CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-799

MEDICAL REVIEW

Medical Officer's Review of NDA 20-799

FLOXIN® Otic

(Ofloxacin Otic Solution) 0.3%

GENERAL INFORMATION

NDA Submission Number:	NDA 20-799 (385 Volumes)
Applicant Identification:	Daiichi Pharmaceutical Corporation One Parker Plaza Fort Lee, New Jersey 07024 Ph: (201) 944-4333 Fax: (201) 944-4364
Applicant Contact Official:	Amy S. Domanowski, Ph.D. Director, Regulatory Affairs Ph: (201) 944-5608
Applicant's Letter Date:	12/18/96
CDER Stamp Date:	12/18/96
Date Assigned to Reviewer:	12/30/96
Date Review Begun:	1/21/97
Amendments:	SU 04/24/97 Safety Update BI 05/12/97 Minor Microbiology AC 05/30/97 Major Chemistry BC 07/31/97 Minor Chemistry BM 09/17/97 Minor Clinical BC 09/25/97 Minor Chemistry BM 10/08/97 Minor Clinical BM 11/04/97 Minor Clinical BM 11/17/97 Minor Clinical BL 11/17/97 Minor Draft Labeling BI 11/18/97 Minor Microbiology BI 11/25/97 Minor Microbiology BS 11/26/97 Minor Statistical BL 12/05/97 Minor Draft Labeling BL 12/12/97 Minor Draft Labeling BL 12/15/97 Minor Draft Labeling
Date Review Completed:	12/31/97

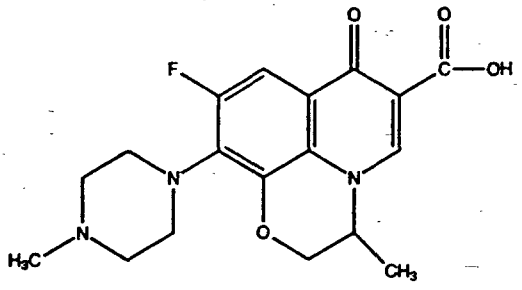
DRUG IDENTIFICATION

Generic Name of Drug: Ofloxacin Otic Solution 0.3%

Proposed Trade Name: FLOXIN® Otic

Chemical Name: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.

Chemical Structure:



Molecular Formula: $C_{18}H_{20}FN_3O_4$

Molecular Weight: 361.38

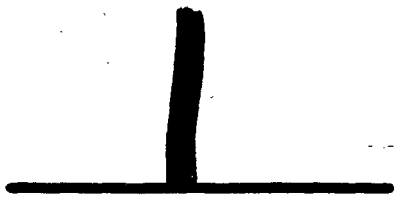
Pharmacologic Category: Ofloxacin is an anti-infective agent of the fluoroquinolone class.

Dosage Form: FLOXIN® Otic is a solution which contains 0.3% (3mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5±0.5.

Route of Administration: FLOXIN® Otic is to be administered topically.

PROPOSED INDICATION AND USAGE SECTION

The following information has been excerpted verbatim from the Applicant's Draft Package Insert:

Redacted 

pages of trade secret and/or confidential commercial information

RELATED DRUGS

The Applicant has listed the following INDs, NDAs and DMF as being cross-referenced in this NDA for FLOXIN® Otic (ofloxacin otic solution) 0.3%:

Ofloxacin has been studied under the following INDs:

IND

IND

IND

IND

The following NDAs are cross-referenced:

NDA 19-735
Ofloxacin Tablets
The R. W. Johnson Pharmaceutical Research Institute

NDA 20-087
Ofloxacin Injection (I.V.)
The R. W. Johnson Pharmaceutical Institute

NDA 19-921
Ofloxacin Ophthalmic Solution
Allergan, Inc.

The following DMF is also cross-referenced:

DMF

REGULATORY BACKGROUND

- Previous Actions on NDA 20-799: None
- End-of-Phase II Meeting: No End-of-Phase II Meeting was held.

CHEMISTRY/MANUFACTURING CONTROLS (CMC)

Ofloxacin otic solution is formulated as a clear pale to light yellow solution containing 0.3% ofloxacin. The vehicle contains 0.0025% benzalkonium chloride (added as a preservative), 0.9% sodium chloride and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH (6.0 - 7.0). Ofloxacin 0.3% otic sterile solution is packaged in 5 ml multiple-dose plastic bottles.

For a complete review of the CMC data, please see the four reviews by B.V. Shetty, Ph.D., dated 1/15/97, 6/4/97, 10/8/97, and 12/1/97.

ANIMAL PHARMACOLOGY/TOXICOLOGY

Studies in animals included 3 pharmacokinetic studies and 18 toxicology studies. The major findings are summarized below:

- Ofloxacin did not induce sensitization in guinea pigs.
- 0.3-0.5% solutions did not cause ocular irritation in rabbits
- Oral dosing (200mg/kg/day) for one month did not appear ototoxic to guinea pigs.
- Guinea pigs dosed intratympanically with ofloxacin for 7-30 days showed no signs of systemic quinolone toxicity.

Findings specifically from 30-day intratympanic administration of ofloxacin to guinea pigs included the following:

- 0.3% ofloxacin solution was not associated with significant hearing loss (measured via ABR)
- 0.3% solution was not associated with significant hair cell loss
- 0.3% solution was minimally irritating to middle ear (not significantly more than vehicle)
- No changes in the ossicles or ossicular articulations were observed.
- In 9/10 animals, 1.0% ofloxacin solution was not associated with signs of ototoxicity.
- One animal had cochlear hair cell loss and moderate hearing loss as measured by ABR.
- 1% solution was irritating to the middle ear, but did not appear to cause "blistering" of the cartilage at ossicular articulations.
- Ofloxacin did not appear to accumulate and no clinical signs of systemic toxicity were seen in the guinea pigs.

For a complete review of the animal pharmacology and toxicology data, please see the review by Amy Ellis, Ph.D., dated 9/25/97.

Medical Officer's Comment: *Based on the information presented on studies performed in guinea pigs, ofloxacin otic 0.3% solution should be reasonably safe for 10-14 days of therapy for the clinical indications requested by the Applicant.*

MICROBIOLOGY

Ofloxacin exerts its antibacterial activity by inactivating subunit A (Gyr A) of the deoxyribonucleic acid (DNA) gyrase holoenzyme, a topoisomerase II, and to a lesser extent, the antagonism of topoisomerase IV.

Based on *in vitro* data, the spectrum of antibacterial activity of ofloxacin includes gram-negative bacteria, including: *Pseudomonas aeruginosa, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, and Proteus mirabilis.*

Ofloxacin also has *in vitro* activity against aerobic gram-positive bacteria such as staphylococci (including *Staphylococcus aureus* and *Staphylococcus epidermidis*); streptococci (including *Streptococcus pneumoniae* and *Streptococcus pyogenes*); and enterococci such as *Enterococcus faecalis.*

Medical Officer's Comment: *The data submitted in this NDA demonstrate that ofloxacin has in vitro activity against a number of microbial species, including the organisms requested by the Applicant in the proposed labeling. However, the intrepretation of in vitro susceptibility data is predicated on breakpoints established for systemic use, and correlation of this data to otic use has not been established.*

For further discussion of the microbiological data presented in this NDA, please see the review of James King, Ph.D., dated 9/3/97.

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

Two Phase I studies were undertaken in the U.S. in order to assess the pharmacokinetic profile of ofloxacin after a single dose administration of the otic solution in subjects with tympanostomy tubes. A secondary objective of these studies was to demonstrate penetration of ofloxacin from the external canal through a patent tympanostomy tube to the middle ear as determined by the presence or absence of fluorescence and bitter taste in the pharynx after dosing. One study was performed in subjects without otorrhea (Protocol 004) and one in subjects with otorrhea (Protocol 005). These two studies are briefly reviewed by the Medical Officer below. For further details, please see the review by Jenny Zheng, Ph.D., dated 7/17/97.

Protocol 8280A-PRT004

Title:

"Single Dose, Double-Blind, Placebo-controlled, Parallel Group Study to Assess the Pharmacokinetics and Penetration of Ofloxacin Otic Solution Through a Tympanostomy Tube in Adults Without Active Otitis Media."

Study Objectives:

To determine the pharmacokinetic profile of ofloxacin after a single dose administration of ofloxacin otic solution, and to determine the time to penetration of ofloxacin from the external ear canal through a patent tympanostomy tube to the middle ear as determined by the presence or absence of fluorescence in the pharynx and bitter taste experience after dosing.

Study Summary:

- Twenty-five subjects who were at least 18 years of age with tympanostomy tubes in place and had no signs or symptoms of middle or external ear infection were enrolled in the study.
- 17 subjects received ofloxacin; 8 subjects received placebo.
- 5/17 ofloxacin-treated subjects had measurable serum levels at sufficient time points to allow for pharmacokinetic calculations.
- The highest C_{max} observed was 5.17ng/ml with a mean C_{max} of 4.1 ng/ml. The mean T_{max} and AUC_t calculated from the serum data available was 0.8 hours and 17.7ng/ml * hour, respectively.
- The concentration of ofloxacin in the serum was a very small fraction of the concentration of ofloxacin in the plasma after systemic administration of the usual doses.
- Following delivery of ofloxacin to the middle ear by tympanostomy tube, the appearance of fluorescence in the pharynx demonstrated that the middle ear had been exposed to ofloxacin.
- Seven of 17 ofloxacin-treated subjects had detectable pharyngeal fluorescence.
- No fluorescence was detected in any time point for the placebo group.
- Proper administration was very important in the delivery of drug to the middle ear. The proper technique to facilitate penetration through the tympanostomy tube is to push forward on the tragus after instillation of the drops.

Protocol 8280A-PRT005

Title:

"Single Dose, Double-Blind, Placebo-controlled, Parallel Group Study to Assess the Pharmacokinetics and Penetration of Ofloxacin Otitc Solution Through a Tympanostomy Tube in Adults with Suppurative Otitis Media with Otorrhea."

Study Objectives:

To determine the pharmacokinetic profile of ofloxacin after a single dose administration of ofloxacin otic solution, and to determine the time to penetration of ofloxacin from the external ear canal through a patent tympanostomy tube to the middle ear in subjects with suppurative otitis media with otorrhea as determined by the presence or absence of fluorescence and bitter taste in the pharynx after dosing.

Study Summary:

- Seven subjects who were at least 18 years of age with tympanostomy tubes in place and a diagnosis of suppurative otitis media with otorrhea were enrolled in the study. (5 ofloxacin-treated subjects; 2 placebo-treated subjects)
- The two treatment groups were similar at Baseline with respect to all demographic characteristics.
- 3 /5 ofloxacin treated subjects had detectable ofloxacin serum levels at one or more time points to allow for pharmacokinetic calculations.
- The highest C_{max} observed was 8.8 ng/ml with a mean C_{max} of 5.4 ng/ml. The mean T_{max} and $AUC_{t(0-6)}$ calculated from the serum data available was 1.3 hours and 2.8 ng/ml * hour, respectively.
- The concentration of ofloxacin in the serum was a very small fraction of the concentration of ofloxacin in the plasma after systemic administration of the usual therapeutic doses.
- Three (3) out of 5 ofloxacin treated subjects had detectable pharyngeal fluorescence. These were the same subjects with detectable serum levels.
- No fluorescence was detected in any time point for the placebo group.

