CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 20-805

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Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				
Administrative Document(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-805

Trade Name: CIPRO HC OTIC

Generic Name: (ciprofloxacin hydrochloride & hydrocortisone otic suspension)

Sponsor: Bayer Corporation

Approval Date: February 10, 1998

Indication: Provides for treatment of acute otitis externa

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-805

APPROVAL LETTER

FEB 10 1998

NDA 20-805

Bayer Corporation
Attn: Ann Marie Assumma, M.S.
Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Assumma,

Please refer to your new drug application dated February 7, 1997, received February 10, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension).

We acknowledge receipt of your submissions dated March 20; August 7, and 14; September 8, 18, and 30; October 3, 10, 15, 17, 24, and 31; November 7, and 21; December 1, 2, 4, 22, 23, and 31, 1997; January 5, 7, 9, 15, 21, and 23; and February 3, 6, and 9, 1998. The User Fee goal date for this application is February 10, 1998.

This new drug application provides for treatment of acute otitis externa.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final draft labeling received via facsimile on February 9, 1998. Accordingly, the application is approved effective on the date of this letter.

In addition, the following CMC commitments were agreed to during a teleconference of February 6, 1998, and confirmed in a fascimile on that same day. Bayer has agreed to provide data from structure elucidation studies on "HC Comp. A RRT 1.33" and the "Largest Single Unknown." Bayer also agreed to re-evaluate the proposed specification limits for these substances.

Furthermore, Bayer has made a commitment to investigate the possibility of reduction in the Cipro HC Otic volume from 10 mL to 5 mL.

The final printed labeling (FPL) must be identical to the draft labeling submitted on February 9, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL

PRINTED LABELING" for approved NDA 20-805. Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Kim Roche, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 20-805
HFD-520/Div. files
HFD-520/PM/Roche
HFD-520/MO/Mann
HFD-590/Chem/Matecka
HFD-590/ChemTL/Schmuff
HFD-520/Micro/Dionne
HFD-520/MicroTL/Sheldon
HFD-520/Pharm/Ellis
HFD-520/PharmTL/Osterberg
HFD-725/Stats/Soon
HFD-725/StatsTL/~~Lin~~ Flyer
HFD-002/ORM (with labeling)
HFD-104/THassall
HFD-101/L.Carter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)

Concurrence: /S/ 2/10/98
HFD-520/SPMS/Bona 2/10/98
HFD-520/MTL/Roberts

Drafted by: /February 9, 1998/
Initialed by: KR 2/10/98

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-805

MEDICAL REVIEW(S)

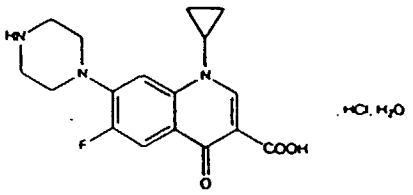
Medical Officer's Review of NDA

1. General Information (For Table of Contents, see page 6.)
   - 1.1 NDA Submission Number: 20-805
   - 1.2 Application Identification
     - 1.2.1 Bayer Corporation
     - 1.2.2 Pharmaceutical Division
       400 Morgan Lane
       West Haven, CT 06516-4175
     - 1.2.3. Ann Marie Assumma, M.S.
       Associate Director, Regulatory Affairs
       (203)-812-3290
   - 1.3 Submission/Review Dates
     - 1.3.1 Date of Submission: February 7, 1997
     - 1.3.2 CDER Stamp Date: February 10, 1997
     - 1.3.3 Date Assigned to Medical Reviewer: July 11, 1997
     - 1.3.4 Date Review Begun: July 11, 1997
     - 1.3.5 Date Review Completed: December 23, 1997
   - 1.4 Drug Identification
     - 1.4.1. Generic Name: Ciprofloxacin Hydrochloride, USP/Hydrocortisone, USP
     - 1.4.2. Proposed Trade Name: Cipro HC OTIC Suspension
     - 1.4.3. Chemical Name:

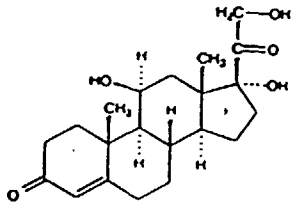
       Ciprofloxacin: 3-quinoline-carboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, monochloride, monohydrate

       Hydrocortisone: pregn-4-ene-3,20-dione,11,17,21-trihydroxy-,(11β)

     - 1.4.4. Chemical Structure:



Ciprofloxacin



Hydrocortisone

     - 1.4.5. Molecular Formula:

       Ciprofloxacin: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$
       Hydrocortisone: $C_{21}H_{30}O_5$

     - 1.4.6. Molecular Weight:

       Ciprofloxacin: 385.8
       Hydrocortisone: 362.5

   - 1.5 Pharmacologic Category: Synthetic fluoroquinolone

   - 1.6 Dosage Form: Otic suspension

Each mL of Ciprofloxacin-Hydrocortisone Otic Suspension contains:

Ciprofloxacin HCl	2 mg
Hydrocortisone	10 mg
Benzyl Alcohol	9 mg
Polysorbate 20	mg
Sodium Acetate, Trihydrate	mg
Glacial Acetic Acid	mg
Modified Soy Lecithin	mg
Sodium Chloride	mg
Polyvinyl Alcohol	mg
Water, Purified	mg

1.7 Route of Administration: Topical

1.8 Proposed Indication and Usage Section:

1.9 Proposed Dosage and Administration Section:

1.10 Related Drugs

Ciprofloxacin-Hydrocortisone Otic Suspension (IND

Other formulations:
Ciprofloxacin Otic Solution (IND

Cipro® Tablets- Approved indications for the treatment of infections caused by susceptible strains of the designated microorganisms in:

lower respiratory tract infections
skin and skin structure infections
bone and joint infections
urinary tract infections
typhoid fever
sexually transmitted diseases
infectious diarrhea

Cipro® I.V.- Approved indications for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below when the intravenous administration offers a route of administration advantageous to the patient:

urinary tract infections-mild, moderate, severe and complicated infections
lower respiratory infections- mild to moderate infections
skin and skin structure infections-mild to moderate infections
bone and joint infections-mild to moderate infections

Ciloxan® (ciprofloxacin HCl) Ophthalmic Solution- Approved indications for the treatment of infections caused by susceptible strains of the designated microorganisms in corneal ulcers and conjunctivitis as listed below.

Corneal Ulcers: *Pseudomonas aeruginosa, Serratia marcescens*, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* (Viridans Group)*

Conjunctivitis: *Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae*

*Efficacy for this organism was studied in fewer than 10 infections.

1.11 Material Reviewed

1.11.1 NDA 20-805 Cipro® HC Otic Suspension: Volumes 1, 14-52
1.11.2 IND
IND
1.11.3 Amendments reviewed: none

1.12 Regulatory Background

On October 27, 1994, a Pre-IND meeting was held with Miles, Inc., Pharmaceutical Division, to discuss the sponsor's plans for the development of an otic ciprofloxacin formulation for the treatment of otitis externa The discussion during this meeting centered around two main issues:

- The sponsor desired guidance in the development of an otic formulation which included hydrocortisone in addition to the antibiotic component since this was felt to be of potential therapeutic benefit and marketing advantage. In accordance with the Combination Rule, the Division recommended a clinical trial design with three treatment arms: ciprofloxacin alone, ciprofloxacin with hydrocortisone, and Cortisporin® otic suspension (as an active comparator agent). In this study, ciprofloxacin with hydrocortisone would have to demonstrate a clinically significant advantage over ciprofloxacin alone. Furthermore, the ciprofloxacin regimen approved for this indication would have to be therapeutically equivalent to Cortisporin® with respect to clinical efficacy.

- Regarding the indication for the sponsor and the Division agreed that the selection of an appropriate comparator agent was problematic since the most commonly used products for this condition, e.g., Cortisporin®, have cautionary labeling against the use of these potentially ototoxic preparations in patients with non-intact tympanic membranes. Therefore, the Division recommended use of an "historical" control for the proposed clinical trial. As in the otitis externa trials, compliance with the Combination Rule would require both a ciprofloxacin arm and a ciprofloxacin with hydrocortisone arm.

