CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-537

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)

Clinical Microbiological Review of NDA 21-537

NDA#: 21-537 **REVIEW #: 1** **COMPLETED DATE:** 07/16/03

Clinical Microbiology Reviewer: Harold V. Silver

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	09/23/02	09/25/02	09/30/02

NAME & ADDRESS OF APPLICANT	U.S. AGENT	CONTACT PERSON
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DRUG PRODUCT NAME:

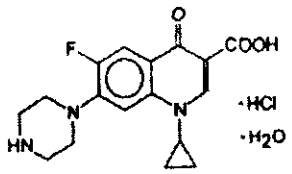
Proprietary: CIPRODEX® Otic Suspension

Non-Proprietary/USAN: ciprofloxacin 0.3% (3 mg) & dexamethasone 0.1% (1 mg) Otic Suspension

Ciprofloxacin:

Molecular Formula: $C_{17}H_{18}FN_3O_3.HCl.H_2O$
Molecular Weight:
Code Name: AL-2507A
CAS No: *86393-32-0*

Structural Formula*:

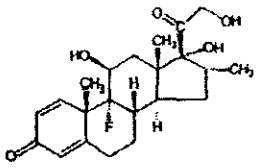


* Adopted from NDA 21-357, Disk 1 of 1, 2.3.S.1, on Page 1.

Dexamethasone

Code Names: AL-817
Molecular Formula: $C_{22}H_{29}FO_5$
Molecular Weight:
CAS No: *50-02-2*

Structural Formula*:



* Adopted from NDA 21-357, Disk 1 of 1, 2.3.S.1., on Page 12.

DOSAGE FORM: *Otic Suspension packaged in a 3 mL (sample size), 5 mL (trade size) and* 10 mL (trade size) mL DROP-TAINER bottles with fill volumes of 1.5 mL, 5 mL, and 7.5 mL, respectively.

STRENGTH: *CIPRODEX Otic suspension*

ciprofloxacin 0.3% = 3 mg ciprofloxacin base
dexamethasone 0.1% = 1 mg dexamethasone

ROUTE OF ADMINISTRATION: Topical (otic / via drops)

DISPENSED: Rx

RELATED DOCUMENT(s):

IND 54,670: CiproDex™ Otic Suspension, ciprofloxacin 3% (3 mg) and 0.1% (1 mg) dexamethasone, Alcon Research, Ltd.

PHARMACOLOGICAL CATEGORY:

Ciprofloxacin, as ciprofloxacin hydrochloride, is a broad-spectrum, second-generation *fluoroquinolone, antimicrobial.*

Dexamethasone is a synthetic glucocorticoid anti-inflammatory (for treatment of swelling, pain, and redness) steroid agent.

FDA APPROVED INDICATIONS for Alcon's CIPRO® HC Otic:

Acute Otitis Externa (AOE):

- For pediatric, adult, and elderly patients, age — and older.
- Treatment: Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days.
- Due to:

Aerobes, Gram-positive

Staphylococcus aureus

Aerobes, Gram-negative

[redacted]
Pseudomonas aeruginosa

Alcon's PROPOSED INDICATIONS for CIPRODEX® Otic:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

PROPOSED DOSAGE AND ADMINISTRATION:

SHAKE WELL IMMEDIATELY BEFORE USING

Acute Otitis Media [redacted] **(AOMT):** The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (age 6 months and older) [redacted] tympanostomy tubes is:

Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear **twice daily** for seven days.

Acute Otitis Externa (AOE): The recommended dosage regimen for the treatment of acute otitis externa is:

For patients (age 6 months and older): Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear **twice daily** for seven days.

REMARKS/COMMENTS:

This is the 1st Clinical Microbiology Review on NDA 21-537, CIPRODEX® [ciprofloxacin 0.3% (3 mg) and dexamethasone 0.1% (1 mg) Otic Suspension. The submission contains new clinical microbiology data on the applicant's proposed 2 indications: Acute Otitis Media (AOMT) and Acute Otitis Externa (AOE)

MICROBIOLOGY EXECUTIVE SUMMARY

Description

CIPRODEX® Otic Suspension is combination product containing ciprofloxacin 0.3% (3 mg) and dexamethasone 0.1% (1 mg). It is a sterile drug product. Ciprofloxacin is in the form as ciprofloxacin hydrochloride.

Ciprofloxacin is a fluoroquinolone and dexamethasone is a glucocorticoid anti-inflammatory steroid agent.

• **AOMT:** Middle Ear Infection with Drainage through a Tube in Children 6 months and older: A middle ear infection is a bacterial infection behind the eardrum. People with a tube in the eardrum may notice drainage from the ear canal.

• **AOE:** Outer Ear Canal Infection in Patients 6 months and older: An outer ear canal infection, also known as "Swimmer's Ear", is a bacterial infection of the outer ear canal. The ear canal and the outer part of the ear may swell, turn red, and be painful. Also, a fluid discharge may appear in the ear canal.

Introduction

The primary objective of CIPRODEX Otic Suspension clinical development is to provide evidence from adequate and well-controlled studies to support topical use of the product to treat otic bacterial infections and inflammation in acute otitis media with otorrhea in tympanostomy tube *patients* (**AOMT**), *and in acute otitis externa patients* (**AOE**).

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.

Ciprofloxacin, as ciprofloxacin hydrochloride, is a broad-spectrum, second-generation fluoroquinolone, antimicrobial.

Dexamethasone is a synthetic glucocorticoid anti-inflammatory (for treatment of swelling, pain, and redness) steroid agent.

Spectrum of Activity

Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms.

Mechanism of Resistance

Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as β-lactams or aminoglycosides.

SUMMARY of AOE and AOMT RESULTS

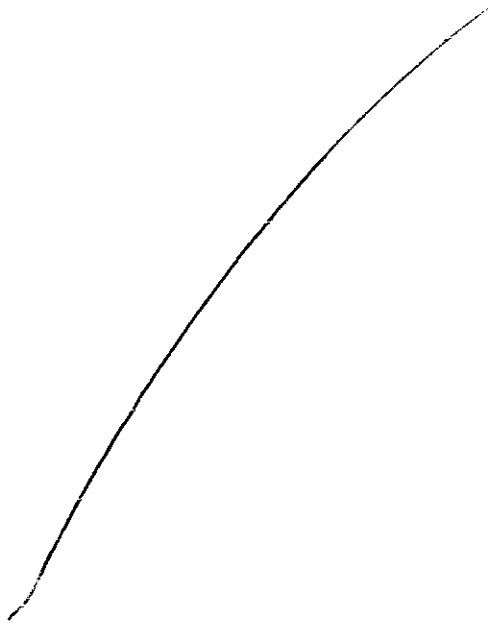
TABLE 1

OVERALL SUMMARY ANALYSES for ACUTE OTITIS EXTERNA (AOE)
PATIENT LISTING for MAJOR PATHOGENS -- ALL SPECIMENS

MPP MICROBIOLOGICAL OUTCOME

Overall *Pseudomonas aeruginosa* isolates = 243
Success = 215/243 (84.9) Failures = 28/146 (15.1%)

Overall *Staphylococcus aureus* isolates = 43
Success = 38/43 (88.4%) Failures = 5/43 (11.6%)



Clinical Microbiologist's Comments:
The relevant and "approved" **AOE** pathogens resulted in the following "MPP" Microbiological Outcomes:

Overall ***Pseudomonas aeruginosa*** isolates = 243: Success = 215/243 (84.9) and Failures = 28/146 (15.1%)

Overall ***Staphylococcus aureus*** isolates = 43: Success = 38/43 (88.4%) and Failures = 5/43 (11.6%)

itcome

TABLE 3

OVERALL SUMMARY ANALYSES for ACUTE OTITIS MEDIA with OTORRHEA THROUGH TYMPANOSTOMY TUBE (AOMT)

PATIENT LISTING for MAJOR PATHOGENS -- ALL SPECIMENS

MPP MICROBIOLOGICAL OUTCOME

Overall *Pseudomonas aeruginosa* isolates = 47
Success = 46/47 (97.9%) Failures = 1/47 (2.1%)

Overall *Staphylococcus aureus* isolates = 54
Success = 49/54 (90.7%) Failures = 5/54 (9.3%)

Overall *Streptococcus pneumoniae* isolates = 47
Success = 37/47 (78.7%) Failures = 10/47 (21.3%)

Overall *Haemophilus influenzae* isolates = 30
Success = 24/30 (80%) Failures = 6/30 (20%)

Overall *Moraxella catarrhalis* isolates = 11
Success = 10/11 (90.9%) Failures = 1/11 (9.1%)

Overal

Clinical Microbiologist's Comments:

The relevant and "approved" **AOMT** pathogens resulted in the following "MPP" Microbiological Outcomes:

Overall ***Pseudomonas aeruginosa*** isolates = 47: Success = 46/47 (97.9%) and Failures = 1/47 (2.1%)
Overall ***Staphylococcus aureus*** isolates = 54: Success = 49/54 (90.7%) and Failures = 5/54 (9.3%)
Overall ***Streptococcus pneumoniae*** isolates = 47: Success = 37/47 (78.7%) and Failures = 10/47 (21.3%)
Overall ***Haemophilus influenzae*** isolates = 30: Success = 24/30 (80%) and Failures = 6/30 (20%)
Overall ***Moraxella catarrhalis*** isolates = 11: Success = 10/11 (90.9%) and Failures = 1/11 (9.1%)

2 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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I. INTRODUCTION

The primary objective of Alcon's CIPRODEX Otic Suspension clinical development is to provide evidence from adequate and well-controlled studies to support topical use of the product to treat otic bacterial infections and inflammation in acute otitis media with otorrhea in tympanostomy tube (AOMT) patients, and in acute otitis externa (AOE) patients.

AOMT and AOE Indications

The AOMT and AOE indications are closely related. Both indications are for treatment of bacterial infections of the ear with inflammation. There are common pathogens found in both AOMT and AOE. Differences between the two diseases include the site of infection and the presence or absence of a tympanostomy tube. The etiology of both diseases includes many water-borne pathogens, although AOMT etiology also includes upper respiratory pathogens. Both diseases are effectively treated with topical therapy because there is a direct connection between the ear canal (site of application) and the site of infection (either external canal or middle ear via tympanostomy tube).

- **AOMT:** Middle Ear Infection with Drainage through a Tube in Children 6 months and older: A middle ear infection is a bacterial infection behind the eardrum. People with a tube in the eardrum may notice drainage from the ear canal.

Otitis media is an infection of the middle ear. Approximately one million children in the United States undergo tympanostomy tube insertions for the treatment of recurrent otitis media with effusion. Acute otorrhea (AOMT) is the most common complication after insertion of the tympanostomy tubes. The incidence of acute otorrhea in the postoperative period ranges from 10% to 50% of the cases. The majority (>90%) of AOMT cases occur in pediatric patients ages 1 year to 12 years. The most commonly isolated microorganisms from AOMT patients include: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The origin of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* otitis media infections is the upper respiratory tract through the eustachian tube. *P. aeruginosa*, *Staphylococcus aureus*, and other organisms enter the middle ear cavity from the external ear canal through the tympanostomy tube. Frequently, AOMT is characterized by its multiple episodes in a young child, often being considered as a chronic infection.

