20	10/20	11/16	14/16	14/16	14/16	7/15	7/15	7/15	6/15
Moraxella catarrhalis	3/6	4/6	4/6	4/6	4/7	6/7	6/7	6/7	3/3	3/3	1/3	2/3
Haemophilus influenzae	11/13	13/13	10/13	11/13	9/10	9/10	9/10	8/10	1/14	3/14	1/14	2/14
Streptococcus pneumonia	1/3	2/3	2/3	3/3	4/5	4/5	4/5	4/5	0/2	0/2	0/2	0/2

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

The MPP population consisted of 142 patients. The clinical success and favorable microbiological response by pathogen for all 142 patients in the MPP population, and 103 patients in the MPP population with only bacterial pathogen at baseline, are shown in Tables 12 and 13.

Table 12 Clinical success and favorable microbiological response by pathogen in the MPP population in study CIFLOTIII/10IA04 with baseline pathogen and viral pathogen.

Baseline pathogen*	**CIPRO (n = 56)**	**CIPRO + FLUO (n = 40)**	**FLUO (n = 46)**

	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC
Pseudomonas aeruginosa	3/6	5/6	5/6	5/6	5/7	6/7	6/7	6/7	1/8	1/8	1/8	1/8
Staphylococcus aureus	9/22	10/22	10/22	9/22	8/12	9/12	9/12	9/12	7/18	7/18	7/18	7/18
Moraxella catarrhalis	5/9	6/9	6/9	6/9	6/9	8/9	8/9	8/9	1/4	2/4	2/4	3/4
Haemophilus influenzae	14/18	17/18	13/18	16/18	9/11	9/11	8/11	9/11	4/16	4/16	3/16	4/16
Streptococcus pneumonia	3/4	4/4	3/4	4/4	5/6	5/6	5/6	5/6	2/6	2/6	2/6	2/6

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

Table 13 Clinical success and favorable microbiological response by pathogen in the MPP population in study CIFLOTIII/10IA04 with baseline bacterial pathogen only.

Baseline pathogen*	**CIPRO (n = 44)**				**CIPRO + FLUO (n = 28)**				**FLUO (n = 31)**			
	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC	CS EOT	FMR EOT	CS TOC	FMR TOC
Pseudomonas aeruginosa	2/4	3/4	3/4	3/4	4/5	5/5	5/5	5/5	1/6	1/6	1/6	1/6
Staphylococcus aureus	8/18	9/18	9/18	8/18	7/9	8/9	8/9	8/9	5/13	5/13	5/13	5/13
Moraxella catarrhalis	3/6	4/6	4/6	4/6	4/7	6/7	6/7	6/7	0/2	0/2	1/2	2/2
Haemophilus influenzae	11/13	13/13	10/13	10/13	6/7	6/7	6/7	6/7	1/9	1/9	0/9	1/9
Streptococcus pneumonia	1/2	2/2	1/2	2/2	3/4	3/4	3/4	3/4	0/2	0/2	0/2	0/2

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

The favorable microbiological response for the CIPRO+FLUO group was slightly better than the CIPRO group for *P. aeruginosa*, *S. aureus*, and *M. catarrhalis* at EOT (Tables 11 and 13). A very small number of patients had recurrences (CIPRO + FLUO, n = 1; CIPRO, n = 3; FLUO, n = 3).

The percentage of sustained microbiological cure in the MITT and MPP populations is presented in Table 14. In the MITT population, sustained microbiological cure (eradication + presumed eradication) 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. Similar observations were made in the MPP population. Sustained microbiological cure was observed in 32 of 39 patients (82.2%) 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.

Table 14: Sustained Microbiological Cure – Without Imputation of Missing Data (MITT and MPP Population) in study CIFLOTIII/10IA04

Sustained Microbiological Cure	**CIPRO + FLUO**	**CIPRO**	**FLUO**
MITT Population			
N	60	65	62
Yes, n (%)	47 (82.5)	43(70.5)	18 (31.6)
No, n (%)	10 (17.5)	22 (29.5)	39 (68.4)
Total, n (%)	57 (100)	61 (100)	57 (100)
Missing	3	4	5
MPP Population			
N	40	56	46
Yes, n (%)	32 (82.2)	37 (68.5)	14 (31.8)
No, n (%)	7 (17.9)	15 (31.5)	30 (68.2)
Total, n (%)	39 (100)	54 (100)	44 (100)
Missing	1	2	2

As in study CIFLOTIII/10IA02, most patients study CIFLOTIII/10IA04 had a history of previous vaccination for *S. pneumoniae* and *H. influenzae*. Most baseline isolates of *H. influenzae* were nontypeable, one isolate belonged to serotype e, suggesting replacement of type b strains with nontypeable strains. The *S. pneumoniae* baseline isolates belonged to the following serotypes: 11A, 11D, 15A, 15C, 16F, 19A, 19F, 21, 23A, 23B, 3, 33F, 35B, and 6C. *S. pneumoniae* serotypes not found in PCV7 or PCV13 vaccines have been recovered from middle ear fluid specimens in the post-vaccination period.