On January 20, 1995, the sponsor submitted concurrent IND applications for Ciprofloxacin Otic Solution (IND and Ciprofloxacin-Hydrocortisone Otic Suspension (IND The sponsor outlined two large clinical trials (220 evaluable patients per arm) designed to demonstrate that ciprofloxacin-hydrocortisone suspension was superior to ciprofloxacin otic solution in the time-to-relief of pain and otorrhea, respectively, for the proposed indications of in patients with non-intact tympanic membranes". Clinical therapeutic equivalence was to be demonstrated with Cortisporin® or for each of these indications, respectively.

Following initial review of the INDs, several safety concerns regarding the two otic preparations were noted, particularly with respect to the studies:

Because of the above safety concerns, the sponsor was notified that Protocol which planned to enroll patients with through a perforated tympanic membrane, had been placed on However, the consensus of the reviewing team was that the external otitis protocol (D94-008) could proceed because only patients with intact tympanic membranes would be enrolled, minimizing potential risks of ototoxity or use of a nonsterile product. Following teleconferences with the sponsor on March 1, 1995, and an outside consultant, on April 6, 1995, an FDA in-house meeting was held on May 31, 1995, to discuss issues related to the product's clinical hold status. The following conclusions were reached:

With respect to Protocol otitis externa), the Medical Officer IND Review outlined the following recommendations:

A Pre-NDA meeting to discuss a planned NDA submission for December 1996. Major issues covered during this meeting included:

To date, the sponsor has not submitted plans for the development of a sterile product formulation or for further animal toxicology studies, both of which will be required to proceed with protocol

2. Table of Contents

3. Chemistry/Manufacturing Controls

Please refer to the Chemistry, Manufacturing, and Controls Review by Dr. Dorota Matecka for detailed analysis. During the IND review process and the pre-NDA meeting, the FDA recommended that Cipro® HC Otic Suspension be prepared as a sterile product. A sterile formulation was recommended in anticipation that the product might be used off-label by physicians in patients with tympanic membrane perforations as is frequently done with the active control used in the clinical trials, Cortisporin® Otic Suspension (a sterile formulation). According to the minutes of the Pre-NDA meeting recorded by the sponsor, the hydrocortisone component of the suspension makes sterilization or filtration of the product problematic. Since the sponsor elected not to pursue a sterile formulation, the product must, by regulation, conform to the USP guideline for microbial limits. A formal consultation for microbial limits was requested from Peter Cooney, ONDC, on July 25, 1997. Dr. Cooney requested that the sponsor perform

4. Animal Pharmacology/Toxicology

Please refer to the Review and Evaluation of Pharmacology and Toxicology Data by Dr. Amy Ellis dated March 17, 1997, for detailed analysis. The sponsor submitted two controlled guinea pig studies performed by using µl of either the % ciprofloxacin or % ciprofloxacin % hydrocortisone otic formulations applied directly to the round window niche b.i.d. for 30 days. Although no ototoxicity of either formulation was detectable by ABR thresholds or alterations in cochlear hair cell morphology, the reviewer maintained that further studies using higher drug concentrations and dose volumes would be necessary to demonstrate that ciprofloxacin is not ototoxic when administered directly into the middle ear. Furthermore, since the drug product is intended for use in pediatric patients, juvenile guinea pig studies with attention to the effects of the product on the ossicles and middle ear mucosa were recommended. Although there was no objection to the use of this product for otitis externa, it was recommended that clinical studies involving a non-intact tympanic membrane be placed on hold until the sponsor further characterizes the potential ototoxicity of larger doses of ciprofloxacin administered into the middle ear with further animal studies.

5. Microbiology

Please refer to the Clinical Microbiological Review by Peter Dionne dated May 8, 1997, for detailed analysis. Briefly, the reviewer emphasized that "since this application is for a topical product and no correlation has been established between MICs or zone diameter breakpoints and clinical efficacy, no breakpoints or susceptibility test methods will be listed in the label," and "the listing of organisms which have a MIC_{90} value less than or equal to the drug's susceptibility breakpoint ... is inappropriate." However, based on the clinical effectiveness and the *in vitro* activity of Cipro® HC Otic Suspension in the two clinical trials, the reviewer recommended that the proposed label be revised to reflect that the product has been shown to be active against most strains of the following microorganisms:

6. Human Pharmacokinetics / Pharmacodynamics

Please refer to the Clinical Pharmacology/Biopharmaceutics Review submitted by Dr. Jenny Zheng dated May 7, 1997, for detailed review. Since Cipro® HC Otic Suspension is submitted for topical use in otitis externa, the sponsor requested a waiver of *in vivo* bioavailability studies. Assuming 100% bioavailability of the product following topical administration, the plasma levels of ciprofloxacin would be below the limits of quantitation. This determination is supported by a study of topical 0.3% ciprofloxacin drops t.i.d. for 14 days in pediatric patients with No serum concentrations of ciprofloxacin were detectable by on day 7 of therapy in any of the patients (Force et al.: Topical ciprofloxacin for systemic absorption, efficacy, and adverse effects. *Pharmacotherapy* 1993;13:680). Similarly, estimated serum levels of hydrocortisone following topical administration would be so low that they could not be differentiated from endogenous cortisol levels. Based on these points, application for a waiver of *in vivo* bioavailability studies was considered acceptable.

7. Human Clinical Experience
   - 7.1 Foreign Experience
     At the time of the NDA submission, the United States was the only country to which Bayer had submitted an application for marketing, according to the sponsor.
   - 7.2 Post-Marketing Experience: None
8. Clinical Studies
   - 8.1 Introduction

The Bayer Corporation has submitted NDA 20-805 to gain approval for ciprofloxacin-hydrocortisone otic suspension (referred to as Cipro HC within this review) in the treatment of acute otitis externa. Two randomized, prospective, non-blinded, multi-center clinical trials were performed comparing the safety and efficacy of ciprofloxacin-hydrocortisone otic suspension to a standard, approved therapy for this indication, polymyxin-B-neomycin-hydrocortisone otic suspension (referred to as PNH in this review). Because the product formulation includes two drug components, a third treatment arm using a solution of ciprofloxacin alone (referred to as Cipro SOLN in this review) was included in each study to demonstrate that the addition of hydrocortisone contributed to the therapeutic benefit of the product as specified by the FDA combination rule (CFR 21 Part 300.50).

Study #D94-008 was conducted from April 1994 through November 1995 in 30 centers throughout the United States enrolling a total of 842 patients. Study #1439 was performed in 30 centers throughout nine European countries from May 1995 through March 1996 and also enrolled a total of 842 patients. The distribution of all patients enrolled in the study drug and control groups was as follows:

Study No.	Cipro HC	PNH	Cipro SOLN
D94-008	282	275	285
1439	282	281	279

8.2 Indication: Acute Otitis Externa

8.2.1. Trial #1: Study No. D94-008 (U.S. Study)

"Prospective, Controlled, Randomized, Non-Blinded, Multi-Center Clinical Trial of Ciprofloxacin Otic Drops With or Without Hydrocortisone Versus Polymyxin B-Neomycin-Hydrocortisone Otic Drops in the Treatment of Acute Diffuse Bacterial Otitis External Otitis" (Volumes 15-31, NDA 20-805)

Objectives/Rationale

According to the sponsor, the objectives of this study were to compare the efficacy and safety of Cipro SOLN (3 drops BID for 7 days of therapy) with Cipro HC (3 drops BID for 7 days of therapy) and PNH (3 drops TID for children 2-12 and 4 drops TID for adults, both for 7 days of therapy) in the treatment of acute otitis externa.

The specific primary comparisons to establish product efficacy were:

C1. To test for equivalence in clinical response rates between Cipro HC and PNH as measured by the rate of clinical resolution and improvement at post-treatment day 3-7;

C2. To establish the equivalence in clinical response rates between Cipro SOLN and PNH as measured by the rate of clinical resolution and improvement at post-treatment day 3-7;

C3. To demonstrate that the time to relief of pain for Cipro HC was superior to the time to relief of pain for Cipro SOLN.

The primary efficacy objectives were:

Objective A: To establish efficacy of Cipro SOLN. This is achieved by showing comparison C2.

Objective B: To establish efficacy of Cipro HC. This is achieved if all the three primary comparisons C1, C2, and C3 are shown.