- **AOE:** Outer Ear Canal Infection in Patients 6 months and older: An outer ear canal infection, also known as "Swimmer's Ear", is a bacterial infection of the outer ear canal. The ear canal and the outer part of the ear may swell, turn red, and be painful. Also, a fluid discharge may appear in the ear canal.

Pseudomonas aeruginosa and *Staphylococcus aureus* are the two pathogens most frequently associated with AOE, although there are a great number of bacterial species that have recovered and reported as AOE causative pathogens.

Clinical Studies

CIPRODEX Otic Suspension is intended for the treatment of infection and inflammation of the ear due to bacterial strains shown to be responsive to ciprofloxacin. A total of 4 clinical trials to evaluate CIPRODEX Otic Suspension are conducted in (a) pediatric patients with AOMT (C-99-59 and C-00-52); and (b) in adult and pediatric patients with AOE (C-98-19 and C-98-18).

TABLE 1 is a brief overview of the clinical efficacy studies conducted and are provided in the summary table below:

TABLE 1* **Overall Clinical Study Overview**

Study Number/Title	Design	Dose Regimen	Total Subjects
AOMT Indication			
C-99-59 Safety and efficacy of CIPRODEX vs. CILOXAN in AOMT	Phase II, multicenter, randomized, observer-masked, active-controlled, parallel-group study in pediatric patients; Visit Days 1, 3, 8, and 14; 14-day study duration; 7-day treatment duration.	Topical otic, CIPRODEX/CILOXAN - 3 drops BID x 7 days	Enrolled - 201 103 CIPRODEX 98 CILOXAN
C-00-52 Safety and efficacy of CIPRODEX vs. FLOXIN in AOMT	Phase III, multicenter, randomized, observer-masked, active-controlled, parallel-group study in pediatric patients; Visit Days 1, 3, 11, and 18; 18-day study duration; 7 or 10-day treatment duration.	Topical otic, CIPRODEX - 4 drops BID x 7 days FLOXIN - 5 drops BID x 10 days	Enrolled - 599 297 CIPRODEX 302 FLOXIN
AOE Indication			
C-98-19 Safety and efficacy of CIPRODEX vs. CORTISPORIN in AOE	Phase III, multicenter, randomized, observer-masked, active-controlled, parallel-group study in pediatric and adult patients; Visit Days 1, 3, 8, and 18; 18-day study duration; 7-day treatment duration.	Topical otic, CIPRODEX - 3 drops (pediatric) or 4 drops (adults) BID x 7 days CORTISPORIN - 3 drops (pediatric) or 4 drops (adults) TID x 7 days	Enrolled - 468 232 CIPRODEX 236 CORTISPORIN
C-98-18 Safety and efficacy of CIPRODEX vs. CILOXAN vs. CORTISPORIN in AOE	Phase III, multicenter, randomized, observer-masked, active-controlled, parallel-group study in pediatric and adult patients; Visit Days 1, 3, 8, and 18; 18-day study duration; 7-day treatment duration.	Topical otic, CIPRODEX and CILOXAN - 3 drops (pediatric) or 4 drops(adults) BID x 7 days CORTISPORIN – 3 drops (pediatric) or 4 drops (adults) TID x 7 days	Enrolled - 909 305 CIPRODEX 305 CILOXAN 299 CORTISPORIN

* Adapted from CD Disk NDA 21-537, Alcon Clinical Study Report: 2.5.4., Overview of Efficacy, Page 2.

Non-Clinical Studies

Alcon Research Ltd., developed an antimicrobial/anti-inflammatory combination product, CIPRODEX Otic suspension [ciprofloxacin (0.3%) / dexamethasone (0.1%)], for the topical treatment of infections of the middle and external ear.

Ciprofloxacin is a fluoroquinolone approved for use as a broad-spectrum antibacterial agent. Approved uses for the ciprofloxacin tablet, oral suspension and IV forms include; acute sinusitis, lower respiratory tract infections, acute uncomplicated cystitis, skin and skin structures infections and prophylaxis of inhalation anthrax.

Dexamethasone is a synthetic adrenocortical steroid primarily used for its potent anti-inflammatory effects in disorders of many organ systems including: endocrine, rheumatic, collagen, dermatologic, respiratory, ophthalmic and hematologic. These single agent drugs are approved in the US for many years and the pharmacotoxicological profiles of both ciprofloxacin and dexamethasone are well established in the scientific literature.

Both agents are selected for use in CIPRODEX Otic suspension combination product based on their documented safety and anticipated efficacy in treating infectious/inflammatory conditions of the ear. The systemic safety of both of these agents is well documented.

TABLE 2* **Non-Clinical Study Overview**

Source of Ciprofloxacin and Dexamethasone Data

Compound	Type of Data	Source
Ciprofloxacin	Oral Tablet for Ciprofloxacin HCl	Bayer AG data and PDR
	Intravenous Ciprofloxacin, NDA	NDA 19-847
	Ciprofloxacin-Hydrocortisone Otic Suspension	NDA 20-805
	CIPRODEX Alcon Data	NDA 21-537: pending
	Literature	Ciprofloxacin product monograph. RTECS Accession No. VB1993800
Dexamethasone	DECADRON Package Insert	PDR
	CIPRODEX Alcon Data	NDA 21-537: pending
	Literature	RTECS Accession No. FU3980000

* Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, Table L-5, pp. 481 to 488.

Combination Antibiotic and Steroid Treatment

Inflammatory response and the resultant AOM are the apparent effects of the disease specific organisms commonly associated with AOM. Accordingly, the effect of steroid administration in combination with antibiotics at reducing inflammatory responses and preventing their sequelae, has been studied. Several clinical studies have demonstrated the efficacy and safety of antibiotic-steroid combinations in the treatment of AOMT

Dexamethasone

The term 'corticosteroids' includes those steroid hormones produced by the adrenal cortex: sex steroids, mineralocorticoids and glucocorticoids. Synthetic glucocorticoids have been used for a variety of diseases including allergic reactions.

Glucocorticoids differ in their anti-inflammatory potencies depending on their chemical characteristics. Corticosteroids exert their beneficial anti-inflammatory effects by multiple mechanisms, many of which are not completely understood. Steroids are known to decrease the synthesis of arachidonic acid-derived inflammatory mediators and PAF in many cell types. Glucocorticoids have been shown to suppress the formation of cytokine receptors: dexamethasone in particular downergulates gene transcription of angiotensin II type 2 receptors.

Dexamethasone also inhibits prostoglandin production by selective inhibition of COX-2 without affecting COX-1 expression. Dexamethasone's anti-inflammatory activity has been reported as approximately 26 times greater than hydrocortisone and 5 times greater than methylprednisolone.

Alcon desired to develop a new antibiotic/steroid treatment for both AOE and AOMT. Since AOMT involves instillation of ear drops into the ear canal and pumping of the tragus to push the drops through a tympanostomy tube, very little volume of medicine would be expected to reach the middle ear. A large amount of solids might impede this process. Therefore, a steroid was sought that afforded good anti-inflammatory activity, and if water-insoluble, a minimal concentration (low solids content).

There are no accepted animal efficacy models for either AOE or AOMT on which to base the choice and concentration of steroid. However, some studies have been done with steroids and ear infections and or inflammation. Investigators reported that combination therapy with antibiotic/steroid (combination of 160,000 units of penicillin G and 1 mg/kg dexamethasone, i.m.) was effective at reducing the treatment period of in acute otitis media (AOM) in rats and preventing persistent mucosal changes, which may decrease the risk of development of secretory otitis media as a sequela of AOM.

It was also reported that CIPRODEX (designated as Dex-Alc) was superior to ciprofloxacin/dexamethasone phosphate (designated as Dex-Phos) as an anti-inflammatory agent in a mouse ear model of inflammation (phorbol esterinduced).

Dexamethasone has poor water solubility and must be formulated as a suspension.

II. PRECLINICAL EFFICACY (*IN VIVO*)

Pharmacokinetics

The pharmacokinetics of ciprofloxacin specifically in the tissues of the ear following topical otic or systemic administration has not been studied by Alcon; however, the absorption of ciprofloxacin in the ear has been described in the literature. Literature data indicate that ciprofloxacin distributes into the middle ear following systemic administration and inner ear following application into the middle ear space; however, middle ear and inner ear levels were substantially less than those in the plasma and middle ear, respectively.

The uptake of ciprofloxacin into the middle ear fluid of chinchillas has been demonstrated after intramuscular injection[1].

Ciprofloxacin

Following a 6 mg/kg injection, the maximal concentration of ciprofloxacin in middle ear fluid is approximately 0.5 µg/mL at 6 hrs. Maximal plasma concentration is about 4-fold higher at about 1.9 µg/mL. The half-life of ciprofloxacin in middle ear fluid is 15 h *versus* the much shorter half-life of 3 h in plasma. These findings demonstrate that significant concentrations of ciprofloxacin can be achieved in the ear following systemic administration.

When locally applied into the middle ear, ciprofloxacin has the capacity to penetrate into the inner ear. Ciprofloxacin (0.1 mg/mL), administered in direct contact with the intact round window membrane of chinchillas (0.005 mL, 0.05 mg dose), resulted in a maximal perilymph concentration of 0.165 µg/mL.[2] This concentration is approximately 600-fold lower than the initial concentration of ciprofloxacin on the round window membrane, indicating that the extent of absorption into the inner ear is relatively low.

Ciprofloxacin (0.3%), administered ototopically TID for 7 days to otorrhea pediatric patients after tympanostomy tube placement, results in serum concentrations below the limit of quantitation (assay quantitation limit: 5 ng/mL)[3]. However, in a study conducted by Alcon (C-00-68) in tympanostomy-tube patients, plasma levels of ciprofloxacin are quantifiable (LOQ: [redacted] with a mean Cmax of 0.00155 µg/mL achieved at 0.25 to 2 h post-dose. These data demonstrate the potential for systemic absorption following topical otic administration[3].

The tissue distribution of ciprofloxacin is adequately evaluated in the rat, dog and monkey, as well as pregnant rats. Following intravenous administration, the volume of distribution of unchanged drug at steady-state amounts to approximately 3 L/kg in the rat and dog, and 1.8 L/kg in the monkey, indicating good apparent tissue distribution. The distribution of 14C ciprofloxacin-related radioactivity to organs and tissues of male and pregnant female rats is investigated by whole-body autoradiography and/or by the quantitative radiometric analysis.

Dexamethasone

The pharmacokinetic properties of dexamethasone is been well characterized in the literature, especially related to human exposure.