HUMAN CLINICAL EXPERIENCE

Foreign Marketing Experience

The following shows the marketing history of ofloxacin otic solution in foreign countries as of December, 1996:

Country	Date Approved for Marketing
Japan	April 1992
Hong Kong	November 1992
People's Republic of China	January 1993
Korea	April 1993
France	November 1995

Tarivid® is a registered trade name for ofloxacin preparations.

At the time of submission of this NDA, five other foreign countries (Indonesia, Malaysia, Philippines, Singapore, and Thailand) were reviewing the Product Licenses for ofloxacin otic solution.

Ofloxacin otic solution has not been withdrawn from investigation or from the market in any country as of 12/96.

Medical Officer's Comment: *A listing of the indications and formulations approved in each foreign country was requested and is forthcoming.*

At the time of this NDA submission, a total of 70 Phase III clinical studies had been conducted in France, Japan, China and other Asian countries, such as Taiwan, Indonesia, Thailand, Hong Kong

and Korea. There were 2 clinical studies in France, 26 clinical studies in Japan, 32 clinical studies in China, and 10 clinical studies in other Asian countries. The studies evaluated the efficacy and safety of ofloxacin otic solution in the treatment of otitis externa and infections of the middle ear. Most of the studies used 0.3% ofloxacin otic solution. A few of the studies evaluated and compared other strengths, such as 0.1% and 0.5% ofloxacin otic solution.

Summary of Safety Data in the Foreign Studies

- > 2200 subjects were evaluated for safety; 360 were children ≤ 12 years of age
- Asian experience-
  - In general, the adverse events were mild and self-limited. These included: nauseated by the cold otic solution, otalgia, constipation, diarrhea, vomiting, rash, itching and erythema of the canal, pain, and irritation, and earache.
  - 6 subjects (all Chinese) of 411 total subjects who underwent audiometric testing showed a deterioration in auditory acuity. Only one of these six had a deterioration that may have been related to ofloxacin.
- French experience-
  - 16 of the 191 subjects (8%) evaluated for safety experienced adverse events. Only 6 of these subjects had events felt to be "possibly" related to study drug.
  - The severity of the adverse events was not described, but only 2/191 subjects (1%) discontinued therapy due to adverse events. These events (external canal edema; otalgia, lingual paresthesia) were possibly treatment-related.
  - One subject experienced sudden bilateral deafness 10 days post-therapy. This was considered serious but unrelated to study medication (submitted to FDA as IND Safety Report This subject was hospitalized and had a favorable outcome with respect to this adverse event.
  - 1/57 subjects who had audiometric testing showed a temporary decline of hearing at the end of treatment. An audiogram performed several months later, was identical to the audiogram at the beginning of treatment.

Post-Marketing Experience

As noted in the preceeding section, the only country for which the post-marketing experience was available was Japan. The Adverse Events reported in the Phase IV study and those seen in the spontaneous reports are outlined below.

Summary of Post-Marketing Phase IV Study Data in Japan

Adverse events reported in the post-marketing Phase IV study in Japan are shown in the table below.

List of Adverse Events in Post-Marketing Phase IV Studies in Japan by Body System

	Number of Adverse Events				
Adverse Event	Year-1 (N=1053)	Year-2 (N=991)	Year-3 (N=1092)	Year-4 (N=277)	Cumulative (N=3413)
Skin & Appendages Disorders					
Itching	1	0	1	0	2
Hearing & Vestibular Disorders					
Ear Pain	1	0	2	0	3
Feeling of Ear Obstruction		1		0	1
Tinnitus			2		2
Central/Peripheral Nervous System Disorders					
Dizziness		1	0	0	1
Light Headed Feeling	1	0	0	0	1
Body-As-A-Whole, General Disorders					
Feeling Bad	0	1	0	0	1
Resistant Mechanisms Disorders					
Fungal Infection	2	1	1	0	4
Number of Adverse Events	5 (0.47%)	4 (0.40%)	6 (0.55%)	0	15 (0.44%)

Year - 1: March 27, 1992 - March 26, 1993
Year - 2: March 27, 1993 - March 26, 1994
Year - 3 March 27, 1994 - March 26, 1995
Year - 4 March 27, 1995 - March 26, 1996
Cumulative: March 27, 1992 - March 26, 1996

In the most recent year of the study, from March 27, 1995 to March 26, 1996, 277 subjects with otitis externa and otitis media were evaluated for safety. No serious adverse events or drug-related adverse events were reported during that time. There has been no change in the frequency of specific adverse events in Japan in the four-year period since the product launch of ofloxacin otic solution in Japan in 1992.

Summary of Post-Marketing Spontaneous Safety Reports in Japan

In addition to the Japanese Post-Marketing Phase IV Study Data, post-marketing surveillance in Japan is conducted by collecting the spontaneous reports of adverse events by physicians. The following table lists the post-marketing adverse events which were spontaneously reported by physicians in Japan since March 1992.

Adverse Events in Post-Marketing Spontaneous Reports in Japan by Body System

Adverse Event	Number of Adverse Events Newly Reported*	Cumulative***
Central/Peripheral Nervous Disorders		
Convulsion	0	1
Headache	0	1
Hearing and Vestibular Disorders		
Perceptive deafness	0	1**
Cardiovascular Disorders, General		
Hypertension	0	1
Respiratory System Disorders		
Interstitial pneumonia	1	1
Other Special Senses Disorders		
Taste abnormality	1	1
Dysosmia	1	1
Body-As-A-Whole, General Disorders		
Chest pressure sensation	0	1
Resistance Mechanism Disorders		
Otitis Externa	1	3
Fungal Infection		1
Total Number of Adverse Events	4	12

* March 27, 1995 - March 26, 1996
** Submitted to the FDA as an IND Safety Report (Serial #043)
*** Cumulative: March 27, 1992 - March 26, 1996

Four adverse events were spontaneously reported during the year from March 27, 1995 to March 26, 1996. The four adverse events were single cases of otitis externa, interstitial pneumonia, taste abnormality, and dysosmia. There have been no notable changes in the type or frequency of specific adverse events in Japan.

APPEARS THIS WAY
ON ORIGINAL

CLINICAL STUDIES

INTRODUCTION

Data from five Phase III studies were submitted to support the three clinical indications sought in the labeling: otitis externa in children age 1 year and older and adults, acute otitis media in children with tympanostomy tubes, and chronic suppurative otitis media in adolescents and adults with a perforated tympanic membrane. These are summarized in the table below:

Summary of Studies

Protocol Number	Indication	Subject Population	Region No. of Sites	Ofloxacin Dose/Duration of Treatment	Comparative Agent Dose/Duration of Treatment	Ofloxacin Subjects	Comparative Subjects
PRT-002	Otitis Externa	Adolescents and Adults with Otitis Externa	U.S. 23 sites	0.3% otic solution 0.5 mL b.i.d. for 10 days	Cortisporin® 0.2 mL q.i.d. for 10 days	ITT Total: 158 Clin Eval: 126 Micro Eval: 48	ITT Total: 156 Clin Eval: 121 Micro Eval: 50
PRT-003	Otitis Externa	Children with Otitis Externa	U.S. 23 sites	0.3% otic solution 0.25 mL b.i.d. for 10 days	Cortisporin® 0.15 mL q.i.d. for 10 days	ITT Total: 143 Clin Eval: 116 Micro Eval: 45	ITT Total: 144 Clin Eval: 111 Micro Eval: 53
PRT-006	Chronic Suppurative Otitis Media	Adolescents and Adults with Perforated Tympanic Membrane	U.S. 36 sites, Latin America 2 sites	0.3% otic solution 0.5 mL b.i.d. for 14 days	*Historical and Current Practice Group	ITT Total: 207 Clin Eval: 162 Micro Eval: 99	All Total: 220 All Total: 63 W/ FU Eval: 185 W/ FU Eval: 54
PRT-007	Acute Otitis Media	Children with Tympanostomy Tubes	U.S. 27 sites	0.3% otic solution 0.25 mL b.i.d. for 10 days	*Historical and Current Practice Group	ITT Total: 226 Clin Eval: 143 Micro Eval: 107	All Total: 309 All Total: 68 W/ FU Eval: 218 W/ FU Eval: 48
PRT-008	Acute Otitis Media	Children with Tympanostomy Tubes	U.S. 33 sites, Latin America 2 sites	0.3% otic solution 0.25 mL b.i.d. for 10 days	Augmentin® 40 mg/kg/day for 10 days	ITT Total: 228 Clin Eval: 140 Micro Eval: 83	ITT Total: 246 Clin Eval: 146 Micro Eval: 93

* Clinically Evaluable Population - All Historical (HP) and Current Practice (CP) Subjects with Follow-up Visit.
* Protocols 2, 3, and 8 were evaluator-blind trials.

Indication #1

OTITIS EXTERNA

Two studies of otitis externa were conducted:

8280A-PRT002 in adults and
8280A-PRT003 in pediatric patients.

OTITIS EXTERNA

Trial #1

8280A-PRT-002

"A Multicenter, Randomized, Evaluator-Blind Study to Compare the Safety and Efficacy of Ofloxacin Otic Solution with that of Cortisporin® Otic Solution in the Treatment of Acute Otitis Externa in Adults"

Study Objective

As stated by the Applicant, the objective of this study was: "To compare the safety and efficacy of ofloxacin otic solution with that of Cortisporin® otic solution in the treatment of acute otitis externa of presumed bacterial origin in subjects 12 years of age or older."

Study Design

This was a multicenter, randomized, evaluator-blind, parallel group, comparative study. Subjects 12 years of age and older with a clinical diagnosis of acute otitis externa of presumed bacterial origin and intact tympanic membrane and who met all inclusion/exclusion criteria were randomized to receive either ofloxacin 0.3% otic solution dosed at 0.5 ml to be instilled twice daily or Cortisporin® otic solution dosed at 0.2 ml to be instilled 4 times daily for 10 consecutive days.

Subjects were to be evaluated at the following timepoints:

Visit	Period	Window (Day of Study)
1	Baseline	Day 1
2	During Therapy	Day 3-5
3	Post-Therapy	Day 11-13
4	Test of Cure	Day 17-20

Medical Officer's Comment:
The acceptable range for Visit 4, the Test of Cure visit, was originally Day 17-24 (7 to 14 days post-treatment), but in Protocol Amendment #1,dated August 2, 1994, this range was changed to Day 17-20 (7 to 10 days post-treatment). The Division requested the amendment in order to ensure an assessment more representative of the treatment and to lessen the likelihood of intercurrent events between visits 3 and 4.