Study Design

This study was a prospective, randomized, non-blinded, multi-center, controlled clinical trial which compared the efficacy and safety of ciprofloxacin otic solution without hydrocortisone (3 drops BID for 7 days of therapy) with ciprofloxacin otic suspension with hydrocortisone (3 drops BID for 7 days of therapy) and polymyxin B-neomycin-hydrocortisone otic suspension (3 drops TID for children 2-12 and 4 drops TID for adults, both for 7 days of therapy) in the treatment of acute otitis externa.

After meeting the inclusion/exclusion criteria and obtaining informed consent, the patients were randomized to receive one of the three seven-day regimens outlined above. The insertion of a wick to facilitate delivery of the drops was permitted at the discretion of the investigator and was noted on the case report form. There was to be one during treatment visit (on day 2 or 3 of therapy) if clinical symptoms were not improved and two post-treatment visits on day 3-7 and day 14-28 following completion of therapy.

Clinical and bacteriologic efficacy determinations were made on the two post-treatment visits; safety of the drug treatment was to be monitored by "careful clinical observations."

MO Comments: Cortisporin Otic Suspension (i.e., PNH) has an approved indication for "the treatment of superficial bacterial infections of the auditory canal caused by organisms susceptible to the action of the antibiotics" at the dosage prescribed in this trial and is an appropriate comparative control.

According to the sponsor, the trial was not blinded because solutions and suspensions cannot be made to look identical. The use of "double dummies" would pose problems with delivery of the study drug into the limited volume of the ear canal, particularly in children. The protocol states that the investigator "was not to be aware of which study drug the patient was to be assigned to until after the patient had been enrolled and randomized," but was apparently not blinded thereafter. Since the primary efficacy endpoint of the study was a clinical evaluation of edema, otalgia, and tenderness on the end of therapy visit, the lack of investigator blinding could theoretically have introduced a rating bias. This point was recognized during the medical officer IND review of this product with recommendations to the sponsor for investigator blinding.

Protocol Overview

Population

Outpatient male and female patients presenting with a diagnosis of acute diffuse otitis externa were considered eligible for enrollment in this trial if they met the following criteria:

Key Inclusion Criteria:

- at least two years of age
- clinical diagnosis of acute diffuse bacterial otitis externa with minimum inclusion parameters of (1) otalgia, (2) edema, and (3) tenderness, confirmed within two days prior to therapy
- signs and symptoms present for less than 3 weeks
- informed consent

Key Exclusion Criteria

- history of allergy to ciprofloxacin or other carboxyquinolone derivatives, polymyxin B sulfate, neomycin sulfate, or hydrocortisone
- clinical presentation with otitis media, invasive malignant otitis externa, or dermatitis (psoriasis or seborrhea) in the area of the affected ear
- diagnosis of and/or treatment for otitis externa within the 30 day period prior to entering the trial
- history of perforated tympanic membrane
- known fungal infection of the ear
- furuncles, mastoid cavities, stenosis, exostosis, or tumors of the ear
- patients known or suspected of having an infection requiring systemic antibacterial therapy
- significant underlying disease, including diabetes, neutropenia, HIV infection or other immunocompromised conditions
- prior enrollment in this trial
- patients receiving another investigational drug within the last 30 days

MO Comments: Children are a high risk population for acute diffuse otitis externa due to swimming-related water exposure to the ear canal. Since there is no scientific evidence to indicate that the bacteriology or pathophysiology of acute otitis externa differs between the adults and children, inclusion of pediatric patients at least two years of age in this clinical trial is appropriate and desirable.
The outlined examination criteria (otalgia, edema, tenderness) and duration of symptoms should effectively screen out patients with chronic otitis externa or underlying dermatologic conditions, from the desired acute otitis externa patient population. Determination of otalgia and tenderness in pediatric patients less than age 3-4 years will likely rely more heavily on investigator observation due to the limited verbal skills in this population.

Evaluability Criteria

For a course of therapy to be judged valid for evaluation of effectiveness of drug therapy, the following criteria were to be met and documented on the case report form:

- a diagnosis of acute, diffuse bacterial external otitis must have been confirmed at pre-treatment by the presence of appropriate clinical signs and symptoms consistent with documented otitis externa as follows:

  -edema
  -otalgia
  -tenderness

  (All three above findings were required for enrollment into the study.)

- The trial drug must have been given for a minimum of seven full days and 90% of doses must have been administered unless an early treatment failure occurred.
- No other antimicrobial therapy must have been administered including the 3-7 and 14-28 day post-treatment follow-up period.
- A clinical response of the patient (primary efficacy variable) at the end of therapy (3-7 days post-therapy) must have been determined.

MO Comment: The evaluability criteria listed above were modified internally by the sponsor during the final data analysis as follows:

1) **Any patient receiving more than eight days of therapy was considered invalid.**
2) **If a patient was valid in all other respects but the patient pain diary was missing, the patient's course of treatment was considered invalid.**
3) **If at the follow-up visit it was found that the patient had received an alternative antibiotic between the end of treatment (3-7 days post-therapy) and follow-up (14-28 days post-therapy), then the evaluation was considered indeterminate for follow-up and was not used in the analysis of efficacy; however, the patient will still be valid for an end of treatment evaluation.**
4) **If the patient's dosing compliance could not be verified, then the course of treatment was considered invalid.**

Clinical Response Endpoints

Serial examinations of the patients were performed to assess the effect of therapy on the signs and symptoms of acute diffuse bacterial otitis externa. There was one during therapy visit (on day 2 or 3) if clinical symptoms were not improving to assess for possible discontinuation from the study (early treatment failure). Otherwise, two post-treatment visits were used to assess clinical response:

End of Therapy Visit (3-7 days after completion of therapy)

At completion of therapy (3-7 days post-therapy), the clinical response was to be graded as follows:

Resolution: Absence of signs and symptoms related to the infection (relative to patient's trial entry baseline). No additional antimicrobial therapy is required.

Improvement: Improvement of most signs and symptoms related to the infection (relative to the patient's trial entry baseline). No additional antimicrobial therapy is required.

Failure: No change, worsening or reappearance of the signs and symptoms of infection. Patient requires additional antimicrobial therapy.

No Evaluation: Data is missing or evaluation not possible because of patient non-availability.

Follow-up Visit (14-28 days after completion of therapy)

At the 14-28 day follow-up, the clinical response was to be graded as follows:

Continued Resolution: Clinically improved or resolved at end of therapy and resolved at 14-28 day follow-up.

Relapse: Clinically resolved or improved at end of therapy, but reappearance of signs and symptoms of infection associated with otitis externa. Reinstitution of antibiotic was required.

No Evaluation: Data is missing or evaluation not possible because of patient non-availability.

*All patients who were treatment failures either during or at the end of therapy were to be treated with an appropriate alternative antimicrobial and then clinically evaluated 14-28 days following the date of their treatment failure on trial drug.

MO Comments: Among the previous and current medical reviewers for this product, there was consensus that one would expect a complete resolution of otalgia during the End of Therapy Visit (Day 3-7 post-therapy) following effective treatment for acute otitis externa. Therefore, the IND Medical Officer Review recommended that patients with persistent otalgia at the End of Therapy Visit be classified as "Failure" rather than "Improvement." The inclusion of such patients in the "Improvement" category in the present NDA raises concerns that these

patients may have incomplete eradication of their infection and could relapse later on. Since the primary clinical efficacy statistical plan proposes inclusion of both "Resolution" and "Improvement" as successful outcomes, these patients could theoretically inflate the product's true success rate.

The primary clinical efficacy determination variable in this protocol was defined as the clinical response at the "End of Therapy" visit on Day 3-7 following completion of the study drug. This time window for the clinical efficacy evaluation was considered acceptable for the following reasons:

1) **A three day period off study drug would allow sufficient time for mechanical clearance of the drops from the external auditory canal so as not to complicate the clinical evaluation of residual edema and otorrhea.**
2) **A three day period off study drug would allow for sufficient time off antimicrobial therapy to detect an early relapse of the infection if the study drug was merely suppressing rather than eradicating the infection.**
3) **The time window does not extend out so far to cause significant chances of re-infection.**

The current NDA summary report for this study outlines several modifications of the statistical plan including expansion of the "End of Therapy" time window from 3-7 days post-therapy to 1-10 days post-therapy. During a teleconference with the sponsor on September 4, 1997, the sponsor explained that this modification was performed following completion of the data collection, and thus was made internally without submission of a protocol amendment to the FDA. The medical officer communicated the Division's concerns regarding a primary clinical efficacy determination in patients who had only been off study drug for 1-2 days; however, the expansion of the time window out to 10 days post therapy was felt to be an acceptable alteration of the statistical plan. Therefore, it was agreed the data would be re-analyzed, using a 3-10 day time window for patients to be considered evaluable for clinical efficacy.