Oral bioavailability is about 60 to 80%, while dermal absorption, a potential route of systemic absorption following topical otic administration, is relatively slow.

Dermal absorption, a potential component of topical otic absorption, is shown to be relatively slow for dexamethasone. Following application of 1% dexamethasone on 500 cm^2 of normal skin of normal human subject, the plasma dexamethasone concentration is maximal at 2 h, with an average absorption of only 0.25% over 8 h. Therefore, systemic access via the skin of the ear canal is limited[4]. Two topical otic studies can be cited. Topical otic administration of dexamethasone BID into both ears of dogs result in adrenocortical suppression, indicative of systemic absorption.

However, the extent of absorption, as measured by plasma levels of dexamethasone, was not determined[5]. In the a topical otic study conducted by Alcon in tympanostomy tube patients (Alcon study C-00-68), administered four drops of CIPRODEX Otic Suspension (0.3% ciprofloxacin: 0.1% dexamethasone), systemic levels of dexamethasone are low but quantifiable (LOQ: [redacted] Maximal plasma concentrations ranged from [redacted] (mean .000086 µg/mL) achieved within 0.17 to 2.1 h post-dose. These results indicate the potential for systemic absorption of dexamethasone following topical otic administration.

Dosage Rationale

In terms of dose delivered, a substantial margin of safety is demonstrated for both ciprofloxacin and dexamethasone administered by the topical otic route. Administration of CIPRODEX Otic suspension under the clinical regimen (4 drops of ciprofloxacin 0.3%/dexamethasone 0.1% dosed bilaterally twice daily) will result in the delivery of approximately 1.68 mg ciprofloxacin and 0.56 mg dexamethasone per day. In a 10 kg child this translates to a dose of 0.168 mg/kg/day ciprofloxacin and 0.056 mg/kg/day dexamethasone. The dose in a 50 kg adult would be equivalent to 0.034 mg/kg/day ciprofloxacin and 0.011 mg/kg/day dexamethasone. Systemic exposure to ciprofloxacin and dexamethasone with ototopical use of CIPRODEX Otic suspension will be minimal and substantially lower than that following doses producing toxic effects in single dose, repeated dose, carcinogenicity, fertility/teratogenicity and other non-clinical safety studies.

Pharmacology

Ciprofloxacin/dexamethasone Combination

The combination of the antibiotic, ciprofloxacin, and the anti-inflammatory agent, dexamethasone, allows for the dual treatment of infection and inflammation in ear infections. There is no data to suggest that the combination of these two actives interfere with the pharmacological activity of either agent alone.

III. CLINICAL EFFICACY

Acute Otitis Media with Tympanostomy Tubes (AOMT)

Study #C-00-52: This study is to provide the microbiology procedures in support of the clinical studies to develop ciprofloxacin plus dexamethasone (CIPRODEX) as a topical anti-infective/steroid combination for the treatment of acute otitis media through a tympanostomy tube.

Title: Safety and Efficacy of Topical CIPRODEX® Otic (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to FLOXIN® Otic (Ofloxacin 0.3%) Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT).

Test Drug / Comparator:

Topical CIPRODEX Otic (ciprofloxacin 0.3%, dexamethasone 0.1%) Suspension / FLOXIN® Otic (ofloxacin 0.3%) Solution

Indication Studied: Acute Otitis Media (middle ear infection) with Tympanostomy tubes (AOMT)

Study Design: Multicenter, active-controlled, randomized, observer-masked, parallel group study with 2 treatment arms: CIPRODEX® Otic Suspension and FLOXIN® Otic Solution.

Multicentered: To ensure a representative geographic and demographic distribution of patients, and to prevent possible bias due to individual investigator judgments.

Active-Controlled: FLOXIN® Otic (Ofloxacin 0.3%) Solution.

Randomization: Patients were sequentially assigned to treatment according to a randomization code provided by the Alcon Biostatistics Department. The randomization was blocked within center to ensure balanced treatment groups within each center.

Masking: Because of the physical distinction between a suspension and a solution, as well as the difference in the dosing regimens, this study was considered observer-masked study with the investigator (evaluator) masked in terms of the patient treatment assignment (randomization).

Parallel Groups: Use of parallel groups with randomization helps to ensure comparability of treatment groups with regard to demographics and other factors that could bias the study results. The two test articles were sequentially assigned in an equal ratio (1:1).

Eligibility Phase including Washout:

Patient eligibility, based on specific inclusion/exclusion criteria, was determined at the screening/baseline visit (Visit 1). To be eligible for enrollment, patients were required to washout of possible interfering therapies, including antibiotics; i.e., short-acting antibiotic agents for 2 days, and long-acting antibiotic agents for 7 to 14 days. These periods were considered sufficient to ensure washout of any residual bactericidal activity and crossover effects that might confound the assessment of the antibacterial activity of the drugs under study.

Non-Inferiority/Superiority: This study was designed to demonstrate the statistical non-inferiority of CIPRODEX relative to FLOXIN in clinical and microbiological response at the TOC visit.

Patient Diary: Patient compliance (i.e., dosing, water exposure) and the presence or absence and time of cessation of otorrhea, assessed twice daily, were captured in a patient diary. Diaries were issued to the parent/guardian at the baseline visit (Visit 1) to be completed daily through the TOC visit, Visit 4 (Days 18-21).

Audiometry: Certified technicians were to perform a complete audiometry exam (including Speech Recognition Threshold) for enrolled patients 4 to 12 years of age at the baseline visit (Visit 1) and at the visit these patients completed and/or exited the study (Visit 4 or upon discontinuation due to treatment failure or AE). These data were analyzed as part of safety to determine if there were any clinically relevant decreases in hearing or speech recognition threshold changes from baseline, or any differences between treatments.

Study Centers: 47 US and 2 Canadian medical center facilities.

Objectives:

1. To demonstrate the non-inferiority of CIPRODEX Otic Suspension relative to FLOXIN® Otic Solution in clinical and microbiological response at the test of cure (TOC) visit.

2. To evaluate the efficacy and safety of topical CIPRODEX Otic (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension in AOMT patients;

Number of Patients Planned/Analyzed:

Approximately 500 pediatric patients with AOMT and post-tympanostomy tube otorrhea (250/arm) were planned. A total of 599 patients were enrolled. There were 382 clinically evaluable (191/arm).

Study Population: Pediatric patients, 1 year to 12 years old, with a patent tympanostomy tube, and clinically diagnosed with AOM with otorrhea of ≤ 3 weeks duration, that is visible by the parent/guardian, were enrolled.

Study Patients:

Five separate data sets were analyzed in this study, defined as follows:

Safety—All patients who received treatment.

Intent-to-Treat (**ITT**)—All patients who received treatment.

Modified Intent-to-Treat (**MITT**) —All patients who received treatment, met inclusion/exclusion criteria at Baseline, and had positive pre-therapy cultures.

Per Protocol (**PP**)—All patients who received treatment, met inclusion/exclusion criteria at Baseline, and returned for the TOC visit or exit visit for treatment failures. Individual patient visits were excluded, if study procedures were violated at only a subset of the patient's visits and if such violations, in the opinion of the medical monitor, did not invalidate the remaining visits.

Modified Per Protocol (**MPP**)—All patients who received treatment, met inclusion/exclusion criteria at Baseline, returned for the TOC visit or exit visit for treatment failures, and had positive pre-therapy cultures.

TABLE 3* The schedule of study visits and procedures conducted during this study is displayed in the following table.

Study Plan for Protocol C-00-52

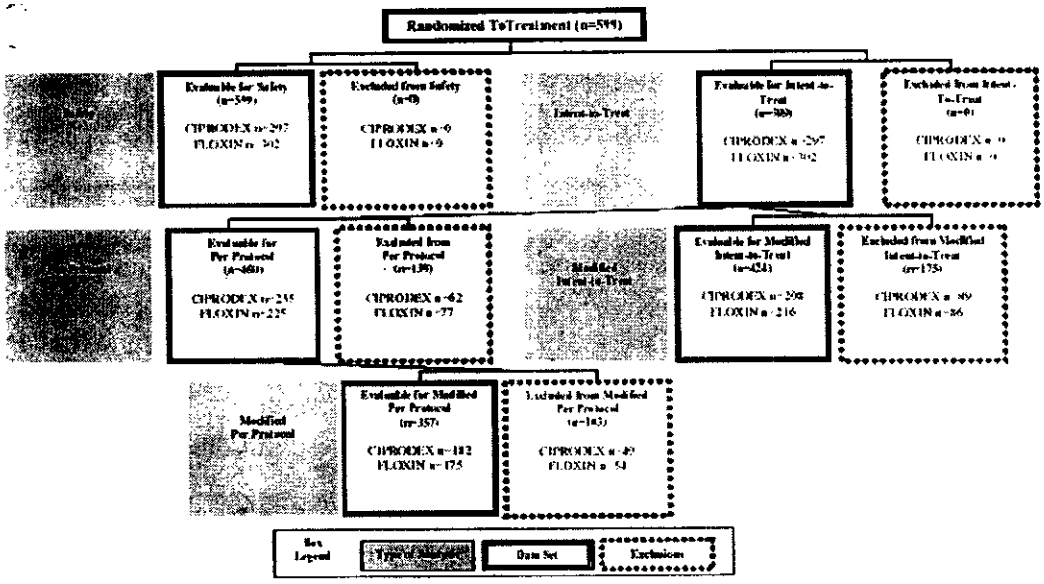
Activity	Visit 1 Day 1	Visit 2 Day 3+2	Visit 3 Day 11+2	Visit 4(TOC)[a] Day 18+3
Screen Patients	X			
Informed Consent	X			
Demographics	X			
Medical History/Meds	X			
Clinical Assessment	X	X	X	X
Audiometry (4-12 yrs)	X	X[b]	X[b]	X
Ear Cleaning (suction)	X	X[c]	X[c]	
Ear Culture	X	X[d]	X[d]	X[d]
Concomitant Meds/AEs		X	X	X
Adverse Events	X	X	X	X
Health Economic Questionnaire	X	X	X	X
Treatment Satisfaction			X	
Review Diary/Instructions	X	X	X	X
Photocopy Diary		X	X	Collect
Dispense Medication	X	X[c]		
Instill First Dose	X			
Daily Phone Calls	Late afternoon or as close to bedtime as possible			
Collect Medication			X	
Complete Exit Form				X[e]

* Adapted from Electronic Document NDA 21-144, Dated: 07/24/02, Table L-5, pp. 481 to 488.

[a] TOC is at least 7 days after the last study dose.
[b] If patient is discontinued.
[c] As needed.
[d] If drainage is present and patient is discontinued or is at the TOC visit.
[e] At the TOC visit or earlier if patient discontinues prior to this visit.

Disposition of Patients:

Figure 1* Disposition of Patients Enrolled in Protocol C-00-52 ALCON Clinical Study Report 004:65:0102, Protocol No.: C-00-52 Page 60 of 1543



* Adapted CD Disk NDA 21-537, Alcon Clin. Stdy. Rept: 004:65:0102, P#: C-00-52, Fig. 10.1-1, Pg. 60, Dated 09/05/02.