Subjects were assigned in a 1:1 ratio to the ofloxacin treatment group or the Cortisporin® treatment group according to a computer-generated randomization scheme supplied by

This study was conducted from July 19, 1994 to November 11, 1994 at a total of 23 centers in the United States and Puerto Rico as listed below:

Center PRT002-01
Thomas Balkany, MD
Department of Otolarnygology
Miami Ear Institute
University of Miami School of Medicine
1666 N.W. 10th Avenue Suite 306
Miami, FL 33136

Center PRT002-02
George Gates, MD
University of Washington Medical Center
Otolaryngology Clinic, HNS CL SS-300 RC-76
1959 NE Pacific Street
Seattle, WA 98195

Center PRT002-03
Thomas Marbury, MD
Orlando Clinical Research Center
4401 South Orange Avenue, Suite 108
Orlando, FL 32806

Center PRT002-04
David Williams, MD
Atlantic Institute of Clinical Research
350 North Clyde Morris Blvd.
Daytona Beach, FL 32114

Center PRT002-05
Joseph Pattison, MD
Riverside Clinic
Clinical Research Department
2005 Riverside Avenue
Jacksonville, FL 32204

Center PRT002-06
Trevor Goldberg, MD
Charlotte Eye, Ear, Nose and Throat Associates
1600 East Third Street
Charlotte, NC 28204

Center PRT002-07
Simon Parisier, MD
Manhattan Eye, Ear and Throat Clinic
Otolaryngology - H&N Surgery
New York, NY 10021

Center PRT002-08
Margaret Drehobl, MD
Centre for Health Care
17190 Bernardo Center Drive
San Diego, CA 92128

Center PRT002-09
Emmet Lee, MD
Palomar Medical Group
625 East Grand Avenue
Escondido, CA 92025

Center PRT002-10
Steven Becker, MD
Memorial City Professional Building II
909 Frostwood, Suite 356
Houston, TX 77024

Center PRT002-11
William Lumry, MD
Allergy and Asthma Research Associates
5499 Glenlake Drive, Suite 110
Dallas, TX 75231

Center PRT002-12
Sofia Anthony, MD
Essex Testing Clinic, Inc.
799 Bloomfield Avenue, Suite 212
Verona, NJ 07044

Center PRT002-13
Roy Wong, MD
Sunnyvale Medical Clinic
301 Old San Francisco Road
Sunnyvale, CA 94086

Center PRT002-14
Scott Heatley, MD
77 Birch Street, Suite B
Redwood City, CA 94602

Center PRT002-15
Eduardo Caro Acevedo, MD
Calle Marginal 51, No. 57
URB Santa Rosa
Bayamon, Puerto Rico 00959

Center PRT002-16
Richard D. Clover, MD
University of Texas, Medical Branch
Department of Family Medicine
415 Texas Avenue
Galveston, TX 77555-0853

Center PRT002-17
Thomas Mieras, MD
San Antonio Diagnostic Clinic
4647 Medical Drive
San Antonio, TX 78284-3100

Center PRT002-18
William Anderson, MD
New Mexico Medical Group, P.C.
303 Mateo Blvd. NE #201
Albuquerque, NM 87108

Center PRT002-19
Chester Stafford, MD
Medical College of Georgia
Department of Medicine/Pediatric-Allergy/Immunology
BG 247
Augusta, GA 30912-3790

Center PRT002-20
Jeffrey Adelglass, MD
RHD Professional Plaza IV
9 Medical Parkway, Suite 202
Dallas, TX 75234

Center PRT002-21
Paul Lambert, MD
University of Virginia Medical Center
Otolaryngology H&N Surgery, Box 430
Charlottesville, VA 22908

Center PRT002-22
Eric Jacobs, MD
Jacobs Medical Center
2025 Woodmere Boulevard
Harvey, LA 70058

Center PRT002-23
Randy Real, MD
Simon Williamson Clinic
833 Princeton Avenue,SW
Birmingham, AL 35211

Protocol Overview

Population and Procedures:

Population

Subjects were to be males and non-pregnant, non-lactating females, 12 years of age or older, with a clinical diagnosis of acute (current episode < 2 weeks) otitis externa of presumed bacterial origin. Subjects were to meet the inclusion criteria and evidence none of the exclusion criteria.

To ensure clinically evaluable data from a minimum of 224 subjects (112 subjects per treatment group) for efficacy analysis, approximately 270 subjects were to be collectively enrolled at approximately 20 investigative centers. Each investigator was to provide up to 30 evaluable cases (amendment dated October 4, 1994).

Study Procedures

The primary efficacy parameter was the overall clinical assessment of the subjects by the investigator for the clinically evaluable population. All other efficacy measures were considered secondary. At each visit, assessments of four clinical signs and symptoms of acute otitis externa (edema, tenderness, erythema and secretion/exudate) were recorded. Each of these four criteria were to be scored according to the following scale:

Score	
0= none	Complete absence of any signs or symptoms
1= mild	Detectable, but minimal involvement
2= moderate	Obvious, easily noted
3= severe	Quite marked, intense

The following table represents the assessments and procedures that were to be conducted at each visit.

	Visit Schedule			
	Visit 1, Pre-Therapy Day 1	Visit 2, During Therapy Day 3-5[6]	Visit 3[1], Post-Therapy Day 11-13	Visit 4, Test of Cure Day 17-20
Medical History	X			
Physical Examination	X	X[2]	X	X[2]
Vital Signs	X	X	X	X
External Canal Measurement	X	X	X	X
Signs, Symptoms, Severity[7]	X	X	X	X
Culture	X	X[3]	X[3]	X[3]
Urine ß-hCG Pregnancy Test	X[4]		X[4]	
Dispense Medication	X	X		
Collect Medication		X	X	
Medication Application	X	———	X	
Adverse Event Assessment	X[5]	X	X	X
Subject Diary	X	———	X	
Subject Satisfaction		X	X	

1 Or upon early withdrawal
2 Focused Physical: vital signs together with ears, nose, throat, head and neck exam.
3 If indicated and secretion/exudate is present (every attempt must be made to obtain cultures in patients considered to be treatment failures)
4 If female of childbearing potential
5 After first instillation performed at investigational site
6 Every effort should be made to schedule the visit on Day 3 or 4
7 Both ears

Study Medications/ Dosage and Administration

- Ofloxacin otic 0.5mL (10 drops) into affected ear(s) twice daily, approximately 12 hours apart
- Cortisporin otic solution 0.2mL (4 drops) into affected ear(s) 4 times daily, approximately 6 hours apart

Medical Officer's Comment: *The Sponsor did not capture the use of wicks on the Case Report Form (CRF).*

Inclusion Criteria

The subject could be included in the study if the following criteria were met:

1.) A clinical diagnosis of acute otitis externa (current episode <2 weeks duration) of presumed bacterial origin was made in an otherwise healthy person age 12 years or older.
2.) The status of the acute otitis externa was stable or exacerbating.

3.) Male or female (non-pregnant, non-lactating)

4.) Subjects with a diagnosis of acute otitis externa involving one or both ears, with a total score of at least 6 in one or both ears. The score of 6 must have included the following criteria:
- Moderate to severe edema and tenderness (score of at least 2 for each)
- Mild to severe erythema (score of at least 1)
- Mild to severe secretion/exudate (score of at least 1) with sufficient quantity to indicate culture.

5.) The subject read and signed a written informed consent to participate (approved by the reviewing IRB) and California Experimental Subject's Bill of Rights prior to participation. The parent or guardian of a subject under the age of 18 must also have read and signed the written informed consent to participate (approved by the reviewing IRB) and California Experimental

Subject's Bill of Rights prior to study participation.

Exclusion Critieria

A subject with any of the following was not eligible for admission into the study:

1.) perforated tympanic membrane, history of a perforated tympanic membrane in the last 6 months, or if a perforated tympanic membrane could not be ruled out by speculum examination, impedance testing tympanometry, pneumatic otoscopy or Valsalva maneuver. Subjects who were diagnosed with a perforated membrane at Visit 2 (During Therapy, Day 3-5) were to have been discontinued immediately;

2.) chronic otitis externa (current episode ≥ 2 weeks);

3.) seborrheic dermatitis involving the external ear canal or pinna;

4.) known or suspected infection of an etiology known to be resistant to the study drugs (e.g., fungus);

5.) invasive otitis externa expected to require systemic antibiotic during the study;

6.) any topical or systemic antibiotic received within 14 days prior to study entry (topical antibiotics for acne were allowed on a chronic basis for subjects who have been on a stable dose for at least 14 days prior to entry);

7.) any topical drying agent or over-the-counter therapy for otitis externa received within 36 hours prior to enrollment;

8.) a topical or systemic dose of any quinolone within 30 days prior to study entry;

9.) known allergy to any of the test medications, including any of the inactive ingredients;

10.) Subjects receiving chemotherapy for cancer;

11.) Subjects receiving medication on a chronic basis for pain (including steroidal or non-steroidal anti-inflammatories) who have not been on a stable dose for at least 1 month prior to entry into the study;

Medical Officer's Comment: *The use of acetaminophen, acetaminophen with codeine, codeine, or synthetic codeine was permitted to treat the pain of acute otitis externa, if indicated during this study.*

12.) immunocompromised state, HIV-positive status, or hepatitis;

13.) pregnancy or lactation;

14.) exposure to any investigational agent within 90 days prior to study entry;

15.) high likelihood of death during the course of the study;

16.) previous enrollment in this study;

17.) inability, for whatever reason, to follow the protocol.

Evaluability Criteria

Safety Evaluability

For a subject to be considered evaluable for the safety analysis, he or she must have been administered at least one dose of the study medication and safety information must have been relayed.

Clinical Efficacy Evaluability

To have been considered evaluable for clinical efficacy in this study, the Applicant required the following conditions to have been met:

1.) None of the exclusion criteria were present and the subject had documented signs and symptoms of acute otitis externa, as defined in the protocol, and satisfied the other inclusion criteria.

2.) Ten consecutive days of treatment with the assigned study drug with a minimum of 75% of the assigned treatment taken. Subjects judged by the blind evaluator to be a clinical failure were to be included if they had received at least 3 days of medication with 75% of the assigned treatment taken in the three days.

3.) No prohibited treatment between Pre-therapy (Visit 1, Day 1) and Test of Cure (Visit 4, Day 17-20) Visits.

4.) Subjects must have returned for the Test of Cure Visit (Visit 4, Day 17-20) unless due to adverse events, or if the subject was a clinical failure.