Time to End of Pain

Each patient/guardian was provided with a patient diary with instructions to record pain severity at least twice daily during the seven day course of therapy using a visual analog scale which ranged from 0 (no pain) to 15 (severe pain). For children less than 12, the sponsor provided pictures of faces showing varying degrees of discomfort to assist in expressing pain severity to the guardian recording the scores. On the final day of therapy the patient/guardian was instructed to record the time/date at which the ear pain ended in a field labeled "Time/Date Pain Ended." This field was used to determine the time to end of pain using the following data conventions:

1. If the "Time/Date Pain Ended" field was not blank, then the time to end of pain was recorded as the length of time between the time of the first dose of study drug and the time entered in the field.
2. If the "Time/Date Pain Ended" field was blank, then pain did not end for the patient while the patient was under observation, and the value of the time to end of pain variable was set to the length of time between the time of the first dose of study drug and the last time point when a pain measurement was recorded. For statistical purposes, such an observation was considered censored.

In this trial, unlike the parallel trial in Europe (Study No. 1439), the pain severity scores were not used in determination of the time to end of pain since "a pain score only measured the intensity of pain at the time point when the patient was making a self-evaluation." Hence, a pain score of zero does not necessarily imply a definitive end of ear pain; it merely states that there was no pain at the time of the self-evaluation.

MO Comment: The visual analog scales were apparently only used as an aid to patients in determining their "Time/Date Pain Ended" entry in the diary since only this entry was used in the calculation of the time to end of pain. The validity of this method of pain severity assessment in pediatric patients, particularly those less than 4 years of age, is uncertain. In very young patients, the parent/guardian is essentially "estimating" the degree of discomfort based on irritability and localizing behaviors (ear pulling, scratching). Based on experience with pain measurements in clinical trials in the Division of Anti-Inflammatory, Analgesic, & Ophthalmic Drug Products, the majority of children age 7 and above appear to be able to reliably report pain severity scores. Review of the time to end of pain should consider possible age-related factors affecting the validity of the assessment in younger pediatric patients.

Bacteriologic Response Endpoints

The bacteriologic response was based on the results of cultures from the "deep portion of the canal" of the affected ear (to avoid contamination from the entrance to the ear canal) using a Transwab ENT with charcoal system provided by the central laboratory. Specimens were transported by Airborne Express back to the central laboratory for processing. Specimens taken before and after therapy and were to be graded as follows:

End of Therapy (3-7 days after completion of therapy)

Presumed Eradication: No material to culture and clinical resolution.

Eradication: Causative organisms absent at the completion of therapy.

Persistence: Causative organism present at the completion of therapy.

Indeterminate: Bacteriological response to the trial drug is not evaluable for any reason (i.e., post-treatment culture unobtainable, not performed when appropriate, etc.)

Superinfection: A new infection causing organism present at any time during therapy or up to seven days after completion of therapy and requiring specific treatment. This response was to be evaluated separately.

Follow-up (14-28 days after completion of therapy)

If within the 14-28 day follow-up the patient presented with clinical signs and symptoms of recurring external otitis, then a repeat culture should have been performed. The culture results were then to be graded as:

Continued Eradication: Causative organism (s) documented or presumed to have been eradicated at end of therapy, absent or no material to culture at follow-up.

Eradication with Recurrence* (relapse): Causative organism(s) documented or presumed to have been eradicated at the end of therapy, but reappearance of the original causative

organism(s) at or before the 14-28 day follow-up visit associated with signs or symptoms of infection requiring antibiotic treatment.

Eradication with Re-infection*: Causative organism(s) documented or presumed to have been eradicated at the end of therapy, but presence of another infecting organism(s) at or before the 14-28 day follow-up visit associated with signs or symptoms of infection requiring antibiotic treatment.

Indeterminate: Bacteriological response to the trial drug is not evaluable for any reason (i.e., post-treatment culture unobtainable, not performed when appropriate, etc.).

* Recurrence (relapse) may be distinguished from reinfection by comparing the genus and species and antibiogram of the organism cultured before therapy with the genus, species, and antibiograms of the organism cultured after therapy. In some cases, serotyping of organisms may be desirable.

MO Comments: Patients with a known fungal infection of the ear were excluded from enrollment into this trial. However, patients who were enrolled and subsequently grew out only fungal organisms on their pre-treatment culture were still considered evaluable patients. The protocol did not address the issue of fungal isolates directly. However, during a teleconference on September 14, 1997, the sponsor stated that fungal isolates were, in general, considered as colonizing organisms rather than pathogens. Thus, patients who had positive fungal cultures but negative bacterial cultures were rated as "eradication" and "continued eradication" for bacterial site efficacy on the "End of Therapy" and "Follow-up" visits, respectively.

Statistical Considerations

Tests of significance were two-sided with alpha=0.05. Comparability of the treatment groups with respect to categorical demographic, medical, and study execution variable characteristics was tested using a Cochran-Mantel-Haenszel test statistic (which adjusts for center) or a chi-square test. Comparability of the treatment groups with respect to continuous variables (age, weight, duration of otitis externa) was determined using a two way analysis of variance. For clinical and bacteriological responses, the Mantel-Haenszel adjusted differences in success rates were computed between the following groups: PNH and Cipro HC, PNH and Cipro SOLN, and Cipro HC and Cipro SOLN. Comparisons of time to end of pain between the groups were performed using a nonparametric method, the log rank test. No interim analysis was planned or performed for this study.

MO Comment: This NDA was a paper submission of data listings compiled by the sponsor from patient case report forms and pain score diaries. Since the original case report forms and patient diaries were not included with the NDA, a random sample of 5% of these documents from the intent-to-treat population was requested from the sponsor. These documents were used to audit the accuracy of transcription of the clinical and microbiological data to the data listings within the NDA. This audit revealed accurate and consistent capture of data from original case report forms and diaries by the sponsor's data listings.

The medical and statistical reviewers concluded that the integrity of the data base and the robustness of the clinical efficacy rates would permit a random sample of the intent to treat population to assess accuracy and consistency of clinical judgments concerning patient evaluability and efficacy/safety determinations. A 10% and a 20% random sample of the efficacy evaluable and efficacy non-evaluable patients, respectively, were performed. The medical officer agreed with the sponsor's determinations of patient evaluability and efficacy determination with one notable exception. By expanding the time window for the End of Therapy visit, the sponsor considered patients who were off study drug for less than three days to

be evaluable for the primary efficacy determination. For the reasons outlined above in the Clinical Response Endpoints section, the Division requested that the sponsor reanalyze the data using a 3-10 post-therapy window for the primary efficacy determination. The revised data base and tables generated by the sponsor (dated November 14, 1997) were judged to be an accurate reflection of the results of this clinical trial by the statistical and medical reviewers. Thus, the sponsor's revised tables were used, with minor format modifications, in the presentation of the study results in the following section.

Study Results

Study Population

A total of 842 patients were enrolled in 30 centers throughout the United States from April 1995 through November 1995 as shown in Table 1. None of the investigators at these centers appear on the FDA's "Disqualified/Restricted/Assurance List for Clinical Investigators." The Curriculum Vitae for each investigator was reviewed and found to be acceptable.

MO Comment: The study centers were generally well balanced with respect to enrollment of patients evaluable for safety and efficacy. The four smallest centers, which enrolled a total of 36 patients, were combined and treated as one center for the statistical analysis of clinical and bacteriological responses controlling for possible center effect. According to the sponsor, this was necessary so that analysis of the primary clinical response variable included all patients. The FDA statistical reviewer, Greg Soon, agreed that the combination of the smaller centers was a valid analytical procedure for this study. The predominance of patients enrolled in southeastern study centers reflects the environmental conditions which predispose patients to develop otitis externa (heat, humidity, outdoor water activities).