Test Drug / Comparator Regimen:

CIPRODEX Otic Suspension: Instill 4 drops twice daily (BID – morning and night) into infected ear for 7 days.

FLOXIN® Otic Solution: Instill 5 drops twice daily (BID – morning and night) into the infected ear for 10 days.

Study Duration:

CIPRODEX Otic Suspension: 14 to 17 days (4 study visits);

FLOXIN® Otic Solution: 17 to 20 days (4 study visits).

Efficacy Assessments:

1° Efficacy:

Clinical Response: Patients rated as resolved by the Investigator for overall clinical response as measured by the Investigator on a 4-point scale (resolved/cured = 0, worsened = 3) at the TOC visit;

Microbiological Response: Patients for whom disease-specific pathogens are present at enrollment and absent at the TOC visit (success or failure).

To assist in determination of the antimicrobial response, an ear culture was collected at baseline and at any subsequent visit if drainage was present and the patient was discontinuing or exiting the study. If exit cultures were available, the microbiological response was documented as success (eradication) or failure. Eradication of bacteria was presumed in the absence of a microbiological specimen as a result of resolution of clinical signs and symptoms. Similarly, microbiological failure was presumed if clinical signs or symptoms persisted although a specimen might not have been available. Details of the microbiological assessments and procedures are provided in Appendix G of the Protocol, Section 16.1.1, Page 361.

2° Efficacy:

Clinical Response at Each Visit: Investigator's assessment of presence or absence of otorrhea, Granulation tissue, Volume and color/type of otic discharge, and Time to cessation of otorrhea, respectively.

Contract Research Organizations (CRO):

[redacted]

[redacted]

Clinical Laboratory:

Primary microbiological analyses are conducted [redacted]

[redacted]

Additional analyses are performed by the R&D Microbiology Department of Alcon Research, Ltd. Fort Worth TX, USA.

Microbiological Inclusion:

Presence of otorrhea at Baseline of ≤ 3 weeks duration, visible by parent/guardian.

Microbiological Exclusions:

Otorrhea > 21 days in duration,

Acute or chronic non-tube otorrhea (through existing perforation of the eardrum);

Acute otitis externa (AOE), or malignant otitis externa (MOE);

Acute or chronic non-tube otorrhea (through existing perforation of the eardrum);

Acute otitis externa (AOE) or malignant otitis externa (MOE) or other conditions which could interfere with evaluation of the study drug;

Known or suspected ear infection of fungal or mycobacterial origin;

Prior history or active herpes simplex, vaccinia or varicella infections or overt viral infection of the tympanic membrane (e.g., myringitis bullosa);

Current or prior history of an immunosuppressive disorder (e.g., HIV-positive), or current immunosuppressive therapy (e.g. cancer chemotherapy) or known acute or chronic renal disorders or active hepatitis;

Diabetic patients; due to decreased immunocompetence and increased vulnerability to malignant otitis externa;

Any systemic disease or disorder, complicating factors or structural abnormality that would negatively affect the conduct or outcome of the study (e.g., cleft palate, Downs Syndrome and cranial-facial problems);

Current or prior use of any topical otic analgesic, anesthetic, antiseptic otic wash (e.g., acetic acid, alcohol, boric acid and astringents) within one (1) day of study entry;

Current or prior use of systemic steroids within the previous 7 days or topical otic/ophthalmic steroids within the previous 3 days prior to study entry;

Current known or suspected infection (other than AOMT) requiring systemic antimicrobial therapy;

Chronic nasal obstruction that required treatment with systemic antibiotics, and/or persistent rhinorrhea. Required use of intranasal steroids with significant systemic absorption and all inhaled steroids at 800 micrograms or greater per day;

Current use of topical otic/ophthalmic or systemic antibiotics; use of topical otic/ophthalmic antibiotics within the previous 3 days or short-acting antibiotics within the previous 2 days or long-acting antibiotics within the previous 7-14 days;

Current use of topical antibiotics for treatment of acne or other superficial skin infections that were started less than 7 days prior to study entry;

Concomitant use of topical or oral analgesics other than acetaminophen (i.e., NSAIDS and aspirin products) which may have anti-inflammatory effects;

Therapy with another investigational drug or device within the past 30 days;

Previous enrollment in one of the other investigational drug trials on CIPRODEX Otic Suspension;

Anticipated change in the use of any systemic medication during the study that may affect the conduct or outcome of the study. Patients must be stabilized on these medications for at least 1 month prior to receiving study drug and continue the same regimen throughout the study.

Removal of Patients from Therapy or Assessment:

A patient could be discontinued at any time according to the discretion of the investigator (and/or sponsor). Reasons for discontinuation included:

Ear Culture Results Positive for Group A *Streptococci*:
Patients with a baseline culture that was positive for Group A *Streptococci* as determined by the central microbiology laboratory were discontinued from the study medication and placed on appropriate therapy;

Ear culture results Positive for Yeast:

Patients with a baseline culture that was positive for yeast as determined by the central microbiology laboratory were discontinued from the study medication and placed on appropriate therapy.

Clinical Evaluability:

All patients who receive drug will be evaluable for safety analyses.

All randomized patients will be evaluable for intent-to-treat (ITT) analyses.

All patients who receive drug meet inclusion criteria and are culture positive for bacteria on Day 1 will be evaluable for the modified intent-to-treat (MITT)

analyses.

For both ITT and MITT, patients who have no measurements after baseline are included as treatment failures.
All patients who comply with the protocol receive study drug and are present for all study visits will be evaluable for the per protocol (PP) analyses.

All PP patients who are culture positive for bacteria on Day 1 will be evaluable for the modified per protocol (MPP) analyses.

Test System: Microorganisms obtained from enrolled patients in Clinical Study C-00-52.
Organism: Organism characterization
Equipment: Antibiotic minimum inhibitory concentration (MICs)

Route of Administration: Topical Otic

Visits and Examinations:

(1) Baseline:	Day 1
(2) During Therapy:	Day 3 - 5
(3) End of Therapy (EOT):	Day 8 - 10 or Day 11 - 13
(4) Test of Cure (TOC):	Day 14 - 17 or Day 17 - 20

-- The purpose of this amendment was to incorporate the FDA's request that the visit days for the end of treatment visit (Visit 3) and the test of cure visit (Visit 4) be the same days (counting from the baseline Visit 1- Day 1) for each of the treatment groups.

Study Comment: The study is preformed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. The Protocol follows guidelines outlined by the International Conference on Harmonization

Enrollment: 599 total patients: 297 CIPRODEX and 302 FLOXIN.

Microbiology Protocol N-00-286

-- **APPENDIX G:** on pages 568 to 577

The applicant provides a description of the following laboratory procedures:

MATERIALS:
- Investigator laboratory supplies
- [redacted] supplies
  - Supplies for shipping bacteria
  - Microbiology testing supplies
  - Equipment

METHODS:
- Procedures for investigators for specimen collection and shipment
- [redacted] procedures
  - Swab specimen processing
  - Organism identification
    - If Group A Streptococci (GSA) is identified or yeast is isolated in pure culture or in combination with bacteria from a pre-therapy specimen the patient will be

exited from the study.

- Any bacteria, yeast, or mold present on plated media will be identified. Additionally, semi-quantitation (1+; 2+; 3+; and 4+) of each organism isolated from the original specimen will be reported whenever possible.
- Semi-quantitative culture results including presumptive organism identification will be reported to the Investigator and Alcon in the [redacted] standard report format. Alcon R&D Clinical Microbiology Procedures

- Processing culture swabs received form [redacted]
  - Swabs supplied by [redacted] to Alcon are processed using standard microbiology practices and procedures for organism isolation, cultivation, and cryopreservation as described in Alcon's standard operating procedures (SOPs).
- Species level identification
  - Microbiology methods described in Alcon's SOPs for the characterization and identification to the species level of the microorganisms isolated in these clinical trials will be used including standard morphological phenotypenic testing and/or genotypic methods.

Definitive Species-Level Identification and Strain-Level Discrimination

The definitive species-level identification of each bacterial isolate was a result of combining phenotypic characterization data with DNA-based characterization data. The standard phenotypic methods are described in Microbiology SOPs (references 6-11). Several groups of bacteria could not be definitively assigned to the species-level when relying solely upon those methods, such as,

Experience has taught that isolates belonging to these groups of bacteria needed additional characterization by DNA-based methods. The method of first choice was [redacted]

Strain Level Characterization

Comparative studies to discriminate between isolates of the same species will be conducted when appropriate, i.e., Pre-therapy isolates versus Test-of-Cure (TOC) isolate.

Strain-level discrimination between isolates of the same species was accomplished by [redacted]

This approach to strain-level discrimination was independent of phenotypic characteristics such as antibiotic resistance. It was, therefore, a valuable technique to investigate treatment failures and reinfections.

Minimal Inhibitory Concentration (MICs)

Antimicrobial susceptibility testing will be done by the Alcon methodologies using standard microbiology practices and procedures as described in the SOPs.

Processing and Interpretation of Microbiology Data

Specific Criteria for Microbiological response

Specimens will be collected at Baseline (Pre-therapy, Day 1). Other specimens will be collected when there are signs and symptoms of otorrhea at any subsequent visit, or at any time a patient is exited from the study as a treatment failure.

General Microbiological Outcome Definitions

Eradication: The original pathogen is absent from the culture of an adequate specimen obtained at any follow-up visit, or is presumed to be absent when no specimen is collected due to lack of clinical signs and symptoms.

Persistence: The continued presence of the pathogen in cultures of specimens obtained at any follow-up, or is presumed to persist when there are clinical signs and symptoms but no specimen was collected.

Superinfection: The emergence of a new pathogen is documented during therapy or with a specimen collected at the End-of-Therapy (EOT), not generally collected in this study, coupled with the emergence or worsening of associated clinical signs and symptoms.

Reinfection: The emergence of a new pathogen documented with the TOC specimen.

Colonization: The presence of an organism other than the original pathogen in the absence of signs of active otic infection.