In order to be evaluable with a favorable outcome, the acceptable visit windows for the Post-Therapy (Visit 3) and Test-of-Cure (Visit 4) Evaluations are presented below:

	Post-Therapy (Visit 3)		Test-of-Cure (Visit 4)	
	Nominal Window	Acceptable Window	Nominal Window	Acceptable Window
PRT002	1- 3 days	0 - 5 days	7- 10 days	6 - 14 days
PRT003	1- 3 days	0 - 5 days	7- 10 days	6 - 14 days

Nominal window - As specified in the protocols. All days refer to number of days post-treatment. (In order to calculate study days, add 10. For example, 1-3 days post-treatment correspond to study days 11-13.)

The Applicant presented ten possible reasons for classifying a subject as "non-evaluable." In the event that a subject met more than one of these criteria, only the first (primary reason) was displayed in tables and listings. These ten reasons were ranked by the Applicant as follows:

1. <75% drug compliance
2. >120% drug compliance
3. Use of unallowed previous or concomitant medication within the time frames specified by protocol
4. Failure to meet inclusion criteria or evidence of any exclusion criteria
5. No Visit 2, 3, or 4
6. No Visit 3 and no Visit 4
7. No Visit 3
8. No Visit 4
9. Visit spacing outside of allowed windows
10. <3 days of treatment

Medical Officer's Comment: The lack of an isolated pathogen at baseline did not make the subject clinically non-evaluable from either the perspective of the Applicant or the Medical Officer. The Medical Officer agreed with the clinical evaluability criteria as outlined by the Applicant.

Microbiological Efficacy Evaluability

The Applicant outlined the following conditions be met in order to consider a subject evaluable for microbiologcal efficacy:

1.) Predominant organism(s) is isolated at Pre-Therapy (Visit 1) culture.
2.) A successful culture obtained at Post-Therapy (Visit 3) and Test of Cure (Visit 4) (provided appropriate specimen was available), or if no appropriate source is present at Visit 3 and Visit 4.
3.) A successful culture obtained in cases of clinical failures.

Medical Officer's Comment: The Medical Officer agreed with the Applicant's microbiological efficacy evaluability criteria.

Endpoint Definitions

Clinical Response

The clinical response, in reference to the baseline evaluation of the clinical signs and symptoms, was to be assessed by the blinded evaluator at the During Therapy Visit (Visit 2, Day 3-5); the Post-Therapy Visit (Visit 3, Day 11-13); and at the Test of Cure Visit (Visit 4, Day 17-20). The Sponsor also made an overall clinical assessment based on the clinical responses at Visit 4. The clinical response definitions for each visit, as originally defined by the Sponsor, are listed below:

During Therapy Visit (Visit 2):

Clinical Cure:	Complete resolution of signs and symptoms with the exception of mild erythema (score of 1) which might be present
Clinical Improvement:	Decrease in total sign/symptom score from baseline without complete resolution (total score of 1 or higher not including a score of 1 for erythema)
No Clinical Change:	No change in total sign/symptom score from baseline
Clinical Exacerbation:	Increase in total sign/symptom score from baseline, but not severe enough to warrant change in antimicrobial therapy
Clinical Failure:	Increase in total sign/symptom score from baseline (after a minimum of 3 days treatment with 75% of dose taken) severe enough to warrant change in antimicrobial therapy
Indeterminate:	Discontinued or lost to follow-up (prior to minimum of 3 days of treatment with 75% of dose taken)

Post-Therapy Visit (Visit 3):

Clinical Cure:	Complete resolution of signs and symptoms of otitis externa with the exception of mild erythema (score of 1) which might be present
Clinical Improvement:	Decrease in total sign/symptom score from baseline without complete resolution (total score of 1 or higher, not including a score of 1 for erythema) and no further antimicrobial therapy required
Clinical Failure:	Persistence or progression of the clinical signs and symptoms of otitis externa or appearance of new signs and symptoms of otitis externa (after a minimum of 3 days treatment with 75% of dose taken) and/or further antimicrobial therapy required
Indeterminate:	Discontinued or lost to follow-up prior to Post-Treatment evaluation

Test-of-Cure Visit:

Sustained Clinical Cure:	Clinical cure at the Post-Therapy and at the Test-of- Cure evaluations
Subsequent Clinical Cure:	Clinical improvement at the Post-Therapy evaluation with Clinical Cure at the Test-of-Cure evaluation
Clinical Failure:	Clinical improvement or clinical cure at the Post- Treatment evaluation with clinical improvement at the Test-of-Cure evaluation. No further antimicrobial therapy required.
Clinical Relapse:	Recurrence of signs and symptoms of otitis externa during the 7-10 day post-treatment follow-up period requiring additional antimicrobial therapy
Indeterminate:	Discontinued or lost to follow-up prior to the Test-of-Cure evaluation

Medical Officer's Comment: The Medical Officer agreed with the possible clinical responses at the Test-of-Cure Visit.

Overall Clinical Response

The Applicant originally proposed that the single primary efficacy variable, Overall Clinical Response, be defined as cure, improvement, or failure. The Division proposed a cure or failure scheme which the Applicant accepted.

Based on the response at the Test-of-Cure Visit, the amended Overall Clinical Responses categories employed by the Applicant were:

Cure: Sustained Clinical Cure and Subsequent Clinical Cure
Failure: Failure, Clinical Relapse, and Indeterminate

Medical Officer's Comment: *The clinical condition of "improvement" was now under the study assessment designation of "failure."*

Microbiological Response

A microbiological response was to be assigned to each pathogen isolated at Baseline and to each subject at the Post-Therapy Visit (Visit 3) and at the Test-of-Cure (Visit 4). At the Test-of-Cure Visit, an overall response was to be assigned, by subject and by pathogen(s), taking into account the individual microbiological responses assigned at Visit 3 and Visit 4. A final Overall Microbiologic/Clinical Assessment was determined by the Applicant based on the combination of clinical and microbiologic assessments.

The microbiologic outcome definitions employed by the Applicant for each valid pathogen isolated at Visits 3 and 4 are as follows:

Microbiological Response at Visit 3

Eradication Documented: Absence of all baseline pathogen(s) from the Visit 3 culture.

Eradication Presumed: Clinical cure or clinical improvement of signs and symptoms of infection without a repeat culture because no source was present.

Persistence: Continued presence of a baseline pathogen in Visit 3 culture (regardless of isolation of other pathogens).

Colonization: Absence of all baseline pathogen(s) from the Visit 3 culture, but the isolation of a new organism(s) without a worsening of clinical signs and symptoms of infection.

Superinfection: Absence of all baseline pathogen(s) from the Visit 3 culture, but the isolation of a new pathogen(s) with worsening signs and symptoms of infection.

Not Evaluable: Subject considered not evaluable for microbiological response under any of the following conditions:

1. Not evaluable for clinical efficacy analysis.
2. No valid pathogen(s) isolated at Baseline.
3. No culture was performed when culture source was present.
4. Inappropriate culture submitted (i.e., culture submitted when no source to culture was reported).
5. No source to culture (i.e., no exudate/secretion) or no pathogen isolated, but a worsening of other clinical signs or symptoms relative to the Baseline

Microbiological Response at Visit 4

Eradication Documented: Absence of all baseline pathogen(s) from the Visit 4 culture.

Eradication Presumed: Sustained or subsequent clinical cure of signs and symptoms of infection without a repeat culture because no source was present.

Persistence: The same pathogen(s) that was present at the baseline and Visit 3 cultures was also isolated in the Visit 4 culture (regardless of isolation of other pathogens).

Recurrence: Absence of all baseline pathogen(s) and signs and symptoms (clinical cure or improvement) at Visit 3, but presence of a baseline pathogen(s) from cultures obtained at Visit 4, accompanied by reappearance of signs and symptoms of infection.

Superinfection: Absence of all baseline pathogen(s) with isolation at Visit 4 of the same superinfecting pathogen(s) which was isolated at Visit 3 culture.

Reinfection: Absence of all baseline pathogen(s) and signs and symptoms at Visit 3, but presence of a different pathogen(s) in cultures obtained at Visit 4, accompanied by reappearance of signs and symptoms of infection.

Colonization:	Absence of all baseline pathogen(s) from a culture or no source to culture at Visit 3, but the isolation of a new organism(s) without a worsening of clinical signs and symptoms of infection.
Not Evaluable:	Subject considered not evaluable for microbiological efficacy under any of the conditions cited for Microbiological Response at Visit 3, above.

Medical Officer's Comment: When reviewing the original protocol, the Medical Officer had requested clarification of what, at the time, was the response at Visit 4 of "superinfection." In Amendment #1 (August 2, 1994), the Applicant changed the classification from "superinfection" to "reinfection." The responses listed above are those the Applicant employed in the study, and while the Medical Officer does not necessarily disagree with them, further clarification of "superinfection" at Visit 4 is warranted. It should be noted that the definition above could reflect a situation wherein the subject had continued signs and symptoms of infection from Visit 3 to Visit 4. However, a subject who was clinically worsening at Visit 3 would not typically be expected to have cultures from Visit 4.

The overall microbiologic response by pathogen was defined by the Applicant as one of the following five responses:

Eradication Documented:	Absence of all baseline pathogen(s) from the Visit 3 and Visit 4cultures.
Eradication Presumed:	Clinical cure or clinical improvement of signs and symptoms at Visit 3 and sustained clinical cure or subsequent clinical cure of signs and symptoms at Visit 4, without a repeat culture, because no source was present at both Visit 3 and Visit 4, or because Visit 3 cultures documented baseline pathogen(s) eradication and Visit 4 cultures were not performed because no source was present.
Persistence:	The same pathogen(s) that was present at baseline was isolated at Visit 3 cultures or at Visit 3 and at Visit 4 cultures (regardless of isolation of other pathogens).
Recurrence:	Absence of all baseline pathogen(s) and signs and symptoms (clinical cure or improvement) at Visit 3, but presence of a baseline pathogen(s) from cultures obtained at Visit 4, accompanied by reappearance of signs and symptoms of infection.
Not Evaluable:	Response at either Visit 3 or Visit 4 was "not evaluable."

The overall microbiologic response assessment by subject was defined by the Applicant as follows:

Eradication:	The microbiological responses at both Visit 3 and Visit 4 were" eradication" (documented or presumed).
Persistence:	The microbiological response at Visit 3 and/or Visit 4 was "persistence."
Recurrence:	The microbiological response was "eradication" (documented or presumed) at Visit 3, and "recurrence" at Visit 4.
Reinfection:	The microbiological response was "eradication" (documented or presumed) at Visit 3 and "reinfection" at Visit 4.
Colonization:	If colonization was observed at Visit 3 or Visit 4.
Superinfection:	The microbiological response was "superinfection" at Visit 3.
Not Evaluable:	The microbiological response was "not evaluable" at Visit 3 or Visit 4.

Medical Officer's Comment: *The Medical Officer agreed with the microbiological efficacy evaluability and response criteria as outlined by the Applicant.*

The Applicant derived an Overall Microbiological/Clinical Assessment of each subject based on a combination of the clinical and microbiologic assessments according to the following classifications:

Success:	Sustained or subsequent clinical cure at Visit 4, with microbiological assessment of eradication or presumed eradication (no appropriate source).
Failure:	Any other combination of microbiological and clinical responses.