TABLE 1
PATIENT ENROLLMENT BY INVESTIGATOR AND TREATMENT GROUP

INVESTIGATOR (Location)	CIP/SOLN			CIP+HC/SUSP			PNH/SUSP		
	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED
MCCARTY (Fresno, CA)	2	2	4	5	0	5	4	0	4
BRANDON (San Diego)	9	0	9	9	0	9	8	2	10
GUTHRIE (Salt Lake City, UT)	8	1	9	8	0	8	10	0	10
JOHNSON (Winchester, VA)	6	6	12	9	2	11	7	4	11
LUCENTE (Brooklyn, NY)	4	0	4	2	2	4	0	2	2
HARPER (Raleigh, NC)	3	4	7	5	2	7	6	0	6
FINN (North Charleston, SC)	13	1	14	11	1	12	9	4	13
NEWMAN (Oceanside, CA)	6	3	9	5	4	9	7	3	10
PRESTIDGE (Dallas, TX)	5	2	7	7	0	7	7	0	7
UNNOPPET (Birmingham, AL)	3	1	4	3	1	4	3	0	3
ONDREJICKA (Jacksonville, FL)	6	0	6	4	2	6	3	3	6
SCHWARTZ/WINNER (Atlanta, GA)	1	1	2	2	0	2	1	1	2
GRAHAM (Altamonte Springs, GA)	9	1	10	8	1	9	6	3	9
ROBERTS (Alabaster, AL)	3	0	3	2	0	2	3	0	3
ROSENTHAL (Houston, TX)	0	5	5	3	3	6	3	3	6
TUCKER (Wenatchee, WA)	9	0	9	10	0	10	7	1	8

TABLE 1 (cont'd)
PATIENT ENROLLMENT BY INVESTIGATOR AND TREATMENT GROUP

INVESTIGATOR (Location)	CIP/SOLN			CIP+HC/SUSP			PNH/SUSP		
	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED
PUOPOLO (Milford, MA)	10	0	10	10	0	10	10	1	11
HAWKINS (Louisville, KY)	3	0	3	1	1	2	1	1	2
PISTORIUS (Shreveport, LA)	19	3	22	20	2	22	19	3	22
DREHOBL (San Diego, CA)	18	2	20	17	3	20	15	4	19
SPERLING (Fountain Valley, CA)	11	5	16	9	7	16	13	3	16
KIRSTEIN (Salt Lake City, UT)	8	1	9	5	3	8	8	0	8
ADELGLASS (Dallas, TX)	10	0	10	8	2	10	10	0	10
BOCK (Harleysville, PA)	15	0	15	14	2	16	13	1	14
BONNET (Lake Hopatcong, NJ)	7	0	7	7	0	7	5	1	6
GOLDSTEIN (Palm Harbor, FL)	8	0	8	7	1	8	7	1	8
HIPPERT (Fleetwood, PA)	5	2	7	7	1	8	5	2	7
JORDAN (Winston-Salem, NC)	6	0	6	5	2	7	6	0	6
WESTBERRY (Vero Beach, FL)	16	5	21	16	4	20	16	3	19
WILLIAMS (Daytona Beach, FL)	16	1	17	17	0	17	16	1	17
TOTAL PATIENTS	**239**	**46**	**285**	**236**	**46**	**282**	**228**	**47**	**275**

Evaluability

Of the 842 patients enrolled in this study, all patients were considered evaluable for safety; 703 (83%) patients were considered evaluable for efficacy analysis. The reasons for exclusion of patients from efficacy analysis are listed in Table 2 below. The most common reasons for disqualification were exclusion/inclusion criteria violations, noncompliance with dosage regimen, and an End of Therapy evaluation that was outside the specified time window (i.e., 3-10 days post-therapy). The overall percentage of patients excluded did not significantly differ among the three groups (P value = 0.950).

MO Comment: The reasons for exclusion of patients from the efficacy evaluable population were similar among the three treatment groups. Since individual case reports were not included in the NDA submission, the Division requested clarification of the nature of the exclusion/inclusion criteria violations which occurred in a total of 49 patients. According to the sponsor, 38 patients had "an insufficient number of protocol required clinical signs or symptoms," 8 patients had received prior antibiotic therapy, two patients had a perforated tympanic membrane, and one patient was diabetic.

TABLE 2

REASONS FOR EXCLUSION FROM EFFICACY ANALYSIS (PATIENT INVALIDITY)
POPULATION: ALL PATIENTS ENROLLED

	CIP/SOLN N = 285		CIP+HC/SUSP N = 282		PNH/SUSP N = 275		PVALUE
	N	PERCENT	N	PERCENT	N	PERCENT	
TOTAL INVALID FOR EFFICACY	46	16.1	46	16.3	47	17.1	0.950
EOT EVALUATION OUT OF WINDOW	7	2.5	8	2.8	10	3.6	
EXCLUSION/INCLUSION CRITERIA VIOLATION	16	5.6	19	6.7	14	5.1	
INADEQUATE DURATION OF TREATMENT	1	0.4	0	0.0	1	0.4	
LOST TO FOLLOW-UP	3	1.1	7	2.5	2	0.7	
NON-COMPLIANCE WITH SUBJECT DIARY	0	0.0	2	0.7	1	0.4	
NONCOMPLIANCE WITH DOSAGE REGIMEN	15	5.3	8	2.8	14	5.1	
PROTOCOL VIOLATION	4	1.4	2	0.7	5	1.8	

PERCENT IS OF TOTAL POPULATION (N IN HEADING)

THE P-VALUES ARE CALCULATED USING A CHI-SQUARE TEST

Demographics

Demographic characteristics for the three treatment arms are depicted in Tables 3 and 4 for the intent-to-treat (ITT) population. Tables 5 and 6 contain the demographic characteristics for the subset of clinically evaluable patients from the ITT population. No significant differences in sex, race, general status of health, or age distribution were present either among the treatment groups or between the ITT and clinically evaluable populations. In all groups, approximately half of the patients were less than sixteen years of age, and approximately ten percent of patients were less than six years of age. The groups were also similarly balanced with respect to two adjunctive treatment measures: debridement of the ear canal and use of an ear wick.

MO Comment: Although no known differences between adult and pediatric acute otitis externa exist with respect to disease pathophysiology or bacteriology, the Division encourages inclusion of pediatric subjects in clinical trials to gain safety and efficacy experience with study drug in this population. The large percentage of pediatric patients enrolled in this trial is helpful in supporting the indication in this population.

Debridement of the ear canal (suctioning, curretage) and wick insertion are considered mainstays of therapy in otitis externa by otolaryngologists, particularly in severe or chronic cases. It is, therefore, important to note these procedures were performed in nearly equal percentages of patients in all treatment groups. The relatively low overall percentage of patients receiving debridement reflects the fact that most patients were seen by primary care physicians who probably did not have the equipment and/or experience to perform a debridement procedure.

Baseline characteristics of otitis externa were very similar across treatment groups with respect to duration of the present episode and the number of prior episodes in the past 12 months as shown in Tables 7 and 8 (Volume 15, pp. 90-92) of the sponsor's U.S. study report in the NDA submission (not shown here).

TABLE 3

CATEGORICAL DEMOGRAPHIC, TREATMENT AND BASELINE MEDICAL CHARACTERISTICS

POPULATION: ALL PATIENTS VALID FOR SAFETY

VARIABLE (P-VALUE)		CIP/SOLN (N=285)		CIP+HC/SUSP (N=282)		PNH/SUSP (N=275)	
		N	PCT	N	PCT	N	PCT
SEX (P=0.378)	FEMALE	143	50.2	152	53.9	132	48.0
	MALE	142	49.8	130	46.1	143	52.0
RACE (P=0.681)	ASIAN	0	0	3	1.1	3	1.1
	BLACK	7	2.5	11	3.9	6	2.2
	HISPANIC	10	3.5	7	2.5	10	3.6
	OTHER	3	1.1	4	1.4	4	1.5
	WHITE	265	93.0	257	91.1	252	91.6
GENERAL STATUS OF HEALTH (P=0.838)	EXCELLENT	193	67.7	197	69.9	185	67.3
	FAIR	2	0.7	1	0.4	3	1.1
	GOOD	90	31.6	84	29.8	87	31.6
LOCATION OF INFECTION (P=0.403)	BILATERAL	41	14.4	46	16.3	32	11.6
	LEFT	117	41.1	123	43.6	127	46.2
	RIGHT	127	44.6	113	40.1	116	42.2
DEBRIDEMENT OF THE EAR? (P=0.493)	NO	249	87.4	251	89.0	249	90.5
	YES	36	12.6	31	11.0	26	9.5
USE OF AN EAR WICK? (P=0.43)	NO	276	96.8	275	97.5	270	98.2
	UNKNOWN	0	0	0	0	1	0.4
USE OF AN EAR WICK? (P=0.43)	YES	9	3.2	7	2.5	4	1.5