-- **Appendix D**: Microbiological Efficacy Code Tables – Page 575

References Used:

4. PERTINENT REFERENCES

1. Alcon Clinical Protocol C-00-52. 2000. Microbiology Support of Clinical Study C-00-52: Safety and Efficacy of Topical CIPRODEX (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to FLOXIN (Ofloxacin 0.3%) Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT).
2. [redacted] C-00-52. 2000
3. Baron, E. J. and S. M. Finegold. 1990. Bailey and Scott's diagnostic microbiology. 8th ed. C. V. Mosby Co., St. Louis
4. Isenberg, H. D. (ed) 1992. Clinical microbiology procedures handbook. American Society for Microbiology, Washington D.C.
5. Koneman, E. W., S. D. Allen, W. M. Janda, P. C. Schreckenberger, and W. C. Winn, Jr. 1997. Color atlas and textbook of diagnostic microbiology. 5th ed J. B. Lippincott Co., Philadelphia.
6. Kreig, N. R. and J. G. Holt (ed). 1984. Bergey's manual of systematic bacteriology, Vol. 1. Williams and Wilkins, Baltimore.
7. Murray, P. R., E. J. Baron, M. A. Pfaller, F. C. Tenover and R. H. Yolken (ed.). 1999. Manual of clinical microbiology. 7th ed. American Society for Microbiology. Washington, D.C
8. National Committee for Clinical Laboratory Standards. 2000. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 5th ed. Approved Standard M7-A5. NCCLS, Villanova, PA.
9. Sneath, P. H. A., N. S. Mair, M. E. Sharpe, and J. G. Holt (ed). 1986. Bergey's manual of systematic bacteriology, Vol. 2. Williams and Wilkins, Baltimore.

List of Appendices: Alcon Clinical Study Report: TR #004:65:0102C-00-052, Protocol No: C-00-52, Module 5 (Clinical), Microbiology Protocol No: N-00-286, Volume 3.8

Appendix A: Contains "Alcon General Guidelines for Presumptive Microorganism Identification (Gram-positive and Gram-negative Bacteria, Yeast and Mold, on Pages 579 to 581 of 1543. In addition, a "Semi-Quantitation of Microorganisms" procedural method is described here:

SEMI-QUANTITATION OF MICROORGANISMS

The microbiologists generally should attempt to estimate the amount of colony growth on streaked media for each strain isolated from the original specimen. The method is generally described by a standard procedure at [redacted] and summarized as follows:

1+ Very light growth, very sparse colonies in area I

2+ Denser growth in area I

3+ Growth in area II

4+ Growth in area III

Otorrhea Volume and Semi-quantitative Bacterial Load: *One of the clinical signs chosen* to characterize the severity of an AOMT infection was the amount of otorrhea draining through the tympanostomy tube, copious amounts of otorrhea categorized a more severe case than scant amounts of otorrhea. Another parameter of the severity of AOMT was a semi-quantitative measure of bacterial load recovered from the otorrhea. Neither the amount of otorrhea nor the bacterial load correlated well with the severity of the disease.

Appendix B: Contains "Shipping Instructions for Laboratory Report Forms and/or Bacterial Cultures, on Pages 582 to 583.

Appendix C: Contains "Defined Pathogens in Patients with Acute Otorrhea", on Page 584.

Appendix D: Contains Codes and Definitions for Microbiological Evaluation, Tables containing information on Pages 586:

TABLE 4 Pre-Therapy (Visit 1) Culture Status, on page 587,

Appendix D

Alcon Codes and Definitions for Microbiological Evaluation

Pre-Therapy (Visit 1) Culture Status

Code No.	Status Terminology	Definition
1-No	**Culture Negative**	No pathogen(s)[a] isolated from pre-therapy specimen
2-Yes	**Culture Positive**	Single pathogen[a] isolated from pre-therapy specimen
3-Yes	**Culture Positive - Polymicrobic Culture**	Multiple pathogens[a] isolated from pre-therapy specimen
4-NA	**Not Analyzable**	Pre-therapy specimen not collected or lost, or specimen data is missing, incomplete, erroneous, or nonclinical, or clinical, protocol noncompliance

[a]*Refer to* DEFINED PATHOGENS (*Appendix C of this Protocol*)

TABLE 5 Microbiology Outcome by Ear-Based on Test-of-Cure (TOC) Specimen, on Page 592

Microbiology Outcome by Ear-Based On Test-of-Cure (TOC) Specimen

Code No.	Terminology	Definition
60	Microbiological Success-Presumed Eradication	In a patient with no signs or symptoms of active otic infection, a specimen is not collected and therefore it is presumed that the pathogen(s) is eradicated.
61	Microbiological Success-Documented Eradication	Documented eradication of pre-therapy pathogen(s); no microorganisms recovered from TOC specimen, if collected.
62	Microbiological Success-Eradication with Colonization	Documented eradication of pre-therapy pathogen(s) with presence of microorganisms isolated from the TOC specimen and no increase in signs of active otic infection relative to those otic signs present at the EOT Visit.
63	Microbiological Failure-Persistence	Documented persistence of pre-therapy pathogen(s) and no microorganisms recovered from TOC specimen.
64	Microbiological Failure-Persistence with Non-pathogen(s)	Documented persistence of pre-therapy pathogen(s) with presence of microorganism(s) isolated from TOC specimen.
65	Microbiological Failure-Persistence with Reinfection	Documented persistence of pre-therapy pathogen(s) and new pathogen recovered from TOC specimen.
66	Microbiological Failure Due to Reinfection	Bacteria recovered from a specimen taken at TOC is a different pathogen from the pretherapy pathogen in a specimen from a patient with signs or symptoms of active otic infection.
67	Microbiological Failure-Presumed Persistence	No specimen collected from a patient with signs or symptoms of active otic infection so it is presumed pathogens persist.
68	Pre-therapy Culture Negative	Pre-therapy culture status code = 1-Culture Negative.
69	Nonanalyzable	Data is missing, incomplete, erroneous, no pre-therapy specimen collected, or protocol noncompliance, or other considerations.

Appendix K: Central Microbiology Laboratory Manual: Alcon Laboratories, Inc., "Microbiology Support of Clinical Study C-00-52: Safety and Efficacy of Topical CIPRODEX Otic [Ciprofloxacin 0.3%, Dexamethasone 0.1%] Suspension Compared to FLOXIN® Otic [Ofloxacin 0.3%] Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes [AOMT], Investigator Laboratory Manual, on Page 627. The Investigator Laboratory Manual contains information and descriptions on subjects, such as: Introduction and General Information,

Ear Culture Collection

1. Remove swab from paper packaging.
2. Swab infected area of ear as described in the Clinical Protocol
3. Remove the cap from the culture tube containing the transport media
4. Insert swab into the culture tube and press down firmly to assure a proper seal.

The preliminary culture reports will be faxed at 48 hours after receipt into the laboratory. Final reports will be faxed to the site upon conclusion of the work. Hard copies of all faxed reports will follow via first class mail.

Acute Otitis Media with Tympanostomy Tubes (AOMT)

Clinical AOMT Study C-99-59:

C-99-59 Safety and efficacy of CIPRODEX vs. CILOXAN in AOMT:

Multicenter, randomized, observer- masked, active-controlled, parallel- group study in pediatric patients; Visit Days 1, 3, 8, and 14; 14- day study duration; 7- day treatment duration.

Topical otic: CIPRODEX/ CILOXAN - 3 drops BID x 7 days

Enrollment: 201 total patients: 103 CIPRODEX and 98 CILOXAN.

Note: Also refer to **TABLE 1** on Page 13.

Acute Otitis Media with Otorrhea through Tympanostomy Tube

AOMT Patient Listing for Major Pathogens -- All Specimens

MITT and MPP Datasets

TABLE 6 AOMT Study C-99-59: **MITT** Data Set: *Streptococcus pneumoniae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drug Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Streptococcus pneumoniae*:

Total *Streptococcus pneumoniae* isolates = 25

Success = 16/25 (64%)

Failures = 9/25 (36%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (10):

Staphylococcus aureus = 2/3 (66.6%)

Haemophilus influenzae = 1/1 (100%)

Moraxella catarrhalis = 2/2 (100%)

*Polymicrobial culture

TABLE 7 AOMT Study C-00-52: **MITT** Data Set: *Streptococcus pneumoniae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drug Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Streptococcus pneumoniae*:

Total *Streptococcus pneumoniae* isolates = 38

Success = 22/38 (57.9%)

Failures = 16/38 (42.1%)

Other Organisms Cultures* and Ciprofloxacin Microbiological Outcome Success (11):

Staphylococcus aureus	= 0/2 (0%)
Haemophilus influenzae	= 0/2 (0%)
Moraxella catarrhalis	= 0/1 (0%)

*Polymicrobial culture

TABLE 8 **Overall analyses on AOMT Study C-99-59 and Study C-00-52: MITT Data Set: *Streptococcus pneumoniae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients**

Drug Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Streptococcus pneumoniae*:

Overall *Streptococcus pneumoniae* isolates = 63

Success = 38/63 (60.3%)

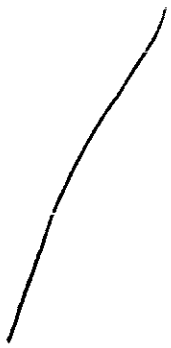
Failures = 25/63 (39.7%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (21):

Staphylococcus aureus = 2/5 (40%)

Haemophilus influenzae = 1/3 (33.3%)

Moraxella catarrhalis = 2/3 (66.6%)



*Polymicrobial culture

TABLE 9 AOMT Study C-99-59: **MPP** Data Set: *Streptococcus pneumoniae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Streptococcus pneumoniae*:

Total *Streptococcus pneumoniae* isolates = 20

Success = 15/20 (75%)

Failures = 5/20 (25%)

Other Organisms Cultured and Ciprofloxacin Microbiological Outcome Success (10):

Staphylococcus aureus = 2/2 (100%)

Haemophilus influenzae = 1/1 (100%)

Moraxella catarrhalis = 2/2 (100%)

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

TABLE 11 **Overall** analyses on AOMT Study C-99-59 and Study C-00-52: **MPP** Data Set: *Streptococcus pneumoniae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drug Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Streptococcus pneumoniae*:

Overall *Streptococcus pneumoniae* isolates = 47

Success = 37/47 (78.7%)

Failures = 10/47 (21.3%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (19):

Staphylococcus aureus = 2/3 (66.6%)

Haemophilus influenzae = 1/2 (50%)

Moraxella catarrhalis = 2/2 (100%)

*Polymicrobial culture

TABLE 12 AOMT Study C-99-59: **MITT** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Total *Staphylococcus aureus* isolates = 21

Success = 17/21 (81%)

Failures = 4/21 (19%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (15):

Streptococcus pneumoniae = 2/3 (66.6%)

Moraxella catarrhalis = 1/1 (100%)

Pseudomonas aeruginosa = 3/5 (60%)

*Polymicrobial culture

TABLE 13 AOMT Study C-00-52: **MITT** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Total *Staphylococcus aureus* isolates = 40

Success = 33/40 (82.5%)

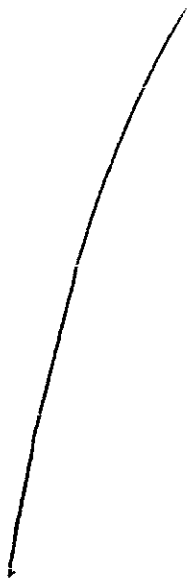
Failures = 7/40 (17.5%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (18):

Streptococcus pneumoniae = 0/1 (0%)

Moraxella catarrhalis = 1/1 (100%)

Pseudomonas aeruginosa = 2/4 (50%)