Medical Officer's Comment: *The Medical Officer agrees with the above Overall Microbiological/Clinical Assessment classifications.*

Statistical Considerations

Sample Size

In the Applicant's development of this study, both of the test products were assumed to have similar efficacy and safety profiles. The goal of the trial was to establish equivalence while allowing opportunities for declaring significant differences if the disparities were sufficiently large. The Applicant's examination of clinical reports and documents suggested that the key variable carried success rates of approximately 80% for both drugs. A two-tailed alpha =0.05 and power = 80% yielded the following sample sizes per treatment:

Success rates for both drugs	80%
Lower Bound Delta	0.15
Sample size per arm	112

Hence, a sample size of about 135 patients per treatment group (270 total subjects) would allow a lower bound of 15% to be within the 95% confidence interval for the differences between success rates.

The targeted number of evaluable subjects needed to meet the efficacy criteria was 224, but the recruitment plan allowed for up to 300 subjects. The estimate of 224 was based on a "best guess" by the Applicant as the literature was devoid of clinical trials for this indication where FDA guidelines were applied.

If the number of evaluble subjects completing the trial were to exceed 250, analyses would be provided for a.) the first 224 subjects, and b.) the final number together with post-study power calculations and 95% confidence intervals.

Analyses Planned

The single primary efficacy variable was "Overall Clinical Response" based on the blinded evaluator's assessment of clinical response. Subjects evaluable for both microbiological efficacy and clinical efficacy were to be assigned an "Overall Microbiological/Clinical Response." However, analyses for efficacy variables other than the "Overall Clinical Response" were to be considered supplementary.

Medical Officer's Comment: *The MO agreed that the primary efficacy variable was "Overall Clinical Response."*

The Applicant defined the following three subject populations:

Intent-to-Treat Population: Included subjects who were randomized to treatment and received at least one dose of study drug.

Clinically Evaluable Population: As defined on page 19 for clinical evaluability

Microbiologically Evaluable Population: As defined on page 20 for microbiological evaluability

Statistical analyses were to be performed on all three populations.

Statistical Methods

In the study synopsis (found in the study report), the Applicant describes the statistical methods employed as follows:

"Continuous variables (age, sign/symptom scores, ear canal diameter, vital signs, pain and discomfort scores, and duration of otitis externa episode) were analyzed using two way analysis of variance including a treatment by center interaction term. The Cochran-Mantel-Haenszel test was used to analyze the discrete variables: gender, race, clinical response rates, microbiological response rates, overall microbiological/clinical response rate, infection type, reference ear status, number of organisms, and satisfaction ratings. The remaining discrete

variables (incidence of adverse events) were analyzed by Fisher's Exact test. To test the equivalence between the ofloxacin and Cortisporin® groups, the lower limit of the 95% confidence interval for the difference in the overall clinical success rates was used (see section 3.7.2.2.1 for equivalence criteria). The lower limit of the 95% confidence interval was also used to test the difference between clinical response rates at each visit, microbiological response rates at each visit, overall, and the overall microbiological/clinical success rates."

Medical Officer's Comment: *For further details of the statistical methods and analyses, please see the review by HFD-725 Biostatistician, Joel Jiang, Ph.D..*

Study Results

Pooling of Centers

For analysis purposes, the Applicant pooled the data of the smaller centers so that each pooled center would have at least 20 subjects per center. This pooling was done before the randomization code was broken. The centers were pooled by the Applicant in the following manner:

Number of Subjects in Pooled Centers per Applicant

Pooled Center	Original Centers	Ofloxacin 0.5ml b.i.d.	Cortisporin® 0.2ml q.i.d.	Total
1	2,7,8	14	17	31
2	3	18	16	34
3	4	15	14	29
4	6	16	16	32
5	9,10,11,12,16	14	14	28
6	13,14,17	19	17	36
7	15	20	20	40
8	18,20	15	14	29
9	19,22	15	15	30
10	21,23	12	13	25
Total		158	156	314

Evaluability and Demographics

-Evaluability

A total of 314 subjects were enrolled and received at least one dose of medication. The distribution of these subjects and their evaluability status according to the Applicant are shown in the following table:

Applicant's Evaluability Per Center

		OFLOXACIN			CORTISPORIN®		
Investigator	Center Number	Intent to Treat	Clinically Evaluable	Micro. Evaluable	Intent to Treat	Clinically Evaluable	Micro. Evaluable
Balkany	01	0	0	0	0	0	0
Gates	02	1	0	0	3	1	0
Marbury	03	18	16	6	16	13	3
Williams	04	15	15	4	14	13	4
Pattison	05	0	0	0	0	0	0
Goldberg	06	16	11	8	16	8	8
Parisier	07	1	1	1	2	0	0
Drehobl	08	12	10	3	12	9	4
Lee	09	3	2	0	4	4	4
Becker	10	4	3	2	4	2	1
Lumry	11	4	3	1	4	3	0
Anthony	12	2	2	1	2	1	1
Wong	13	5	4	3	4	4	3
Heatley	14	5	2	0	4	3	2
Caro Acevedo	15	20	17	2	20	18	3
Clover	16	1	1	0	0	0	0
Mieras	17	9	4	2	9	9	3
Anderson	18	5	3	2	3	2	2
Stafford	19	6	5	0	6	5	1
Adelglass	20	10	9	8	11	9	6
Lambert	21	11	8	4	10	10	5
Jacobs	22	9	9	1	9	5	0
Real	23	1	1	0	3	2	0
Totals	23	158	126	48	156	121	50

The accountability of these 314 subjects, as assessed per the Applicant, is summarized in the following table.

Subject Accountability

Parameter	Ofloxacin 0.5ml b.i.d	Cortisporin® 0.2ml q.i.d.	Total
Number of Subjects Enrolled	158	156	314
Received Drug	158	156	314
Completed Visit 2	154	152	306
Completed Visit 3	147	147	294
Completed Visit 4	130	136	266
Intent-to-Treat Population	158	156	314
Clinically Evaluable Population	126	121	247
Microbiologically Evaluable	48	50	98

Of the 8 subjects who did not complete Visit 2, the four subjects in the ofloxacin treatment group and three of the Cortisporin® subjects had protocol violations. One subject in the comparator arm did not return for personal reasons.

A total of 12 subjects did not return for Visit 3: 3/7 in the ofloxacin arm and 1/5 in the comparator arm had protocol violations; 1/5 in the comparator arm did not meet entrance criteria; 1 subject in each arm did not return to the study as a result of ADE(s); 1/7 subjects in the ofloxacin arm was a treatment failure; and 2 subjects in the ofloxacin arm did not return for personal or "other" reasons.

A total of 29 subjects (18 ofloxacin-treated and 11 Cortisporin®-treated subjects)did not return for Visit 4. It should be noted that one subject in the ofloxacin-treated group returned for Visit 4, but had missed Visit 3. This explains the total of 130, rather than 129, for subjects completing Visit 4 in the ofloxacin treatment group. Treatment failure (11/18 ofloxacin-treated and 8/11 Cortisporin®-treated subjects) was the most common reason for study discontinuation before completing Visit 4.

The following table summarizes the number of days of treatment for the two treatment groups:

Number of Days on Treatment

Days	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value
<10	14	(8.9%)	13	(8.3%)	0.403
10	138	(87.3%)	133	(85.3%)	
>10	6	(3.8%)	10	(6.4%)	
Total	158		156		

As shown in the Subject Accountability table, several patients in each arm were excluded from the respective intent-to-treat populations to form the clinically and microbiologically evaluable populations. The primary reasons the Applicant excluded subjects from the clinically evaluable and microbiologically evaluable populations are summarized in the following table:

Applicant's Primary Reasons for Exclusion from Analyzed Populations

	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.	
Total Number of Subjects Enrolled	158		156	
Excluded from Intent-to-Treat	0		0	
Total Intent-to-Treat Population	158		156	
Excluded from Clinically Evaluable:	32	(20.3%)	35	(22.4%)
<75% Compliance	2	(1.3%)	7	(4.5%)
>120% Compliance	3	(1.9%)	1	(0.6%)
Concomitant Medication	9	(5.7%)	7	(4.5%)
Inclusion/Exclusion	8	(5.1%)	8	(5.1%)
No Visit 2, 3 and 4	3	(1.9%)	3	(1.9%)
No Visit 3 and 4	3	(1.9%)	3	(1.9%)
No Visit 3 only	1	(0.6%)	1	(0.6%)
No Visit 4 only	2	(1.3%)	1	(0.6%)
Visit Spacing	1	(0.6%)	4	(2.6%)
Total Clinically Evaluable Population	126		121	
Excluded from Microbiologically Evaluable:	110	(69.6%)	106	(67.9%)
Not Clinically Evaluable	32	(20.3%)	35	(22.4%)
No Baseline Pathogen	66	(41.8%)	55	(35.3%)
Follow-up Culture Missing	6	(3.8%)	1	(0.6%)
Inappropriate Culture	0		5	(3.2%)
Clin. Failure & No Pathogen Present	6	(3.8%)	10	(6.4%)
Total Microbiologically Evaluable Population	48		50	

The primary reasons for excluding subjects from the intent-to-treat population to form the clinically and microbiologically evaluable populations appear to be similar between the two groups.

After completing a full review of the data, the Medical Officer changed only six subjects. However, not all of these changes were actual changes of overall clinical assessment, rather two of these changes reflect differing terminology based on the timing of the assessment. The Medical Officer's six total changes, which had no substantial impact on efficacy results, are shown in the table below:

MO Changes in Subject Clinical Evaluability and Overall Clinical Assessment

Subject	Treatment	Applicant Evaluability	Applicant Assessment	MO Evaluability	MO Assessment
	Cortisporin®	Evaluable	Cure[1]	Evaluable	Cure[1]
	Cortisporin®	Evaluable	Failure[2]	Evaluable	Failure[2]
	Cortisporin®	Not Evaluable	Cure	Evaluable	Cure
	Cortisporin®	Evaluable	Cure[3]	Evaluable	Failure
	Cortisporin®	Evaluable	Failure	Not Evaluable	-
	Ofloxacin	Evaluable	Cure	Not Evaluable	-

[1]The change the Medical Officer made in the assessment of this patient reflects that the MO assessment at Visit 4 was Subsequent Clinical Cure, rather than Sustained Clinical Cure per the Applicant.

[2]The Applicant assessed this subject as a "Clinical Relapse (Failure)" at Visit 4, but at Visit 3 the Investigator had assessed the patient as a "Clinical Failure." Though the overall assessment is the same, the MO would assign the outcome assessment at Visit 3 regardless of a return visit.

[3]This subject is one of those that the Applicant re-evaluated after unblinding. The MO assessment of "Failure" is in keeping with the Applicant's reassigned outcome.