TABLE 4

DEMOGRAPHICS - AGE
POPULATION: ALL PATIENTS VALID FOR SAFETY

RESULTS FOR POOLED DATA

	CIP/SOLN N=285			CIP+HC/SUSP N=282			PNH/SUSP N=275		
DISTRIBUTION (YRS)	N	(%)	(CUM %)	N	(%)	(CUM %)	N	(%)	(CUM %)
	31	10.9	10.9	25	8.9	8.9	32	11.6	11.6
	77	27.0	37.9	89	31.6	40.4	66	24.0	35.6
	29	10.2	48.1	25	8.9	49.3	38	13.8	49.5
	148	51.9	100.0	143	50.7	100.0	139	50.5	100.0
MEAN		25.0			23.3			25.0	
MEDIAN		18			17			17	
STANDARD DEVIATION		18.5			16.9			18.7	
RANGE									

P-VALUES OF F STATISTICS USED TO TEST FOR EQUALITY OF MEANS FOR MAIN EFFECTS:
DRUG=0.4 CENTER=0.0001
STATISTICS CALCULATED USING SS3 CRITERIA.

TABLE 5
CATEGORICAL DEMOGRAPHIC, TREATMENT AND BASELINE MEDICAL CHARACTERISTICS
POPULATION: ALL PATIENTS VALID FOR EFFICACY

VARIABLE (P-VALUE)		CIP/SOLN (N=239)		CIP+HC/SUSP (N=236)		PNH/SUSP (N=228)	
		N	PCT	N	PCT	N	PCT
SEX (P=0.4)	FEMALE	120	50.2	129	54.7	110	48.2
	MALE	119	49.8	107	45.3	118	51.8
RACE (P=0.678)	ASIAN	0	0	2	0.8	2	0.9
	BLACK	7	2.9	10	4.2	5	2.2
	HISPANIC	8	3.3	6	2.5	6	2.6
	OTHER	3	1.3	1	0.4	4	1.8
	WHITE	221	92.5	217	91.9	211	92.5
GENERAL STATUS OF HEALTH (P=0.882)	EXCELLENT	172	72.0	167	70.8	157	68.9
	FAIR	2	0.8	1	0.4	2	0.9
	GOOD	65	27.2	68	28.8	69	30.3
LOCATION OF INFECTION (P=0.365)	BILATERAL	37	15.5	37	15.7	24	10.5
	LEFT	98	41.0	101	42.8	104	45.6
	RIGHT	104	43.5	98	41.5	100	43.9
DEBRIDEMENT OF THE EAR? (P=0.44)	NO	211	88.3	212	89.8	209	91.7
	YES	28	11.7	24	10.2	19	8.3
USE OF AN EAR WICK? (P=0.555)	NO	231	96.7	229	97.0	224	98.2
	YES	8	3.3	7	3.0	4	1.8

TABLE 6
DEMOGRAPHICS - AGE
POPULATION: ALL PATIENTS VALID FOR EFFICACY

RESULTS FOR POOLED DATA

	CIP/SOLN N=239		CIP+HC/SUSP N=236		PNH/SUSP N=228	
DISTRIBUTION (YRS)	N	(%)	N	(%)	N	(%)
	26	10.9	21	8.9	27	11.8
	66	27.6	77	32.6	53	23.2
	27	11.3	21	8.9	34	14.9
	120	50.2	117	49.6	114	50.0
MEAN	24.6		23.6		24.3	
MEDIAN	17		16		17	
STANDARD DEVIATION	18.5		17.4		17.6	
RANGE						

P-VALUES OF F STATISTICS USED TO TEST FOR EQUALITY OF MEANS FOR MAIN EFFECTS:
DRUG=0.8414 CENTER=0.0001
STATISTICS CALCULATED USING SS3 CRITERIA.

Clinical Efficacy

Clinical Response at End of Therapy and Followup

From the ITT population, a total of 703 patients (83%) were evaluable for clinical efficacy: 239 Cipro SOLN patients, 236 Cipro HC patients, 228 PNH patients. Of these patients, between 97% and 98% received a full course of treatment per the study guidelines. A total of 20 patients in the efficacy evaluable population received five days or less of therapy due to either adverse events or insufficient therapeutic effect (treatment failure): six Cipro SOLN patients, seven Cipro HC patients, and seven PNH patients.

Although approximately 10-15% of patients in the treatment groups had bilateral infections, clinical response was recorded at the patient level rather than at the individual ear level. Patient level responses were used because the responses of the right and left ears in these patients were not likely to be independent, according to the sponsor. The response of the worse of the two ears in these patients was recorded as the patient level response.

Table 7 summarizes the clinical efficacy results at the End of Therapy (primary efficacy variable). Patients recorded as "missing" at the End of Therapy visit had submitted a valid pain score diary but did not have an End of Therapy visit within the designated time window. These patients were only considered evaluable for the time to end of pain efficacy analyses, and thus do not appear in the calculation of clinical response rates.

The clinical success rates (resolution + improvement) at the End of Therapy visit for Cipro SOLN patients, Cipro HC patients, and PNH patients were 92.8%, 90.1%, and 87.2%, respectively. The 2-tailed 95% confidence interval for the Mantel-Haenszel weighted estimate of differences in efficacy rates between treatment arms is shown at the bottom of Table 7. For clinical success defined as resolution + improvement, the estimated difference in efficacy rates between Cipro HC and PNH was 0.02 at the End of Therapy visit. Since the lower bound of the 95% confidence interval was -0.0339, the Division's criteria for therapeutic equivalence (greater than -0.10) of the two drugs is met. If success is defined as resolution only, the estimated difference in efficacy rates was -0.0367. Since an equivalence delta of 0.20 is used for efficacy rates less than 80%, the lower bound of the confidence interval of this difference (-0.1142) also meets the criteria for therapeutic equivalence.

Clinical efficacy data from the Follow-up Visit (Day 11-30 post-therapy) were available for 223 Cipro SOLN patients, 223 Cipro HC patients, and 214 PNH patient as shown in Table 8, representing 95%, 96% and 94% of the efficacy evaluable patients in the three groups, respectively. Similar rates of continued resolution, relapse, and failures (carried forward from the End of Therapy Visit), were noted for the three groups.

MO Comment: Therapeutic equivalence of Cipro HC with the FDA-approved comparator for this indication is demonstrated when success is defined as either "resolution + improvement" or "resolution" at the primary efficacy endpoint. Low rates of relapse (<4%) are noted for all three groups at the Follow-up visit which supports the use of "resolution+improvement" as the definition of a successful outcome in the primary efficacy analysis.

TABLE 7
SUMMARY OF PATIENT CLINICAL RESPONSES AT END OF THERAPY

POPULATION: ALL PATIENTS VALID FOR EFFICACY

VARIABLE		CIP/SOLN (N=239)		CIP+HC/SUSP (N=236)		PNH/SUSP (N=228)	
		N	PCT	N	PCT	N	PCT
CLINICAL RESPONSE AT END OF THERAPY	RESOLUTION	179	74.9	165	69.9	167	73.2
	IMPROVEMENT	40	16.7	45	19.1	31	13.6
	FAILURE	17	7.1	23	9.7	29	12.7
	MISSING	3	1.3	3	1.3	1	0.4

			Mantel-Haenszel Estimate of Difference in Rates		
Variable	Drug Group	Rate	Contrast	Estimate	95% Conf. Interval
Patient Clin Resp EOT (1)	CIP/SOLN	219/236 = 92.80%	CIP/SOLN - PNH/SUSP:	0.0520	(-.0009, 0.1049)
	CIP+HC/SUSP	210/233 = 90.13%	CIP+HC/SUSP - PNH/SUSP:	0.0227	(-.0339, 0.0793)
	PNH/SUSP	198/227 = 87.22%			
Patient Clin Resp EOT (2)	CIP/SOLN	179/236 = 75.85%	CIP/SOLN - PNH/SUSP:	0.0225	(-.0532, 0.0982)
	CIP+HC/SUSP	165/233 = 70.82%	CIP+HC/SUSP - PNH/SUSP:	-.0367	(-.1142, 0.0409)
	PNH/SUSP	167/227 = 73.57%			

(1) RESOLUTION + IMPROVEMENT vs FAILURE.
(2) RESOLUTION vs IMPROVEMENT + FAILURE.
Rates and confidence intervals were calculated controlling for possible center effect.
Five small centers (1, 5, 12, 15,20) were combined so that the analysis of the primary variable (EOT clin response) included all centers.