*Polymicrobial culture

TABLE 14 **Overall analyses on AOMT Study C-99-59 and Study C-00-52: MITT Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients**

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Overall *Staphylococcus aureus* isolates = 61

Success = 50/61 (82%)

Failures = 11/61 (18%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (33):

Streptococcus pneumoniae = 2/4 (50%)

Moraxella catarrhalis = 2/2 (100%)

Pseudomonas aeruginosa = 5/9 (55.60%)

*Polymicrobial culture

TABLE 15 AOMT Study C-99-59: **MPP** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Total *Staphylococcus aureus* isolates = 17

Success = 17/17 (100%)

Failures = 0/17 (0%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (11):

Streptococcus pneumoniae = 2/2 (100%)

Moraxella catarrhalis = 1/1 (100%)

Pseudomonas aeruginosa =3/3 (100%)

*Polymicrobial culture

TABLE 16 AOMT Study C-00-52: **MPP** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Total *Staphylococcus aureus* isolates = 37

Success = 32/37 (86.5%)

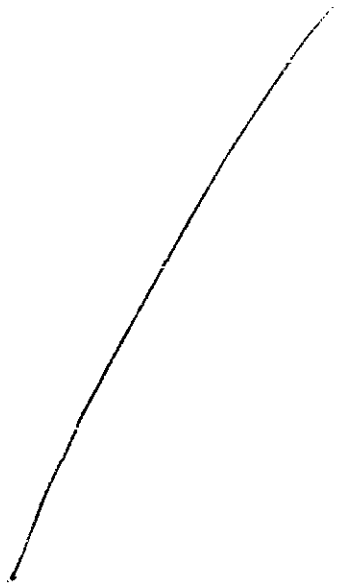
Failures = 5/37 (13.5%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (17):

Streptococcus pneumoniae = 2/2 (100%)

Moraxella catarrhalis = 0/1 (0%)

Pseudomonas aeruginosa = 2/2 (100%)



* Polymicrobial culture

TABLE 17 **Overall** analyses AOMT Study C-99-59 and Study C-00-52: **MPP** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: *ciprofloxacin*

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Overall *Staphylococcus aureus* isolates = 54

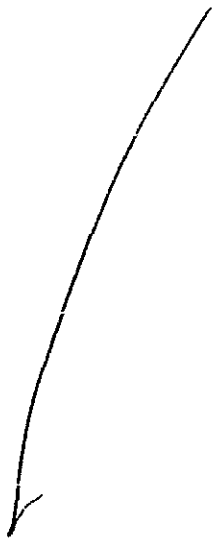
- Success = 49/54 (90.7%)
- Failures = 5/54 (9.3%)

Overall Other Organisms Cultured and Ciprofloxacin Microbiological Outcome Success (28):

Streptococcus pneumoniae = 4/4 (100%)

Moraxella catarrhalis = 1/2 (50%)

Pseudomonas aeruginosa = 5/5 (100%)



* Polymicrobial culture

TABLE 18 AOMT Study C-99-59: **MITT** Data Set: *Haemophilus influenzae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Haemophilus influenzae*:

Total *Haemophilus influenzae* isolates = 9

Success = 6/9 (66.6%)

Failures = 3/9 (33.3%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5):

Streptococcus pneumoniae = 1/1 (100%)

Haemophilus influenzae subsp. nov. = 0/1 (0%)

Moraxella catarrhalis = 1/1 (100%)

* Polymicrobial culture

TABLE 19 AOMT Study C-00-52: **MITT** Data Set: *Haemophilus influenzae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Haemophilus influenzae*:

Total *Haemophilus influenzae* isolates = 29

Success = 19/29 (65.5%)

Failures = 10/29 (34.5%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (22):

Streptococcus pneumoniae = 0/2 (0%)

Moraxella catarrhalis = 0/1 (0%)

* Polymicrobial culture

TABLE 20 **Overall** analyses on AOMT Study C-99-59 and C-00-52: **MITT** Data Set: *Haemophilus influenzae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Haemophilus influenzae*:

Overall *Haemophilus influenzae* isolates = 38

Success = 25/38 (65.8%)

Failures = 13/38 (34.2%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (27):

Streptococcus pneumoniae = 1/3 (33.3%)

Moraxella catarrhalis = 1/2 (50%)

* Polymicrobial culture

TABLE 21 AOMT Study C-99-59: **MPP** Data Set: *Haemophilus influenzae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Haemophilus influenzae*:

Total *Haemophilus influenzae* isolates = 5

Success = 5/5 (100%)

Failures = 0/0 (0%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (4):

Streptococcus pneumoniae = 1/1 (100%)

Haemophilus influenzae subsp. nov. = 0/1 (0%)

Moraxella catarrhalis = 1/1 (100%)

* Polymicrobial culture

TABLE 22 AOMT Study C-00-52: **MPP** Data Set: *Haemophilus influenzae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Haemophilus influenzae*:

Total *Haemophilus influenzae* isolates = 25

Success = 19/25 (76%)

Failures = 6/25 (24%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (18):

Streptococcus pneumoniae = 0/1 (0%)

Moraxella catarrhalis = 0/1 (0%)

* Polymicrobial culture

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TABLE 23 Overall analyses on AOMT Study C-99-59 and Study C-00-52: MPP Data Set: *Haemophilus influenzae* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Haemophilus influenzae*:

Overall *Haemophilus influenzae* isolates = 30

Success = 24/30 (80%)

Failures = 6/30 (20%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (22):

Streptococcus pneumoniae = 1/2 (50%)

Moraxella catarrhalis = 1/2 (50%)

* Polymicrobial culture

TABLE 24 AOMT Study C-99-59: **MITT** Data Set: *Moraxella catarrhalis* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Moraxella catarrhalis*:

Total *Moraxella catarrhalis* isolates = 4

Success = 4/4 (100%)

Failures = 0/0 (0%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5):

Staphylococcus aureus = 1/1 (100%)

Streptococcus pneumoniae = 2/2 (100%)

Haemophilus influenzae = 1/1 (100%)

* Polymicrobial culture

TABLE 25 AOMT Study C-00-52: **MITT** Data Set: *Moraxella catarrhalis* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Moraxella catarrhalis*:

Total *Moraxella catarrhalis* isolates = 10

Success = 6/10 (60%)

Failures = 4/10 (40%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (6):

Staphylococcus aureus = 1/1 (100%)

Streptococcus pneumoniae = 0/1 (0%)

Haemophilus influenzae isolates = 0/1 (0%)

* Polymicrobial culture

TABLE 26 **Overall** analyses on AOMT Study C-99-59 and Study C-00-52: **MITT** Data Set: *Moraxella catarrhalis* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Moraxella catarrhalis*:

Overall *Moraxella catarrhalis* isolates = 14

Success = 10/14 (71.4%)

Failures = 4/14 (28.6%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (11):

Staphylococcus aureus = 2/2 (100%)

Streptococcus pneumoniae = 2/3 (66.6%)

Haemophilus influenzae isolates = 1/2 (50%)

* Polymicrobial culture

TABLE 27 AOMT Study C-99-59: **MPP** Data Set: *Moraxella catarrhalis* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Moraxella catarrhalis*:

Total *Moraxella catarrhalis* isolates = 4

Success = 4/4 (100%)

Failures = 0/0 (0%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5):

Staphylococcus aureus = 1/1 (100%)

Streptococcus pneumoniae = 2/2 (100%)

Haemophilus influenzae = 1/1 (100%)

* Polymicrobial culture

TABLE 28 AOMT Study C-00-52: **MPP** Data Set: *Moraxella catarrhalis* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Moraxella catarrhalis*:

Total *Moraxella catarrhalis* isolates = 7

Success = 6/7 (85.7%)

Failures = 1/7 (14.3%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5):

Staphylococcus aureus = 1/1 (100%)

Haemophilus influenzae isolates = 0/1 (0%)

* Polymicrobial culture

TABLE 29 **Overall** analyses on AOMT Study C-99-59 and Study C-00-52: **MPP** Data Set:
Moraxella catarrhalis **Recovered** at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Moraxella catarrhalis*:

Overall *Moraxella catarrhalis* isolates = 11

Success = 10/11 (90.9%)

Failures = 1/11 (9.1%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (10):

Staphylococcus aureus = 2/2 (100%)

Streptococcus pneumoniae = 2/2 (100%)

Haemophilus influenzae = 1/2 (50%)

* Polymicrobial culture

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TABLE 30 AOMT Study C-99-59: **MITT** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

Total *Pseudomonas aeruginosa* isolates = 14

Success = 11/14 (78.6%)

Failures = 3/14 (27.3%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (8):

Staphylococcus aureus = 3/5 (60%)

* Polymicrobial culture

TABLE 31 AOMT Study C-00-52: **MITT** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

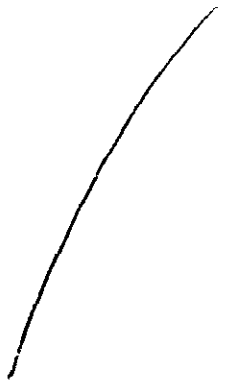
Total *Pseudomonas aeruginosa* isolates = 41

Success = 36/41 (87.8%)

Failures = 5/41 (12.2%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (20):

Staphylococcus aureus = 3/4 (75%)



* Polymicrobial culture

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TABLE 32 **Overall** analyses on AOMT Study C-99-59 and Study C-00-52: **MITT** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

Overall *Pseudomonas aeruginosa* isolates = 55

Success = 47/55 (85.5%)

Failures = 8/55 (14.5%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (28):

Staphylococcus aureus = 6/9 (66.6%)

* Polymicrobial culture

TABLE 33 AOMT Study C-99-59: **MPP** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

Total *Pseudomonas aeruginosa* isolates = 11

Success = 11/11 (100%)

Failures = 0/11 (0%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5):

Staphylococcus aureus = 3/3 (75%)

* Polymicrobial culture

TABLE 34 AOMT Study C-00-52: **MPP** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

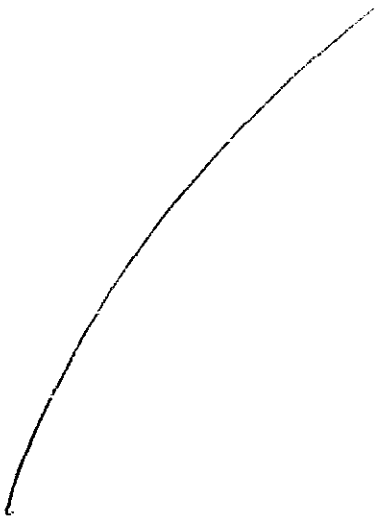
Overall *Pseudomonas aeruginosa* isolates = 36

Success = 35/36 (97.2%)

Failures = 1/36 (2.8%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (17):

Staphylococcus aureus = 2/2 (100%)



* Polymicrobial culture

TABLE 35 **Overall** analyses on AOMT Study C-00-52: **MPP** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit **from** CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