In the pooled studies, favorable microbiological response was observed in AOMT patients treated with ciprofloxacin (0.3%) plus fluocinolone acetonide (0.025%) with baseline *P. aeruginosa* (95.0%), *S. aureus* (84.2%), *M. catarrhalis* (92.3%), *H. influenzae* (78.6%), and *S. pneumoniae* (72.7%) isolates (Table 15). Sustained microbiological response was observed in 84.1% (74/88) patients treated with ciprofloxacin (0.3%) plus fluocinolone acetonide (0.025%) in the MPP population compared to 69.2% (72/104) patients treated with ciprofloxacin and 36.0% (31/86) patients treated with fluocinolone acetonide.

Table 15: Clinical success and favorable microbiological response by pathogen in the MPP population with baseline bacterial and viral pathogen from pooled studies (CIFLOTIII/10IA02 and CIFLOTIII/10IA04).

Baseline pathogen*	**CIPRO (n = 119)**				**CIPRO + FLUO (n = 109)**				**FLUO (n = 107)**			
	CS EOT	FMR	CS TOC	FMR	CS EOT	FMR	CS TOC	FMR	CS EOT	FMR	CS TOC	FMR

		EOT		TOC		EOT		TOC		EOT		TOC
Pseudomonas aeruginosa	8/17 (47.1%)	11/17 (64.7%)	10/17 (58.8%)	12/17 (70.6%)	16/20 (80.0%)	19/20 (95.0%)	17/20 (85.0%)	18/20 (90.0%)	3/20 (15.0%)	3/20 (15.0%)	4/20 (20.0%)	4/20 (20.0%)
Staphylococcus aureus	24/48 (25.0%)	27/48 (56.3%)	25/48 (52.1%)	26/48 (54.2%)	29/38 (76.3%)	32/38 (84.2%)	31/38 (81.6%)	31/38 (81.6%)	12/34 (35.3%)	13/34 (38.2%)	13/34 (38.2%)	12/34 (35.3%)
Moraxella catarrhalis	7/13 (53.8%)	9/13 (69.2%)	10/13 (76.9%)	10/13 (76.9%)	9/13 (69.2%)	12/13 (92.3%)	11/13 (84.6)	12/13 (92.3%)	2/7 (28.6%)	5/7 (71.4%)	4/7 (57.1%)	5/7 (71.4%)
Haemophilus influenzae	24/35 (68.6%)	29/35 (82.9%)	25/33 (75.8%)	27/35 (81.8%)	23/28 (82.1%)	22/28 (78.6%)	19/28 (67.9%)	20/28 (71.4%)	8/38 (21.1%)	11/38 (28.9%)	11/38 (28.9%)	12/38 (31.6%)
Streptococcus pneumonia	9/13 (69.2%)	12/13 (92.3%)	11/13 (84.6%)	12/13 (92.3%)	8/11 (72.7%)	8/11 (72.7%)	8/11 (72.7%)	8/11 (72.7%)	3/15 (20.0%)	6/15 (40.0%	7/15 (46.7%)	7/15 (46.7%)

* includes mixed baseline pathogen
CS EOT = Clinical success at EOT; FMR EOT = Favorable Microbiological response (eradication + presumed eradication) at EOT; CS TOC = Clinical success at TOC, FMR TOC = Favorable Microbiological response (eradication + presumed eradication) at TOC