Subsequently, the Applicant notified the MO that the study records of Investigator, Dr. Eric Jacobs were not available for review.

Medical Officer's Comment: *The Medical Officer excluded data from this investigative site (Site 22) from the efficacy and safety analyses in this study.*

Additionally, an FDA inspection was carried out between May 7 and July 22, 1997 at Site 15, where the Principal Investigator was Dr. Eduardo Caro Acevedo. Findings of this inspection included significant discrepancies between data on the case report forms (CRFs) and the medical records (where available) for several subjects. The data on the CRFs could not be verified, and due to the absence of source documents, patient interviews were conducted.

Numerous violations of the informed consent process were noted. Some of these violations were the following: 1.) Some subjects (or the subjects' parents stated) that the signatures on the informed consent forms were not theirs or the signatures did not appear to be theirs., 2.) Some subjects (or the subjects' parents) were not aware that they were participating in a study for which they could receive an investigational drug., 3.) Some subjects (or subjects' parents) stated they did not read the informed consent form nor were the contents of the informed consent form explained to them by anyone.

Drug accountability records were incomplete and the quantity of study drug received by the clinical investigator could not be verified.

Medical Officer's Comment: *Dr. Caro Acevedo participated in two protocols: PRT002 and PRT003. The findings mentioned above applied to both studies and are not all inclusive of the objectionable observations made by representatives of the Division of Scientific Investigations. Additional observations are noted on the Form FDA 483, a copy of which may be obtained via the Freedom of information Act (FOIA).*

The nature of these observations, and the inadequate response by Dr. Caro Acevedo to the Form FDA 483 observations, raised concerns about the data integrity and led the Clinical Investigations Branch to recommend that no data from this study site ~~not~~ be used in support of efficacy and/or safety claims for the New Drug Application.

The Medical Officer excluded all data from Dr. Caro Acevedo's study site from safety and efficacy evaluations for both Protocol 002, and Protocol 003 in this NDA.

The MO changed the status of six subjects as listed in the table above, and excluded all subjects from Sites 15 and 22. The following table shows the Medical Officer's evaluability per center.

Medical Officer's Evaluability Per Center-PRT002

		OFLOXACIN			CORTISPORIN		
Investigator	Center Number	Intent to Treat	Clinically Evaluable	Micro. Evaluable	Intent to Treat	Clinically Evaluable	Micro. Evaluable
Balkany	01	0	0	0	0	0	0
Gates	02	1	0	0	3	1	0
Marbury	03	18	16	6	16	13	3
Williams	04	15	15	4	14	13	4
Pattison	05	0	0	0	0	0	0
Goldberg	06	16	11	8	16	9	8
Parisier	07	1	1	1	2	0	0
Drehobl	08	12	10	3	12	9	4
Lee	09	3	2	0	4	4	4
Becker	10	4	3	2	4	2	1
Lumry	11	4	3	1	4	3	0
Anthony	12	2	2	1	2	1	1
Wong	13	5	4	3	4	4	3
Heatley	14	5	1	0	4	3	2
Caro Acevedo	15	0	0	0	0	0	0
Clover	16	1	1	0	0	0	0
Mieras	17	9	4	2	9	9	3
Anderson	18	5	3	2	3	2	2
Stafford	19	6	5	0	6	5	1
Adelglass	20	10	9	8	11	9	6
Lambert	21	11	8	4	10	9	5
Jacobs	22	0	0	0	0	0	0
Real	23	1	1	0	3	2	0
Totals		129	99	45	127	98	47
Total Number of Centers Providing Evaluable Efficacy Data							
	19	19	18	13	18	17	14

The exclusion of these two centers, sites 15 and 22, by the MO resulted in a loss of 58 total subjects from the Intent-to-Treat Population, 29 in each treatment arm.

The loss of these 58 subjects represented a loss of 26 evaluable subjects (all cures) from the ofloxacin arm (17 from Dr. Caro Acevedo and 9 from Dr. Jacobs), and a loss of 23 evaluable subjects from the Cortisporin® arm. Of the 23 lost from the Cortisporin® arm, Dr. Caro Acevedo had

contributed 17 evaluable cures and 1 evaluable failure, and Dr. Jacobs had contributed 5 evaluable cures.

There were six total subjects contributed by Drs. Caro Acevedo and Jacobs whom the Applicant had considered microbiologically evaluable and were excluded by the MO. There was one ofloxacin-treated subject of Dr. Jacobs, and 3 Cortisporin®-treated and 2 ofloxacin-treated subjects of Dr. Caro Acevedo lost from the Microbiologically Evaluable Population.

-Demographics

The demographics of the Applicant's Intent-to-Treat population are presented in the following table:

Summary of Demographic Data for the Applicant's Intent-to-Treat Population

	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value*
Number of Subjects	158		156		
Age (yrs.)					
Mean ± S.D.	37.6 ± 17.6		38.0 ± 18.4		0.757
Gender (no. subjects)					
Male	82	(52%)	71	(46%)	0.284
Female	76	(48%)	85	(55%)	
Race (no. subjects)					
Caucasian	115	(73%)	118	(76%)	0.682
African American	15	(10%)	12	(8%)	
Asian	2	(1%)	1	(1%	
Hispanic	25	(16%)	24	(15%)	
Native American/Alaskan	0		1	(1%)	
Other	1	(1%)	0		
Infection					
Unilateral	128	(81%)	119	(76%)	0.227
Bilateral	30	(19%)	37	(24%)	
Reference Ear					
Right	83	(53%)	79	(51%)	
Left	75	(48%)	77	(49%)	
Reference Ear Status					
Exacerbating	119	(75%)	114	(73%)	0.549
Stable	39	(25%)	42	(27%)	
Duration of Otitis Externa (Days)					
Mean ± S.D.	5.1 ± 3.4		4.6 ± 2.9		0.214
Total Signs/Symptoms Score					
Mean ± S.D.	8.2 ± 1.5		8.2 ± 1.4		0.883
Number of Organisms**/Subjects					
Polymicrobial	51	(32%)	56	(36%)	0.696
Monomicrobial	54	(34%)	52	(33%)	
None	53	(34%)	48	(31%)	
Organism Type					
Single Pathogen	48	(30%)	50	(32%)	
Multiple Pathogens	30	(19%)	30	(19%)	
Pathogen with Fungi	2	(1%)	1	(1%)	
Fungi only	4	(3%)	2	(1%)	
Normal Flora only	21	(13%)	25	(16%)	
None	53	(34%)	48	(31%)	

* Cochran-Mantel-Haenszel General Association Test was used to compare gender, race, infection, reference ear status, and number of organisms; age, duration of otitis external and total signs/symptoms score were compared using 2-way ANOVA test.

** Regardless of pathogenicit

The two groups in the Intent-to-Treat Population were comparable in demographic characteristics and signs and symptoms of acute otitis externa. The mean ages of the treatment groups were similar. The distribution of subjects with respect to gender and race was similar between the two treatment groups. The means of the total signs/symptom scores were similar between the two groups, and no significant differences were seen between the two groups with respect to laterality of infection, reference ear status, duration of otitis externa, and number of organisms per subject.

Also, the demographic and baseline disease characteristics for the subjects in the Applicant's Clinically Evaluable Population were balanced between the two treatment arms.

Medical Officer's Comment:

In the MO's Clinically Evaluable Population, mean age, gender distribution, and ear infection characteristics were all similar to those of the ITT population. Racial composition changed due to the loss of a center in Puerto Rico.

The demographics and baseline disease characteristics of the subjects in the Applicant's Microbiologically Evaluable Population were similar between the two treatment groups, and were similar to those in the Intent-to-Treat Population.

The Medical Officer excluded a total of six subjects (3 subjects in each arm) from the Applicant's Microbiologically Evaluable Population. The Medical Officer's Microbiologically Evaluable Population was otherwise the same as the Applicant's. The few changes made by the MO did not substantially change the distribution of demographic or disease characteristics between the two treatment groups. Therefore, the data presented in this review will be based on the data presented by the Applicant, but with the changes resulting from the Medical Officer's exclusion of the six subjects delineated as necessary.

Efficacy

-Clinical Efficacy

The Applicant presented an Intent-to-Treat Population of 314 subjects, and a Clinically Evaluable Population of 247 subjects. In reviewing the data as presented in the NDA, the Medical Officer made so few changes that it did not substantially change the statistical assessments. Had no other information come to the attention of the Medical Officer, the conclusions drawn by the Applicant would have been accepted by the MO. However, because the MO excluded two investigative centers the population sizes derived by the MO are much different than those of the Applicant. Therefore, the Medical Officer will present the efficacy analyses for the Applicant's clinically and microbiologically evaluable populations, and for the Medical Officer's clinically and microbiologically evaluable populations.

The subject populations now break down as shown in the table below:

Study PRT-002 Subject Populations
Before and after the Exclusion of Two Centers

Treatment Group for Clinical Response	Subjects Included	
	Ofloxacin	Cortisporin®
Intent-to-Treat Population	158	156
Modified Intent-to-Treat Population*	129	127
Applicant Clinically Evaluable	126	121
MO Clinically Evaluable	99	98
Applicant's Microbiologically Evaluable Population	48	50
MO's Microbiologically Evaluable Population	45	47

*Excludes Centers 15 and 22

The following table is the Applicant's Overall Clinical Assessment for their Intent-to-Treat Population.

Overall Clinical Assessment for the Applicant's Intent-to-Treat Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value	95% C.I.
Cure	108	(68.4%)	111	(71.2%)	0.612	(-13.6%, 8.0%)
Failure	50	(31.6%)	45	(28.8%)		
Total	158	(100%)	156	(100%)		

The following table outlines these results for the Applicant's Clinically Evaluable Population as presented in the NDA.

Overall Clinical Assessment for the Applicant's Clinically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value	95% C.I.
Cure	103	(81.7%)	101	(83.5%)	0.560	(-12.0%, 8.5%)
Failure	23	(18.3%)	20	(16.5%)		
Total	126	(100.0%)	121	(100.0%)		

Medical Officer's Comment: *Therapeutic equivalence of the two treatment groups was established by the Applicant in their clinical assessment of patients, both in the ITT and evaluable populations.*

The following table shows the Overall Clinical Response of the subjects in the Modified Intent-to-Treat Population.

Overall Clinical Response Modified Intent-to-Treat Population (after the Exclusion of Two Centers)		
Clinical Response	Ofloxacin (N=129)	Cortisporin® (N=127)
Cure	81 (62.8%)	89 (70.1%)
Failure	48 (37.2%)	38 (29.9%)
Ofloxacin vs. Cortisporin® by cure	-7.8%, 95%CI; -19.6%, 5.0%	

The response rates in the Modified Intent-to-Treat Population were similar to those seen in the Applicant's Intent-to-Treat Population. It is not unexpected that the efficacy rates in the Intent-to-Treat Populations are lower than those seen in the clinically evaluable subjects.