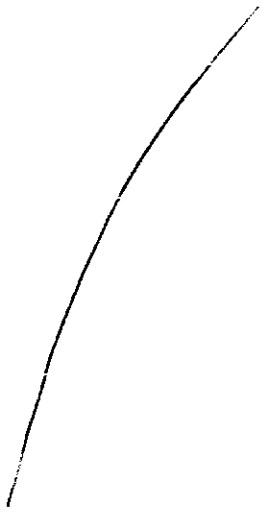
Overall *Pseudomonas aeruginosa* isolates = 47

Success = 46/47 (97.9%)

Failures = 1/47 (2.1%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (22):

Staphylococcus aureus = 5/5 (100%)



* Polymicrobial culture

Acute Otitis Media with Otorrhea through Tympanostomy Tube

AOMT Patient Listing for Major Pathogens -- All Specimens

Additional MPP Datasets

TABLE 36 AOMT Study C-00-59: **MPP** Data Set. Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (17):

Streptococcus pneumoniae = 1/1 (100%)

* Polymicrobial culture

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TABLE 37 AOMT Study C-00-52: **MPP** Data Set Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured and Ciprofloxacin Microbiological Outcome Success (20):

Streptococcus pneumoniae = 3/3 (100%)

Haemophilus influenzae = 3/5 (60%)

Moraxella catarrhalis = 1/2 (50%)

Pseudomonas aeruginosa = 4/4 (100%)

TABLE 38 Overall analyses on AOMT Study C-00-59 and Study C-00-52: MPP Data Set
Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (21):

Streptococcus pneumoniae = 4/4 (100%)

Haemophilus influenzae = 3/5 (60%)

Moraxella catarrhalis = 1/2 (50%)

Pseudomonas aeruginosa = 4/4 (100%)

* Polymicrobial culture

TABLE 39 Overall analyses on AOMT Study C-00-59: **MPP** Data Set
Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (4):

Streptococcus pneumoniae = 1/1 (100%)

Haemophilus influenzae = 1/1 (100%)

Moraxella catarrhalis = 1/1 (100%)

* Polymicrobial culture

TABLE 40 AOMT Study C-99-59: **MPP** Data Set — Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus —

Table 41 AOMT Study C-00-52: **MPP** Data Set: — Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus —

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (2):

Staphylococcus aureus = 1/1 (100%)

* Polymicrobial culture

TABLE 42 Overall analyses on AOMT Study C-99-59 and Study C-00-52: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (20):

Staphylococcus aureus = 1/1 (100%)

* Polymicrobial culture

TABLE 43

OVERALL SUMMARY ANALYSES of the ACUTE OTITIS MEDIA with OTORRHEA THROUGH TYMPANOSTOMY TUBE (AOMT)

PATIENT LISTING for MAJOR PATHOGENS -- ALL SPECIMENS

MPP MICROBIOLOGICAL OUTCOME

Overall *Pseudomonas aeruginosa* isolates = 47
Success = 46/47 (97.9%) Failures = 1/47 (2.1%)

Overall *Staphylococcus aureus* isolates = 54
Success = 49/54 (90.7%) Failures = 5/54 (9.3%)

Overall *Streptococcus pneumoniae* isolates = 47
Success = 37/47 (78.7%) Failures = 10/47 (21.3%)

Overall *Haemophilus influenzae* isolates = 30
Success = 24/30 (80%) Failures = 6/30 (20%)

Overall *Moraxella catarrhalis* isolates = 11
Success = 10/11 (90.9%) Failures = 1/11 (9.1%)

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Acute Otitis Externa (AOE)

AOE Patient Listing for Major Pathogens -- All Specimens

MPP Datasets

TABLE 77 AOE Study C-98-18: **MPP** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Total *Staphylococcus aureus* isolates = 19

Success = 17/19 (89.5%)

Failures = 2/19 (10.5%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (12):

Pseudomonas aeruginosa = 1/4 (25%)

*Polymicrobial culture

TABLE 78 AOE Study C-98-19: **MPP** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Total *Staphylococcus aureus* isolates = 24

Success = 21/24 (87.5%)

Failures = 3/24 (12.5%)

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (19):

Pseudomonas aeruginosa = 2/2 (100%)

*Polymicrobial culture

TABLE 79 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: *Staphylococcus aureus* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

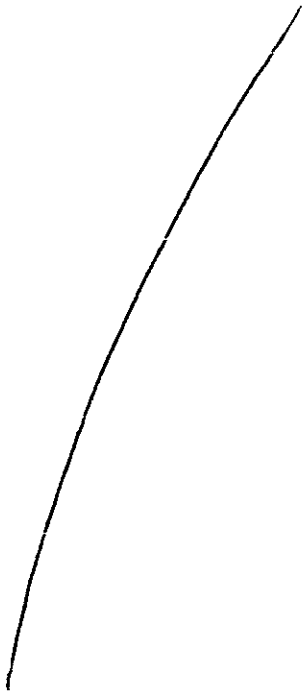
Microbiological Outcomes for Ciprofloxacin versus *Staphylococcus aureus*:

Overall *Staphylococcus aureus* isolates = 43

- Success = 38/43 (88.4%)
- Failures = 5/43 (11.6%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (31):

Pseudomonas aeruginosa = 3/6 (50%)



*Polymicrobial culture

TABLE 80 AOE Study C-98-18: **MPP** Data Set. Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (11):

Staphylococcus aureus = 1/1 (100%)

Pseudomonas aeruginosa = 5/6 (83.3%)

*Polymicrobial culture

TABLE 81 AOE Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (6):

Staphylococcus aureus = 1/1 (100%)

Pseudomonas aeruginosa = 1/2 (50)

*Polymicrobial culture

TABLE 82 Overall analyses on AOE Study C-98-18 and Study C-98-19: MPP Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (17):

Staphylococcus aureus = 2/2 (100%)

Pseudomonas aeruginosa = 6/8 (75%)

* Polymicrobial culture

TABLE 83 AOE Study C-98-18: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (15)

Staphylococcus aureus = 1/1 (100%)

Pseudomonas aeruginosa = 6/8 (75%)

*Polymicrobial culture

TABLE 84 AOE Study C-98-19 **MPP** Data Set: s Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (6)

Staphylococcus aureus = 2/2 (100%)

Pseudomonas aeruginosa = 1/2 (50%)

Polymicrobial culture

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TABLE 85 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (21)

Staphylococcus aureus = 3/3 (100%)

Pseudomonas aeruginosa = 7/10 (70%)

*Polymicrobial culture

TABLE 86 AOE Study C-98-18: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (2)

Pseudomonas aeruginosa = 1/2 (50%)

*Polymicrobial culture

TABLE 87 AOE Study C-98-19: **MPP** Data Set Recovered at
Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (11)

Staphylococcus aureus = 1/2 (50%)

Pseudomonas aeruginosa = 2/5 (40%)

*Polymicrobial culture

Note: The following are included in the aforementioned organisms. The organisms are cultured from 1-patient, i.e., a polymicrobial culture, however, the "Visit" is designated as "U" (unknown). All are microbiological "Not Success" ("Microbiological Failures").

Staphylococcus aureus
Pseudomonas aeruginosa

TABLE 88 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (13)

Staphylococcus aureus = 1/2 (50%)

Pseudomonas aeruginosa = 3/7 (42.9%)

*Polymicrobial culture

TABLE 89 AOE Study C-98-18: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (10)

Pseudomonas aeruginosa = 4/5 (80%)

*Polymicrobial culture

TABLE 90 AOE Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (6)

Pseudomonas aeruginosa = 4/4 (100%)

TABLE 91 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: **Recovered at** Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (16)

Pseudomonas aeruginosa = 8/9

*Polymicrobial culture

TABLE 92 AOE Study C-98-18: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (4)

Pseudomonas aeruginosa = 1/2 (50%)

*Polymicrobial culture

TABLE 93 AOE Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (3)

Staphylococcus aureus = 1/1 (100%)

Pseudomonas aeruginosa = 2/2 (100%)

*Polymicrobial culture

TABLE 94 **Overall** Analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: Recovered at **Pre-therapy** Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (7)

Staphylococcus aureus = 1/1 (100%)

Pseudomonas aeruginosa = 3/4 (75%)

*Polymicrobial culture

TABLE 95 AOE Study C-98-18 **MPP** Data Set: ecovered at Pre-therapy Visit
from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (6)

Pseudomonas aeruginosa = 2/2 (100%)

*Polymicrobial culture

TABLE 96 AOE Study C-98-19 **MPP** Data Set: Recovered at Pre-therapy Visit
from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (2)

Pseudomonas aeruginosa = 1/1 (100%)

*Polymicrobial culture

TABLE 97 Overall analyses on AOE Study C-98-18 and Study C-98-19 MPP Data Set: .ecovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (8)

Pseudomonas aeruginosa = 3/3 (100%)

*Polymicrobial culture

TABLE 98 AOE Study C-98-18: **MPP** Data Set Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (8)

Pseudomonas aeruginosa = 3/4 (75%)

*Polymicrobial culture

TABLE 99 AOE Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (1)

Pseudomonas aeruginosa = 1/1 (100%)

*Polymicrobial culture

TABLE 100 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set , Recovered at **Pre-therapy** Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (9)

Pseudomonas aeruginosa = 4/5 (80%)

*Polymicrobial culture

TABLE 101 AOE Study C-98-18: **MPP** Data Set: Recovered at
Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (3)

Pseudomonas aeruginosa = 2/2 (100%)

*Polymicrobial culture

TABLE 102 AOE Study C-98-19: **MPP** Data Set Recovered at
Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (1)

Pseudomonas aeruginosa = 1/1 (100%)

*Polymicrobial culture

TABLE 103 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: **Recovered at Pre-therapy** Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success(4)

Pseudomonas aeruginosa = 3/3 (100%)

*Polymicrobial culture

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TABLE 104 AOE Study C-98-18: **MPP** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

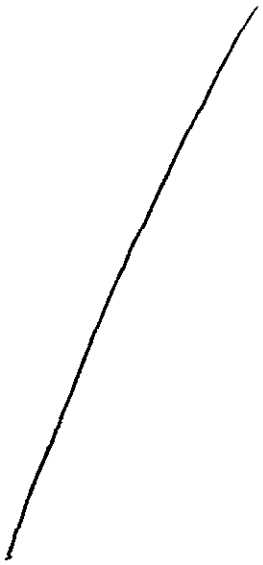
Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

Total *Pseudomonas aeruginosa* isolates = 146

Success = 124/146 (84.9)
Failures = 22/146 (15.1%)

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (50)

Staphylococcus aureus = 2/4 (50%)



*Polymicrobial culture

TABLE 105 AOE Study C-98-19: **MPP** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