FOR PTS WITH VALID BILATERAL INFECTIONS, RESPONSE IS THE WORSE OF THE TWO

TABLE 8
SUMMARY OF PATIENT CLINICAL RESPONSES AT FOLLOW-UP
POPULATION: ALL PATIENTS VALID FOR EFFICACY

VARIABLE		CIP/SOLN (N=223)		CIP+HC/SUSP (N=223)		PNH/SUSP (N=214)	
		N	PCT	N	PCT	N	PCT
CLINICAL RESPONSE AT FOLLOW-UP	CONTINUED RESOLUTION	200	89.7	196	87.9	178	83.2
	RELAPSE	6	2.7	4	1.8	7	3.3
	FAILURE	17	7.6	23	10.3	29	13.5

Follow-up Clinical Response of Patients Rated as "Improvement" at End of Therapy

As discussed in the Clinical Response Endpoints section, the medical reviewers were concerned about the sponsor's classification of patients with residual pain and tenderness as "Improvement" in certain instances. Specifically, the reviewers were concerned that these residual pain symptoms may have represented an incomplete resolution of infection. Therefore, follow-up on all patients classified as "Improvement" was requested from the sponsor to ensure that these patients did not subsequently have a relapse of their infection. In a written response dated September 18, 1997, the sponsor identified a total of 36 patients with a clinical response of "Improvement" at the End of Therapy visit for whom a follow-up clinical response was available: 12 Cipro SOLN patients, 14 Cipro HC patients, 10 PNH patients. Only 3 patients, one per treatment arm, subsequently developed a relapse of their infection. All remaining patients were rated as "Continued Resolution."

MO Comment: Again, the low incidence of relapse in patients rated as "Improvement" at the End of Therapy visit supports the validity of combining the "Improvement" and "Resolution" populations as the primary clinical efficacy definition of a successful outcome.

Clinical Response by Age Group

Table 9 summarizes the clinical response at the End of Therapy by age group. Adult patients (≥17 years) in all treatment arms appeared to have a higher rate of clinical failure and incomplete resolution (i.e., "improvement") when compared to the pediatric population.

MO Comment: All three otic preparations demonstrated clinical efficacy rates in pediatric patients which appeared to equal or exceed efficacy rates in adults. Although the pathophysiology of otitis externa is thought to be similar in children or adults, a number of factors could account for the observed differences in efficacy rates. The effectiveness of administering the otic drops into the ear canal may have been better by parents treating their children than in adults attempting to medicate themselves. Increased hair and cerumen in adult external ear canals (particularly in males) could have interfered with the penetration of the otic drops into the medial canal. Other complicating factors including underlying undiagnosed dermatologic conditions, fungal infections, and vascular disease may have adversely influenced the outcome in adult patients.

TABLE 9
SUMMARY OF CLINICAL RESPONSE AT END OF THERAPY BY AGE GROUP

POPULATION: ALL PATIENTS VALID FOR EFFICACY

		CIP/SOLN (N=239)		CIP+HC/SUSP (N=236)		PNH/SUSP (N=228)	
		N	%	N	%	N	%
AGE GROUP	CLINICAL RESPONSE EOT						
YEARS	RESOLUTION	104	87.4	96	81.4	98	86.0
	IMPROVEMENT	9	7.6	17	14.4	10	8.8
	FAILURE	6	5.0	5	4.2	6	5.3
YEARS	RESOLUTION	75	64.1	69	60.0	69	61.1
	IMPROVEMENT	31	26.5	28	24.3	21	18.6
	FAILURE	11	9.4	18	15.7	23	20.4
ALL PATIENTS	RESOLUTION	179	75.8	165	70.8	167	73.6
	IMPROVEMENT	40	17.0	45	19.3	31	13.7
	FAILURE	17	7.2	23	9.9	29	12.8

Bacteriological Efficacy

Bacteriologic Response by Patient

For the efficacy evaluable population, one or more causative organisms were isolated in a valid ear at pretreatment in 65% of the Cipro SOLN group (156/239), 64% of the Cipro HC group (150/236), and 63% of the PNH group (144/228). As shown in Table 10, rates of eradication, presumed eradication, persistence, and superinfection were similar among the three groups in patients with an End of Therapy bacteriological response recorded.

> **MO Comment: Some patients with a valid pre-treatment pathogen had either "indeterminate" or "missing" bacteriological responses at the End of Therapy visit. Table 10 summarizes the bacteriological responses by treatment group only for those patients with at least one valid pre-treatment pathogen *and* a valid End of Therapy bacteriological response ("eradication", "presumed eradication", "persistence", or "superinfection") recorded. Thus, the number of patients with a valid pretreatment pathogen *and* a valid bacteriological response at the End of Therapy visit for each group is as follows: 146 Cipro SOLN patients, 137 Cipro HC patients, and 135 PNH patients.**

The overall bacteriological responses rates and the difference of response rates between groups appear at the bottom of Table 10. When assessing success as "eradication + presumed eradication," the overall bacteriological response rate was 92.5% for Cipro SOLN, 94.9% for Cipro HC, and 87.4% for PNH. Two-sided 95% confidence interval for the difference between Cipro HC and PNH was (0.0076, 0.1421).

> **MO Comment: Both Cipro SOLN and Cipro HC demonstrated at least equivalent bacteriological efficacy compared to the approved comparator at the End of therapy visit. The 95% confidence interval for the difference in efficacy rates between Cipro HC and PNH suggests possible superiority of Cipro HC, although the trial was not designed to demonstrate a superiority claim.**

In the efficacy evaluable patients with a documented bacteriological response at the Follow-up visit (Day 11-30 post-therapy), the percentage of patients with "eradication" remained high for all groups: 93.5% (43/46) for Cipro SOLN, 94% (49/52) for Cipro HC, and 95.5% (43/45) for PNH (refer to Table 18 in Volume 15, p.106 of the NDA submission).

> **MO Comment: The bacteriological response rates at the Follow-up visit are based on those patients with a successful bacteriological response at the End of Therapy visit who returned for the Follow-up visit and were assigned a valid bacteriological response. In this population, less than 7% of patients in the Cipro SOLN and Cipro HC groups developed a relapse or reinfection. However, since bacteriological failures from the End of Therapy visit were not carried forward, the response rates at the Follow-up visit are inflated.**

TABLE 10
SUMMARY OF PATIENT BACTERIOLOGIC RESPONSES AT END OF THERAPY
POPULATION: ALL PATIENTS WITH A VALID EFFICACY RESPONSE

VARIABLE		CIP/SOLN (N=146)		CIP+HC/SUSP (N=137)		PNH/SUSP (N=135)	
		N	PCT	N	PCT	N	PCT
BACT. RESPONSE AT END OF THERAPY	ERADICATION	117	80.1	107	78.1	99	73.3
	PRESUMED ERADICATION	18	12.3	23	16.8	19	14.1
	PERSISTENCE	3	2.1	3	2.2	13	9.6
	SUPERINFECTION	8	5.5	4	2.9	4	3.0

			Mantel-Haenszel Estimate of Difference in Rates		
Variable	Drug Group	Rate	Contrast	Estimate	95% Conf. Interval
Patient Bact Resp EOT (1)	CIP/SOLN	135/146 = 92.47%	CIP/SOLN - PNH/SUSP:	0.0506	(-.0201, 0.1213)
	CIP+HC/SUSP	130/137 = 94.89%	CIP+HC/SUSP - PNH/SUSP:	0.0748	(0.0076, 0.1421)
	PNH/SUSP	118/135 = 87.41%			

(1) ERADICATION + PRESUMED ERADICATION vs PERSISTENCE + SUPERINFECTION.