The Overall Clinical Assessment of the Medical Officer's Clinically Evaluable Population is shown in the following table:

Overall Clinical Response MO Clinically Evaluable Subjects (after the Exclusion of Two Centers)		
Clinical Response	Ofloxacin (N=99)	Cortisporin® (N=98)
Cure	76 (76.8%)	79 (80.6%)
Failure	23 (23.2%)	19 (19.4%)
Ofloxacin vs. Cortisporin® by cure	-3.8%, 95%CI; -16.3%, 8.6%	

As shown in the table above, while the overall response rates remained approximately the same between the two treatment groups, the ofloxacin cure rate dropped to below 80%, and the lower bound of the confidence interval became -16.3%. In the MO's Clinically Evaluable Population, by the DAIDP Criteria, therapeutic equivalence of the two treatments is no longer demonstrated. However, it is worth noting that the lower bound of the confidence interval is just beyond the cut-off of -15.0%.

Medical Officer's Comment: *The most notable demographic changes that resulted from the MO's exclusion of subjects were a decrease in the non-white subjects and those in the ≥ 65 years age group. However, the overall cure rates for these groups did not change that much, and the two treatment arms remained balanced.*

The secondary clinical efficacy variables the Applicant reported were: the changes in the signs and symptoms scores from Baseline and the clinical response rates at the During Therapy, Post-Therapy, and Test-of-Cure Visits (Visits 2, 3, and 4 respectively) for both the Intent-to-Treat Population and the Applicant's Clinically Evaluable Population. In both the Applicant's Intent-to-Treat and Clinically Evaluable Populations, the mean scores between the two treatment groups were similar for each of the signs/sy...ptoms at Baseline. And the mean changes from Baseline for all signs/symptoms scores and total scores were similar for the two treatment groups at all post-baseline visits. Because the clinical response is linked to the change in the signs and symptoms scores at each visit, and the groups had similar characteristics of disease at baseline, the Medical Officer considers it somewhat superfluous to present all of this information. Thus, the Medical Officer will not reproduce this information or present that for the Medical Officer's Clinically Evaluable Population.

The following table shows the Overall Clinical Response of the subjects in the Modified Intent-to-Treat Population.

Overall Clinical Response Modified Intent-to-Treat Population (after the Exclusion of Two Centers)		
Clinical Response	Ofloxacin (N=129)	Cortisporin® (N=127)
Cure	81 (62.8%)	89 (70.1%)
Failure	48 (37.2%)	38 (29.9%)
Ofloxacin vs. Cortisporin® by cure	-7.8%, 95%CI; -19.6%, 5.0%	

The response rates in the Modified Intent-to-Treat Population were similar to those seen in the Applicant's Intent-to-Treat Population. It is not unexpected that the efficacy rates in the Intent-to-Treat Populations are lower than those seen in the clinically evaluable subjects.

The Overall Clinical Assessment of the Medical Officer's Clinically Evaluable Population is shown in the following table:

Overall Clinical Response MO Clinically Evaluable Subjects (after the Exclusion of Two Centers)		
Clinical Response	Ofloxacin (N=99)	Cortisporin® (N=98)
Cure	76 (76.8%)	79 (80.6%)
Failure	23 (23.2%)	19 (19.4%)
Ofloxacin vs. Cortisporin® by cure	-3.8%, 95%CI; -16.3%, 8.6%	

As shown in the table above, while the overall response rates remained approximately the same between the two treatment groups, the ofloxacin cure rate dropped to below 80%, and the lower bound of the confidence interval became -16.3%. In the MO's Clinically Evaluable Population, by the DAIDP Criteria, therapeutic equivalence of the two treatments is no longer demonstrated. However, it is worth noting that the lower bound of the confidence interval is just beyond the cut-off of -15.0%.

Medical Officer's Comment: *The most notable demographic changes that resulted from the MO's exclusion of subjects were a decrease in the non-white subjects and those in the ≥ 65 years age group. However, the overall cure rates for these groups ~~not~~ did not change that much, and the two treatment arms remained balanced.*

The secondary clinical efficacy variables the Applicant reported were: the changes in the signs and symptoms scores from Baseline and the clinical response rates at the During Therapy, Post-Therapy, and Test-of-Cure Visits (Visits 2, 3, and 4 respectively) for both the Intent-to-Treat Population and the Applicant's Clinically Evaluable Population. In both the Applicant's Intent-to-Treat and Clinically Evaluable Populations, the mean scores between the two treatment groups were similar for each of the signs/symptoms at Baseline. And the mean changes from Baseline for all signs/symptoms scores and total scores were similar for the two treatment groups at all post-baseline visits. Because the clinical response is linked to the change in the signs and symptoms scores at each visit, and the groups had similar characteristics of disease at baseline, the Medical Officer considers it somewhat superfluous to present all of this information. Thus, the Medical Officer will not reproduce this information or present that for the Medical Officer's Clinically Evaluable Population.

-Microbiological Efficacy

Microbiological Assessment by Subject

The following tables outline the Visit 3 and 4 assessments as presented by the Applicant, and for the Medical Officer's Microbiologically Evaluable Population.

***Medical Officer's Comment**: The 95% confidence interval and P-values shown in the Applicant tables refer to the comparison between ofloxacin versus Cortisporin® with respect to eradication (documented plus presumed if distinguished). The 95% confidence intervals for the data in the Medical Officer's tables are described just below the table.*

Microbiological Assessment at Visit 3
Applicant's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value	95% C.I.
Documented Eradication	13	(27.1%)	12	(24.0%)	0.371	(-3.9%, 7.9%)
Presumed Eradication	35	(72.9%)	37	(74.0%)		
Persistence	0		1	(2.0%)		
Total	48		50			

Microbiological Assessment at Visit 4
Applicant's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value	95% C.I.
Documented Eradication	2	(4.5%)	1	(2.2%)	0.221	(-8.9%, 4.4%)
Presumed Eradication	41	(93.2%)	44	(97.8%)		
Recurrence	1	(2.3%)	0			
Total	44		45			

Microbiologic Assessment at Visit 3
Medical Officer's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.	
Documented Eradication	13	(28.9%)	11	(23.4%)
Presumed Eradication	32	(71.1%)	35	(74.5%)
Persistence	0		1	(2.1%)
Total	45		47	
Ofloxacin vs. Cortisporin by Eradication	2.1%, 95%: -4.2%, 8.4%			

Microbiologic Assessment at Visit 4
Medical Officer's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.	
Documented Eradication	2	(4.9%)	1	(2.4%)
Presumed Eradication	38	(92.7%)	41	(97.6%)
Recurrence	1	(2.4%)	0	
Total	41		42	
Ofloxacin vs. Cortisporin by Eradication	-2.4%, 95% CI: -9.6%, 4.7%			

The Overall Microbiological Assessment per subject was derived from the microbiological assessments at Visits 3 and 4. The Overall Microbiological Assessments for the Applicant's and the

Medical Officer's respective Microbiologically Evaluable Populations are shown in the following two tables.

Overall Microbiological Assessment by Subject
Applicant's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value	95% C.I.
Eradication	47	(97.9%)	49	(98.0%)	0.824	(-7.7%, 7.6%)
Persistence	0		1	(2.0%)		
Recurrence	1	(2.1%)	0			
Total	48		50			

Overall Microbiological Assessment by Subject
Medical Officer's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.	
Eradication	44	(97.8%)	46	(97.9%)
Persistence	0		1	(2.1%)
Recurrence	1	(2.2%)	0	
Total	45		47	

Ofloxacin vs. Cortisporin® by Eradication -0.1%, 95%: -8.2%, 8.0%

The eradication rates in the Medical Officer's evaluable subject population are essentially identical to those derived by the Applicant. Based on the equivalence guidelines used by the DAIDP, the 95% confidence interval for the difference in microbiological success rates between ofloxacin (97.8% eradication) and Cortisporin®(97.9% eradication) populations suggests therapeutic equivalence between the two treatments.

Subgroup Analysis of Overall Microbiological Assessment by Subject

For the Microbiologically Evaluable Population, the sample sizes among the usual subgroups are small. Therefore, there is insufficient power to allow the making of proper inferences from the 95% confidence intervals from these subgroups.

Overall Microbiologic Assessment by Pathogen

Overall Microbiological Assessment by Pathogen for the Applicant's Microbiologically Evaluable Population-PRT002

	Ofloxacin 0.5ml b.i.d.			Cortisporin® 0.2ml q.i.d.		
Pathogen	Eradication	Recurrence	Total	Eradication	Persistence	Total
*Pseudomonas aeruginosa** †	32	0	32	39	1	40
Staphylococcus aureus†	6	0	6	8	0	8
Enterococcus faecalis†	6	0	6	5	0	5
Klebsiella pneumoniae†	5	0	5	2	0	2
Proteus mirabilis†	3	0	3	8	0	8
Enterobacter cloacae†	3	0	3	2	0	2
Enterobacter aerogenes	1	1	2	2	0	2
Xanthomonas maltophilia	2	0	2	2	0	2
Enterococcus durans	2	0	2	0	0	0
Klebsiella oxytoca	2	0	2	0	0	0
Escherichia coli	1	0	1	2	0	2
Serratia marcescens	1	0	1	2	0	2
Streptococcus agalactiae	1	0	1	2	0	2
Morganella morganii	1	0	1	1	0	1
Alcaligenes xylosoxidans	1	0	1	0	0	0
Citrobacter diversus	1	0	1	0	0	0
Enterobacter agglomerans	1	0	1	0	0	0
Enterococcus casseliflavus	1	0	1	1	0	1
Proteus vulgaris	1	0	1	0	0	0
Providencia stuartii (Urea +)	1	0	1	0	0	0
Streptococcus pyogenes	1	0	1	0	0	0
A. calcoaceticus V. anitratus	0	0	0	2	0	2
Pseudomonas fluorescens	0	0	0	2	0	2
Providencia stuartii	0	0	0	1	0	1
Pseudomonas maltophilia	0	0	0	1	0	1
Pseudomonas stutzeri	0	0	0	1	0	1
Total			74			84

* Comparison of the two treatment groups with respect to eradication rate of *Pseudomonas aeruginosa* gave a p-value of 0.386 and a 95% C.I. of (-5.2%,10.2%).

† Organisms requested by Applicant to be included in labeling for Otitis Externa indication

The distribution of baseline pathogens in the Applicant's Microbiologically Evaluable Population is similar to that of the Intent-to-Treat Population. As expected, *Pseudomonas aeruginosa* was the most frequently isolated pathogen in the microbiologically evaluable subjects also. The *Pseudomonas aeruginosa* isolates accounted for 45.6% of the total number of pathogens isolated from the Applicant's Microbiologically Evaluable Population.