***In vitro* susceptibility:**

The pathogens isolated at baseline, EOT and TOC visits in studies CIFLOTIII/10IA02 and CIFLOTIII/10IA04 were tested for antimicrobial susceptibility against ciprofloxacin and appropriate comparators. Antimicrobial susceptibility testing results were summarized for the target bacterial species commonly isolated from patients with AOMT (i.e., *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *P. aeruginosa*) with the number of isolates recovered at each visit along with MIC range (Tables 16, 17, 18). The ciprofloxacin MIC range for *S. pneumoniae* isolates (n = 49) was 0.12 to 2 μg/mL. The ciprofloxacin MIC range for *H. influenzae* isolates (n = 78) was 0.004 to 0.06 μg/mL. The ciprofloxacin MIC range for *M. catarrhalis* isolates (n = 24) was ≤0.008 to 0.03 μg/mL. The ciprofloxacin MIC range for *S. aureus* isolates (n = 145) was ≤0.008 to >128 μg/mL. The ciprofloxacin MIC range for *P. aeruginosa* isolates (n = 51) was 0.06 to 128 μg/mL. The highest ciprofloxacin MIC against *S. aureus* and *P. aeruginosa* isolates in the clinical studies was 128 μg/mL. These MIC values are within the ciprofloxacin concentration achieved during otic administration of the Ciprofloxacin (0.3%) + Fluocinolone Acetonide (0.025%). No susceptibility interpretive criteria are proposed as this is a topic product for otic administration.

Table 16: Ciprofloxacin MIC against target pathogens at baseline – MITT population (appended from the submission).

	CIFLOTIII/10IA02			CIFLOTIII/10IA04		
MIC (µg/mL)	**CIPRO+FLUO (N=65)**	**CIPRO (N=70)**	**FLUO (N=60)**	**CIPRO+FLUO (N=65)**	**CIPRO (N=70)**	**FLUO (N=60)**
Streptococcus pneumoniae	5	9	4	6	6	8
MIC range	0.25 - 2	0.12 - 1	0.12 - 1	0.5 - 1	0.25 - 1	0.5 - 1
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Haemophilus influenzae	7	10	11	8	14	11
MIC range	0.004 - 0.03	0.004 - 0.015	0.004 - 0.015	0.008 - 0.008	0.008 - 0.06	0.004 - 0.06
MIC_{50}	NA	0.008	0.008	NA	0.008	0.008
MIC_{90}	NA	0.015	0.008	NA	0.015	0.015
Moraxella catarrhalis	3	5	1	4	4	5
MIC range	0.015 - 0.03	≤0.008 - 0.015	≤0.008 - ≤0.008	0.015 - 0.03	0.015 - 0.03	0.015 - 0.03
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Staphylococcus aureus	20	24	17	15	23	19
MIC range	≤0.008 - >128	0.06 - >128	0.06 - 32	0.12 - 128	0.06 - 128	0.12 - 64
MIC_{50}	0.5	0.25	1	8	0.25	0.25
MIC_{90}	64	32	32	128	64	32
Pseudomonas aeruginosa	8	8	8	6	5	6
MIC range	0.06 - 0.5	0.06 - 0.12	0.12 - 0.25	0.06 - 1	0.12 - 0.5	0.12 - 128
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA

Table 17: Ciprofloxacin MIC against target pathogens at EOT– MITT population (appended from the submission).

	CIFLOTIII/10IA02			CIFLOTIII/10IA04		
MIC (µg/mL)	**CIPRO+FLUO (N=65)**	**CIPRO (N=70)**	**FLUO (N=60)**	**CIPRO+FLUO (N=65)**	**CIPRO (N=70)**	**FLUO (N=60)**
Streptococcus pneumoniae	0	0	4	0	0	6
MIC range	NA	NA	0.12 - 0.5	NA	NA	0.5 - 1
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Haemophilus influenzae	0	0	3	1	0	7
MIC range	NA	NA	0.004 - 0.06	0.008 - 0.008	NA	0.004 - 0.06
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Moraxella catarrhalis	0	0	1	0	0	1
MIC range	NA	NA	0.015 - 0.015	NA	NA	0.015 - 0.015
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Staphylococcus aureus	1	5	6	1	4	5
MIC range	>128 - >128	0.06 - >128	0.12 - 64	128 - 128	0.25 - 64	0.12 - 128
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Pseudomonas aeruginosa	0	1	5	0	0	3
MIC range	NA	0.12 - 0.12	0.06 - 0.5	NA	NA	0.12 - 16
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA

Table 18: Ciprofloxacin MIC against target pathogens at TOC – MITT population (appended from the submission).