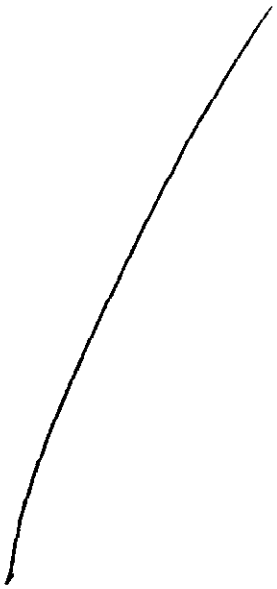
Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

Total *Pseudomonas aeruginosa* isolates = 97

Success = 91/97 (93.8%)
Failures = 6/97 (6.2%)

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (35)

Staphylococcus aureus = 2/2 (100%)



*Polymicrobial culture

TABLE 106 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: *Pseudomonas aeruginosa* Recovered at Pre-therapy Visit from CiproDex-Treated Patients

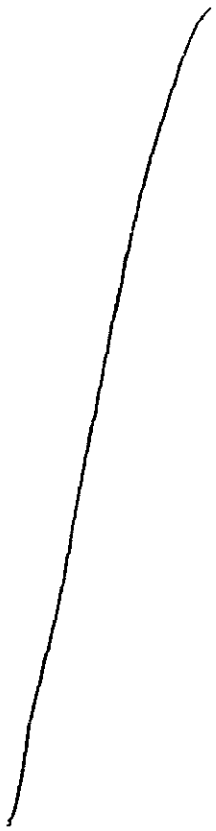
Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus *Pseudomonas aeruginosa*:

Overall *Pseudomonas aeruginosa* isolates = 243

- Success = 215/243 (84.9)
- Failures = 28/146 (15.1%)

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (85)
Staphylococcus aureus = 4/6 (66.6%)



* Polymicrobial culture

TABLE 107 AOE Study C-98-18: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (2)

Staphylococcus aureus = 1/1 (100%)

*Polymicrobial culture

TABLE 108 AOE Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (8)

Staphylococcus aureus =3/3 (100%)

*Polymicrobial culture

TABLE 109 Overall analyses on AOE Study C-98-18 and Study C-98-19: MPP Data Set
Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

5

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (10)

Staphylococcus aureus =4/4 (100%)

*Polymicrobial culture

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TABLE 110 AOE Study C-98-18: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5)

*Polymicrobial culture

TABLE 111 AOE Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (4)

Pseudomonas aeruginosa = 1/1 (100%)

*Polymicrobial culture

TABLE 112 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (9)

Pseudomonas aeruginosa = 1/1 (100%)

* Polymicrobial culture

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TABLE 113 AOE Study C-98-18: **MPP** Data Set:
Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (1)

* Polymicrobial culture

TABLE 114 AOE Study C-98-19: **MPP** Data Set:
Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versu

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (2)

Pseudomonas aeruginosa = 1/1 (100%)

* Polymicrobial culture

TABLE 115 Overall analyses on AOE Study C-98-18 and Study C-98-19: MPP Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (3)

Pseudomonas aeruginosa = 1/1 (100%)

* Polymicrobial culture

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TABLE 116 AOE Study C-98-18: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5)

Pseudomonas aeruginosa = 2/2 (100%)

Polymicrobial culture

TABLE 117 AOE Study C-98-19: **MPP** Data Set: Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Total Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (5)

Pseudomonas aeruginosa = 2/2 (100%)

TABLE 118 **Overall** analyses on AOE Study C-98-18 and Study C-98-19: **MPP** Data Set
Recovered at Pre-therapy Visit from CiproDex-Treated Patients

Drugs Tested: ciprofloxacin

Microbiological Outcomes for Ciprofloxacin versus

Overall Other Organisms Cultured* and Ciprofloxacin Microbiological Outcome Success (10)

Pseudomonas aeruginosa = 4/4 (100%)

*Polymicrobial culture

TABLE 119

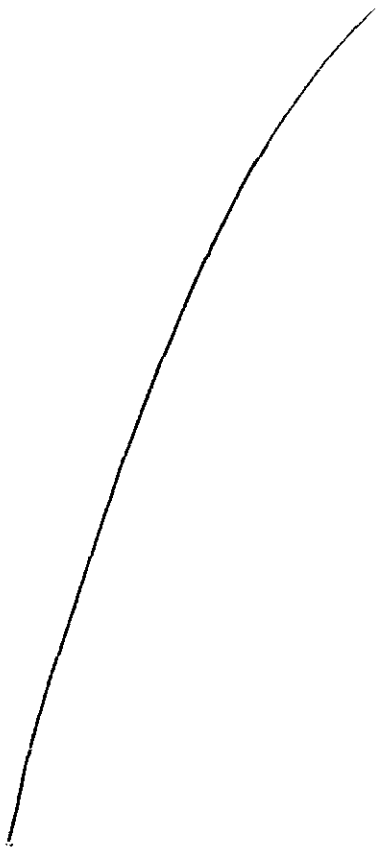
OVERALL SUMMARY ANALYSES for ACUTE OTITIS EXTERNA (AOE)

PATIENT LISTING for MAJOR PATHOGENS -- ALL SPECIMENS

MPP MICROBIOLOGICAL OUTCOME

Overall *Pseudomonas aeruginosa* isolates = 243
Success = 215/243 (84.9) Failures = 28/146 (15.1%)

Overall *Staphylococcus aureus* isolates = 43
Success = 38/43 (88.4%) Failures = 5/43 (11.6%)



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V. CLINICAL MICROBIOLOGY REVIEWER'S CONCLUSIONS ON NDA 21-537

From the Clinical Microbiology Reviewer's perspective, an "approval" letter should be issued to Alcon Inc. after negotiation of the most current revised "draft" labeling on NDA 21-537. This includes all the Agency's labeling recommendations in the **MICROBIOLOGY** section, and found in this Clinical Microbiology Review on the aforementioned pages 154 to 157, respectively.

cc: Orig. NDA 21-537
HFD-638
HFD-520/DivFile
HFD-520/Div.Dir./J.Soreth
HFD-520/TL/J.Mulinde
HFD-520/MO/T.Smith
HFD-880/BP/P.Buehler
HFD-520/PM/D.Nguyen
HFD-520/PM/S.Samanta
HFD-520/Micro/H.V.Silver
Filename: N21537FIN
APPROVAL

Concurrence Only:
HFD-520/TLMicro/A.T.Sheldon
RD & Final Initialed 7/17/03 ATS
HFD-520/DepDir/L.Gavrilovich

VI. BIBLIOGRAPHY

[1] Lovdahl M., J. Steury, H. Russllile and D.M. Canafax. 1993. Determination of Ciprofloxacin Levels in Chinchilla Middle Ear Effusion and Plasma by High-Performance Liquid Chromatography with Fluorescence Detection. *J. Chromatog.* **617**:329-333.

[2] Bagger-Sjoback, D., L. Lundman, and I. Nilsson-Ehle. 1992 Ciprofloxacin and the Inner Ear – A Morphological and Round Window Menbrane Permeability Study. J. Otorhinolaryngol. **54**(1):5–9.

[3] Force R.W., M.C. Hart, S.A. Plummer, D.A. Powell, and M.C. Nahata. 1995 Topical ciprofloxacin for otorrhea after tympanostomy tube placement. *Arch Otolaryngol Head Neck Surg.* **121**(August): 880- 884.

[4] Zirker, D. K., B.S. Gerald G. Krueger, M.D., and A. Wayne Merkle, M.D. 1976. PERCUTANEOUS ABSORPTION OF DEXAMETHASONE ESTIMATED By A PLASMA RADIOIMMUNOASSAY. Diuision of Dermatalogy (DKZ, GGK), Uniuersity of Utah College of Medicine, and Departments of Medicine (AWM), Veterans Administration Hospital and University of Utah College of Medicine, Salt Lake City, Utah.

[5] Moriello, Karen A., D.V.M., Susan L. Fehrer-Sawyer, D.V.M., D.J. Meyer, D.V.M. and, Brett Feder, B.S. 1988. Adrenocortical suppression associated with topical otic administration of glucocorticoids in dogs. *JAVMA*. Vol. 193, No. 3, August 1.

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/s/

Harold Silver
7/17/03 01:40:30 PM
MICROBIOLOGIST

Albert Sheldon
7/17/03 03:11:56 PM
MICROBIOLOGIST

Lillian Gavrilovich
7/21/03 04:58:24 PM
MEDICAL OFFICER

Product Quality Microbiology Review

Consult review for HFD-520

3 FEBRUARY, 2003

NDA:	NDA 21-537
Name of Drug:	CIPRODEX Otic suspension
Review Number:	1
Submission Date:	25 July, 2002
Applicant:	Alcon Research, Ltd.
Name of Reviewer:	Vinayak Pawar
Conclusion:	The application is recommended for approval from microbiological standpoint.

APPEARS THIS WAY
ON ORIGINAL

Product Quality Microbiology Data Sheet

A. 1. **NDA:** NDA 21-537

2. **REVIEW NUMBER:** 1

3. **REVIEW DATE:** 3, February, 2003

4. **TYPE OF SUPPLEMENT:** NA

5. **APPLICATION FOR:** New suspension for Otic infections

6. **APPLICANT/SPONSOR:**

Name: Alcon Research, Ltd.
Representative: Seane D. Jones
Telephone: 817-568-6296

7. **MANUFACTURING SITE:** Fort Worth, Texas

8. **DRUG PRODUCT NAME:**
Proprietary: Ciprodex Otic suspension
Non-proprietary: Ciprofloxacin HCL [redacted] Dexamethasone 0.1% otic suspension
Drug Priority Classification: Standard

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Cipro 0.3% w/v & Dex 0.1% w/v

10. **METHOD (S) OF STERILIZATION:** [redacted]

11. **PHARMACOLOGICAL CATEGORY:** Otic suspension

B. 1. **DOCUMENT/LETTER DATE:** July 25, 2002
2. **RECEIPT DATE:** July 9, 2002
3. **CONSULT DATE:** Sept 23, 2002
4. **DATE OF AMENDMENTS:** NA
5. **ASSIGNED FOR REVIEW:** October 21, 2002
6. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** The consult requests review of a new drug application NDA 21-537 for the manufacture of Ciprodex Otic Suspension in the treatment of Acute otitis externa and acute otitis media with tympanostomy tubes (AOE & AOMT). One volume of the application was submitted for review of sterilization validation package.

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The sterilization validation data assures adequate product safety and therefore the application is recommended for approval from the microbiology standpoint.

B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable
NA

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology
The product is manufactured

B. Brief Description of Microbiology Deficiencies
None

C. Assessment of Risk Due to Microbiology Deficiencies-
None

III. Administrative

A. Reviewer's Signature _____

B. **Endorsement Block**
Vinayak Pawar/3 February, 2003
Peter H. Cooney/

C. CC Block
cc:
Original NDA 21-537
HFD-520/Division File/Daniel Nguyen

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Vinayak Pawar
2/20/03 01:33:40 PM
MICROBIOLOGIST

Peter Cooney
2/21/03 08:12:51 AM
MICROBIOLOGIST