When the six subjects were excluded to create the Medical Officer's Microbiologically Evaluable Population, the eradication rate of the most commonly isolated baseline pathogens was as shown in the table below:

PRT-002 Overall Pathogen Eradication Rate for Most Common Baseline Pathogens in the Medical Officer's Microbiologically Evaluable Population

Pathogen	Ofloxacin	Cortisporin®
P. aeruginosa	32/32 (100%)	38/39 (97.4%)
S. aureus	6/6 (100%)	6/6 (100%)
E. faecalis	5/5 (100%)	5/5 (100%)
K. pneumoniae	5/5 (100%)	1/1 (100%)
P. mirabilis	3/3 (100%)	6/6 (100%)
E. cloacae	3/3 (100%)	2/2 (100%)
Ofloxacin vs. Cortisporin® for *P. aeruginosa* 2.6%, 95%CI: -5.2%, 10.4%		

As shown in the above table, there was equivalence between the two treatment groups for eradication of *Pseudomonas aeruginosa* in the MO's Microbiologically Evaluable Population. The other five baseline pathogens listed were entirely eradicated from both treatment groups.

Overall Microbiological/Clinical Assessment

A final Overall Microbiologic/Clinical Assessment was determined by the combination of clinical and microbiologic assessments in the microbiologically evaluable population. The overall microbiological/clinical designation could either be "success" or "failure." The following tables show the overall microbiological/clinical assessments by the Applicant and the Medical Officer:

Overall Microbiological/Clinical Assessment
Applicant's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value	95% C.I.
Success	41	(85.4%)	44	(88.0%)	0.975	(-18.1%, 12.9%)
Failure	7	(14.6%)	6	(12.0%)		
Total	48		50			

Overall Microbiological/Clinical Assessment
Medical Officer's Microbiologically Evaluable Population

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value	95% C.I.
Success	38	(84.4%)	41	(87.2%)		(-19.2, 13.6%)
Failure	7	(15.6%)	6	(12.8%)		
Total	45		47			

Medial Officer's Comment: *The success rates in the MO's Microbiologically Evaluable Population were about the same as seen in the Applicant's. The 95% confidence interval for the difference in overall microbiological/clinical success rates did not meet equivalence criteria in either population. However, there are a small number of subjects in these subgroups, and the study was not necessarily powered sufficiently for a subgroup analysis to be meaningful.*

Of the 45 ofloxacin-treated subjects in the MO's Microbiologically Evaluable Population, there were 7 clinical failures. The only baseline pathogen not eradicated was one isolate of *Enterobacter aerogenes*. Of the six pathogens the Applicant is requesting in the labeling, any that were found at baseline in the other six clinical failures were documented to be eradicated at the

time of the subject's clinical failure. The following table shows the combined clinical cure and microbiological eradication rates for the six pathogens requested in the labeling, as assessed by the Applicant and by the Medical Officer.

Combined Clinical Cure and Microbiological Eradication (Success) Rates by Pathogen for Ofloxacin-treated subjects (Applicant vs. Medical Officer)-PRT002		
Baseline Pathogen Requested in Labeling	Applicant	Medical Officer
Pseudomonas aeruginosa	28/32 (87.5%)	28/32 (87.5%)
Staphylococcus aureus	6/6 (100%)	6/6 (100%)
Enterococcus faecalis	5/6 (83.3%)	4/5 (80.0%)
Klebsiella pneumoniae	4/5 (80.0%)	4/5 (80.0%)
Proteus mirabilis	2/3 (66.7%)	2/3 (66.7%)
Enterobacter cloacae	1/3 (33.3%)	1/3 (33.3%)

Safety Analyses-PRT002

The safety analyses were performed on the Intent-to-Treat population of 314 subjects (158 treated with ofloxacin and 156 treated with Cortisporin®). The Medical Officer reviewed all of the case report forms and case tabulations. The Medical Officer agreed with the safety data as presented by the Applicant. However, as noted in the Clinical Efficacy section, two centers were excluded by the Medical Officer. Therefore, the information presented in this section of the review is based upon the Applicant's presentation of the safety data with the differences made by the Medical Officer changes delineated where applicable.

All Adverse Events

The following table, as constructed by the Applicant, shows the number (%) of subjects in the Intent-to-Treat Population submitted in the NDA who experienced adverse events during the study:

Adverse Events During the Study in the Intent-toTreat Population as Presented in the NDA

Parameter	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value
Number of Subjects	158		156		
Subjects with any AE	67	(42.4%)	51	(32.7%)	0.081
Subjects with Treatment-related AEs	25	(15.8%)	18	(11.5%)	0.325
Subjects with Severe or Life-threatening AEs[1]	6	(3.8%)	3	(1.9%)	0.502
Subjects with Serious AEs[2]	3	(1.9%)	2	(1.3%)	1.000
Subjects Discontinued due to AEs	4	(2.5%)	2	(1.3%)	0.685

1 The severity of AEs was classified by the investigator as: mild, moderate, severe, or life-threatening.
2 The sponsor classified an AE as serious if the AE: was life-threatening; resulted in hospitalization, permanent disability, or death; was cancer, congenital anomaly, or overdose; or was indicative of a systemic immediate hypersensitivity reaction (diffuse rashes) or those which might indicate CNS toxicity.

The Applicant noted, as this table shows, that the two treatment groups had similar incidence profiles of adverse events (P=.081).

Medical Officer's Comment: The Medical Officer notes that there was no statistically significant difference between the two groups with respect to subjects experiencing treatment-related adverse events, severe or life-threatening adverse events, serious adverse events, or being discontinued from therapy due to an adverse event. All P-values shown in the tables in this safety section were calculated by the Fisher's Exact Test unless otherwise noted.

The following table shows these same parameters for the modified Intent-to-Treat Population (after the exclusion of Centers 15 and 22.)

Adverse Events During the Study in the Modified Intent-toTreat Population (Excludes Centers 15 & 22)

Parameter	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value
Number of Subjects	129		127		
Subjects with any AE	57	(44.2%)	47	(37.0%)	0.255
Subjects with Treatment-related AEs	24	(18.6%)	17	(13.4%)	0.307
Subjects with Severe or Life-threatening AEs[1]	6	(4.7%)	3	(2.4%)	0.500
Subjects with Serious AEs[2]	3	(2.3%)	2	(1.6%)	1.000
Subjects Discontinued due to AEs	4	(3.1%)	2	(1.6%)	0.684

1 The severity of AEs was classified by the investigator as: mild, moderate, severe, or life-threatening.

2 The sponsor classified an AE as serious if the AE: was life-threatening; resulted in hospitalization, permanent disability; or death; was cancer, congenital anomaly, or overdose; or was indicative of a systemic immediate hypersensitivity reaction (diffuse rashes) or those which might indicate CNS toxicity.

Deaths and Other Serious Adverse Events

No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication. Six ofloxacin-treated subjects and 3 Cortisporin®-treated subjects were reported as having severe adverse events. Three ofloxacin-treated subjects and 2 Cortisporin®-treated subjects experienced adverse events that were considered to be serious.

With respect to these safety parameters, there were no significant differences between the two treatment groups in the modified Intent-to-Treat Population. While there was no statistically significant difference between the two groups, the percentages of the population affected did rise somewhat.

Most Frequent Adverse Events

The following table outlines those adverse events that were the most frequently reported (reported in 10 or more subjects across both treatment groups) in the Intent-to-Treat Population as presented in the NDA.

Most Frequently Reported Adverse Events in the Intent-to-Treat Population as Presented in the NDA-PRT002

Adverse Event	Ofloxacin 0.5ml b.i.d. (N=158)		Cortisporin® 0.2ml q.i.d. (N=156)		P-value
Pruritus	14	(8.9%)	11	(7.1%)	0.678
Headache	10	(6.3%)	3	(1.9%)	0.086
Rhinitis	7	(4.4%)	4	(2.6%)	0.542
Earache	6	(3.8%)	8	(5.1%)	0.597
Application Site Reaction	6	(3.8%)	6	(3.8%)	1.00

Of the 29 total ofloxacin-treated subjects who were excluded by the Medical Officer, 10 had been reported to have had adverse events. Two subjects were from Site 15, and the other 8 were from Site 22. Of the 29 Cortisporin®-treated subjects excluded by the MO, there were four (two from each excluded center) who had had adverse events reported. The following table shows the total counts of the most frequently reported adverse events after the removal of these subjects by the MO.

Most Frequently Reported Adverse Events in the Modified Intent-to-Treat Population-PRT002 (Excludes Centers 15 and 22)					
Adverse Event	**Ofloxacin 0.5ml b.i.d. (N=129)**		**Cortisporin® 0.2ml q.i.d. (N=127)**		**P-value**
Pruritus	14	(10.9%)	10	(7.9%)	0.521
Headache	4	(3.1%)	3	(2.4%)	1.000
Rhinitis	6	(4.7%)	4	(3.1%)	0.749
Earache	6	(4.7%)	8	(6.3%)	0.595
Application Site Reaction	6	(4.7%)	6	(4.7%)	1.000

Medical Officer's Comment: *There was no statistically significant difference between the two treatment groups with respect to the incidence of any of these particular adverse events.*

Of the most frequently reported adverse events listed in the table above, there was only 1 of the MO excluded Cortisporin®-treated subjects who experienced one of these adverse events. This subject had the AE of pruritus. Therefore, of the MO Cortisporin®-treated ITT population there were 10/127 (7.9%) who experienced pruritus versus 11/156 (7.1%) of the Intent-to-Treat Population presented in the NDA. The number of Cortisporin®-treated subjects in the MO's ITT population who experienced headache, rhinitis, earache, and/or application site reaction did not differ from what was presented in the NDA. But, because of the smaller population the percentages increased slightly.

The following is a list of all of the adverse events (severity and their relationship to study drug) that were seen in all of the subjects who were excluded by the Medical Officer.

Ofloxacin-treated subjects

Subject	Adverse Event	Severity	Relationship to Study Drug
Subject	Rhinitis	Mild	Not related
Subject	Skin disorder (burn on thumb)	Mild	Not related
Subject	Pharyngitis	Mild	Not related
	Headache	Mild	Not related
Subject	Eye Injury, Hematoma	Mild	Not related
	Skeletal Pain (shoulder Pain)	Mild	Not Related
	Arthalgia (Knee Pain)	Mild	Not Related
Subject	Headache	Mild	Possibly Related
Subject	Headache	Mild	Not Related
	Bullous eruption (fever blisters)	Moderate	Not Related
Subject	Dysmenorrhoea	Moderate	Not Related
	Headache	Moderate	Not Related
Subject	Headache	Mild	Not Related
Subject	Back Pain	Moderate	Not Related
Subject	Headache	Mild	Not Related

Cortisporin®-treated subjects

Subject	Pruritus	Mild	Possibly Related
Subject	Lymphadenopathy (cervical adenopathy)	Mild	Not Related
Subject	Upper Respiratory Tract Infection	Mild	Not Related
Subject	Pharyngitis	Mild	Not Related