	CIFLOTIII/10IA02			CIFLOTIII/10IA04		
MIC (µg/mL)	CIPRO+FLUO (N=65)	CIPRO (N=70)	FLUO (N=60)	CIPRO+FLUO (N=65)	CIPRO (N=70)	FLUO (N=60)
Streptococcus pneumoniae	0	0	0	0	0	1
MIC range	NA	NA	NA	NA	NA	0.5 - 0.5
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Haemophilus influenzae	1	1	0	1	1	2
MIC range	0.008 - 0.008	0.004 - 0.004	NA	0.015 - 0.015	0.03 - 0.03	0.008 - 0.008
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Moraxella catarrhalis	0	0	0	0	0	0
MIC range	NA	NA	NA	NA	NA	NA
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Staphylococcus aureus	1	0	1	0	0	3
MIC range	128 - 128	NA	32 - 32	NA	NA	0.12 - 64
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA
Pseudomonas aeruginosa	0	0	1	0	0	0
MIC range	NA	NA	0.5 - 0.5	NA	NA	NA
MIC_{50}	NA	NA	NA	NA	NA	NA
MIC_{90}	NA	NA	NA	NA	NA	NA

Pharmacokinetics (PK): The PK sub-studies in studies CIFLOTIII/10IA02 and CIFLOTIII/10IA04 in AOMT did not show detectable concentrations of fluocinolone acetonide in plasma after 7 days of treatment except for 1 sample (ciprofloxacin concentration in plasma of 3.0 µg/L after 7 days of treatment). The systemic exposure to ciprofloxacin is low after otic administration.

LABELING:

LABELING PROPOSED BY THE APPLICANT:

The following includes section 1 and 12 of the applicant's version of the labeling

1. INDICATIONS AND USAGE

(b) (4)

Acute otitis media in pediatric patients (b) (4) with tympanostomy tubes (AOMT) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

(b)(4)

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

(b) (4) ciprofloxacin, a fluoroquinolone (b) (4) [see (b) (4) 12.4], (b) (4)

Fluocinolone acetonide inhibits the local biosynthesis of prostaglandins, which explains part of its anti-inflammatory efficacy. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes and the complement system.

12.4. Microbiology

The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA.

Bacterial resistance to quinolones can develop through chromosomal or plasmid mediated mechanisms.

(b) (4)

(b) (4) *In vitro* studies demonstrated cross-resistance between ciprofloxacin and some fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

(b) (4) ciprofloxacin has been shown to be active against most isolates of the following bacteria, both in vitro and (b) (4) infections [see (b) (4) 1]:

(b) (4)

(b) (4)

NDA 208251/0001 (SDN1-17)
OTOVEL (Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution)
Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

(b) (4)

LABELING PROPOSED BY AGENCY:
The Agency's recommended format of the Microbiology subsection should read as follows: Deletions are in red and strikethrough font; additions are in blue Font and double underlined. The proposed changes are to meet current standard format for MICROBIOLOGY subsection.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

(b)(4) Ciprofloxacin, is a fluoroquinolone antibacterial (b)(4) (b)(4) *[see Microbiology (12.4)].*

Fluocinolone acetonide, a corticosteroid, inhibits the local biosynthesis of prostaglandins, which explains part of its anti-inflammatory efficacy. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes and the complement system.

12.4. Microbiology

Mechanism of Action:
The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA.

Resistance:
Bacterial resistance to quinolones can develop through chromosomal or plasmid mediated mechanisms.

(b)(4)

(b)(4) *In vitro* studies demonstrated cross-resistance between ciprofloxacin and some fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Antimicrobial Activity:

(b)(4) Ciprofloxacin has been

shown to be active against most isolates of the following bacteria, both in vitro and clinically in (b)(4) otic infection (b)(4) *[see Indications and Usage (1)].*

Aerobic Bacteria:
Gram-positive Bacteria
Staphylococcus aureus
(b)(4)
Streptococcus pneumonia

Gram-negative Bacteria
Pseudomonas aeruginosa
Haemophilus influenzae
Moraxella catarrhalis

(b)(4)

NDA 208251/0001 (SDN1-17)
OTOVEL (Ciprofloxacin 0.3% plus Fluocinolone Acetonide 0.025% otic solution)
Laboratorios SALVAT S.A. (SALVAT)
Date Review Completed: 03/16/2016

SIGNATURES:

Kalavati Suvarna, Ph.D.	{See appended signature}
Clinical Microbiology Reviewer	Signature/Date
Avery Goodwin, Ph.D. .	{See appended signature}
Acting Clinical Microbiology Team Leader	Signature/Date

CC:
Original NDA
DAIP CSO/DeBellas, Carmen
DAIP CDTL/Iarikov, Dmitri
DAIP MO/ Ghosh, Mayurika

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/s/

KALAVATI C SUVARNA
03/16/2016

AVERY C GOODWIN
03/16/2016