Bacteriologic Response by Pathogen

Bacteriological response for selected organism species for the three treatment arms is shown in Table 11. (A complete listing of bacteriologic response by organism at the End of Therapy visit appears in Appendix I of this review.) Approximately two hundred organisms per group were isolated from pre-treatment cultures. Approximately 30% of patients in each treatment arm had multiple organisms isolated from pre-treatment cultures. In accordance with previous bacteriology studies in otitis externa, the two most common isolates (total of all three arms) were *Pseudomonas aeruginosa* (n=420) and *Staphylococcus aureus* (n=44). For *Pseudomonas aeruginosa,* the rates of eradication + presumed eradication for the Cipro SOLN, Cipro HC, and PNH groups were 91.9%, 89.8%, and 85.9%, respectively. For *Staphylococcus aureus,* the rates of eradication + presumed eradication for the Cipro SOLN, Cipro HC, and PNH groups were 92.9%, 88.9%, and 100%, respectively. Excellent activity (100% eradication) was also noted against *Acinetobacter anitratus* in the Cipro SOLN (n=6) and the Cipro HC (n=9) groups. Rates of persistence of the major pathogens were generally very low, although *Pseudomonas aeruginosa* persisted in 11/135 cases (8.1%) in PNH-treated patients (see Appendix I).

MO Comment: Both Cipro SOLN and Cipro HC demonstrated good rates of eradication for *P. aeruginosa* and *S. aureus* which were similar to the active comparator, PNH.

TABLE 11
BACTERIAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

ALL EARS VALID FOR EFFICACY

ORGANISM	TREATMENT GROUP								
	CIP/SOLN			CIP+HC/SUSP			PNH/SUSP		
	n	# erad*	% erad	n	# erad*	% erad	n	# erad*	% erad
PSEUDOMONAS AERUGINOSA	148	136	91.9	137	123	89.8	135	116	85.9
STAPHYLOCOCCUS AUREUS	14	13	92.9	18	16	88.9	12	12	100
STENOTROPHOMONAS MALTOPHILIA	9	6	66.7	5	5	100	6	6	100
ACINETOBACTER ANITRATUS	6	6	100	9	9	100	5	4	80
PROTEUS MIRABILIS	3	3	100	6	6	100	4	3	75
ENTEROBACTER AEROGENES	4	4	100	3	3	100	7	6	85.7

*Eradication numbers and rates include patients with "eradication + presumed eradication" of the bacterial pathogens. The denominator includes all evaluable patients with the causative organism isolated pre-therapy including indeterminate and missing responses.

Untoward Microbiologic Events

Superinfections

Table 12 illustrates that a total of 36 superinfecting organisms were isolated from the three treatment groups: 13 Cipro SOLN, 7 Cipro HC, and 16 PNH. The most common superinfecting organisms were *Acinetobacter anitratus* (n=7), *Acinetobacter lwoffi* (n=6), *Staphylococcus aureus* (n=3), and *Achromobactori xylosoxidans* (n=3).

MO Comment:The overall rate of superinfections in this study was low and equally distributed among the three treatment arms.

Fungal Isolates

Although 3% of patients evaluable for efficacy had fungus isolated from a valid ear at pretreatment, none received alternative therapy for a fungal infection. Therefore, all fungal isolates in this study were classified as colonizing organisms based on Bayer's definition that "any organisms isolated during or at the end of therapy are considered colonizers if the patients were not treated with appropriate alternative therapy." At the End of Therapy visit, 4/7 patients in the Cipro SOLN group, 2/8 patients in the Cipro HC group, and 0/6 patients in the PNH group remained culture positive for fungus.

A total of 78 patients had positive fungal cultures at the End of Therapy visit: 37 Cipro SOLN patients, 40 Cipro HC patients, and 1 PNH patient. Six of these patients also had a positive fungal culture at pre-treatment (4 Cipro SOLN patients, 2 Cipro HC patients). Only 18 of the 78 patients with positive fungal cultures at the End of Therapy visit were classified as clinical failures, although two Cipro SOLN patients and one Cipro HC patient were later classified as relapses at the follow-up visit.

MO Comment: Although pre-treatment cultures showed a relatively even distribution of fungal isolates among the treatment arms, the End of Therapy cultures demonstrated a striking increase in the number of fungal isolates in the Cipro SOLN, and Cipro HC treatment groups compared to the active comparator, PNH. Topical application of high doses of antimicrobials to the skin surface of the ear canal likely eradicates a large percentage of the pathogenic and normal bacterial flora, predisposing the patient to develop fungal colonization or superinfection. The increased rate of fungal isolates in the Cipro HC and Cipro SOLN groups could reflect greater "pan-bacteriocidal" activity than PNH, resulting in higher rates of fungal overgrowth. Alternatively, a component in the PNH suspension (e.g., polymyxin B) could have a suppressive effect on fungal growth compared to the other treatment arms. Although many patients with positive fungal cultures were asymptomatic at the time of culture, fungal infection may have been responsible for some of the treatment failures and relapses seen in this study. Based on these results, fungal superinfection should be considered in patients with persistent symptoms following therapy with Cipro SOLN and Cipro HC. This information should be included in the product label.

Table 12
SUPERINFECTING ORGANISMS (ALL EARS VALID FOR EFFICACY)

ORGANISM	# OF EARS IN WHICH ORGANIM WAS ISOLATED									
	CIP/SOLN			CIP+HC/SUSP			PNH/SUSP			
	Pre-Rx Culture Negative	Pre-Rx Culture Positive	Total	Pre-Rx Culture Negative	Pre-Rx Culture Positive	Total	Pre-Rx Culture Negative	Pre-Rx Culture Positive	Total	Total
K. PNEUMONIAE	1		1							1
K. OXYTOCA								2	2	2
PS. AERUGINOSA							2		2	2
STENOTROPH MALTOPHILIA					1	1				1
STAPH. AUREUS		2	2					1	1	3
PS. FLUORESCENS					1	1	1		1	2
ENT. AGGLOMERANS	1		1							1
AER. HYDROPHILA								2	2	2
ACHR. XYLOSOXIDANS		2	2		1	1				3
ACIN. ANITRATUS	1		1		1	1	2	3	5	7
ACIN. LWOFFI	1	1	2	2	1	3		1	1	6
FLAV. GROUP IIB		1	1							1
FLAVOBACTERIUM MULTIVORUM								1	1	1
PAST. MULTOCIDA		1	1							1
PSEUDOMONAS SP.		1	1							1
PS. VESICULARIS	1		1							1
STREP. BETA HEMOLYTIC								1	1	1
Total	5	8	13	2	5	7	5	11	16	36

Time to End of Pain Analysis

Because Cipro HC Otic Suspension is a combination drug product, the sponsor was required by FDA regulation to demonstrate a significant clinical benefit for the addition of hydrocortisone to the ciprofloxacin otic formulation. The sponsor studied the time to end of pain (TEOP) as a means of demonstrating the clinical superiority of Cipro HC over Cipro SOLN. Baseline pain measurements were not significantly different among treatment groups (p=0.3344) as shown in Table 13. The majority of patients in all groups had baseline scores on a visual analog scale between 5 and 12 corresponding clinically to moderate to severe pain according to the sponsor (0= no pain, 15= most severe pain).

A total of 703 patients were included in the TEOP analysis: 239 Cipro, 236 Cipro HC, and 228 PNH. The TEOP was a censored observation in approximately 13% of patients in all groups because no time to end of pain was recorded. Survival functions for the time to end of pain using the Kaplan-Meier product limit method are plotted in Table 14. Cipro HC had a signficantly shorter duration of the TEOP when compared to Cipro SOLN (p=0.039). No significant differences in the time to end of pain were noted between PNH and either Cipro SOLN or Cipro HC.

Further exploratory analyses of the TEOP were conducted by age group (reference Table 33A, Volume 15, pp. 134-135 of the NDA submission). The by-age survival plots were similar to the plot for all patients in the 7-12, 13-16, and $\geq$ 17 year age groups, with Cipro HC demonstrating shorter median TEOP than Cipro SOLN. Only the 2-6 year age group showed Cipro HC to have a longer median TEOP than Cipro SOLN.

MO Comment: By demonstrating superiority of Cipro HC compared to Cipro SOLN with respect to TEOP, the requirement of the Combination Rule is met. The difference in median TEOP between the groups was nearly one day (21.1 hr) which, in the judgement of medical reviewers, represents a clinically meaningful benefit from the addition of hydrocortisone to the ciprofloxacin formulation. The discrepancy of TEOP results in the youngest age group may have resulted from the difficulty in accurately recording pain scores in this age group.

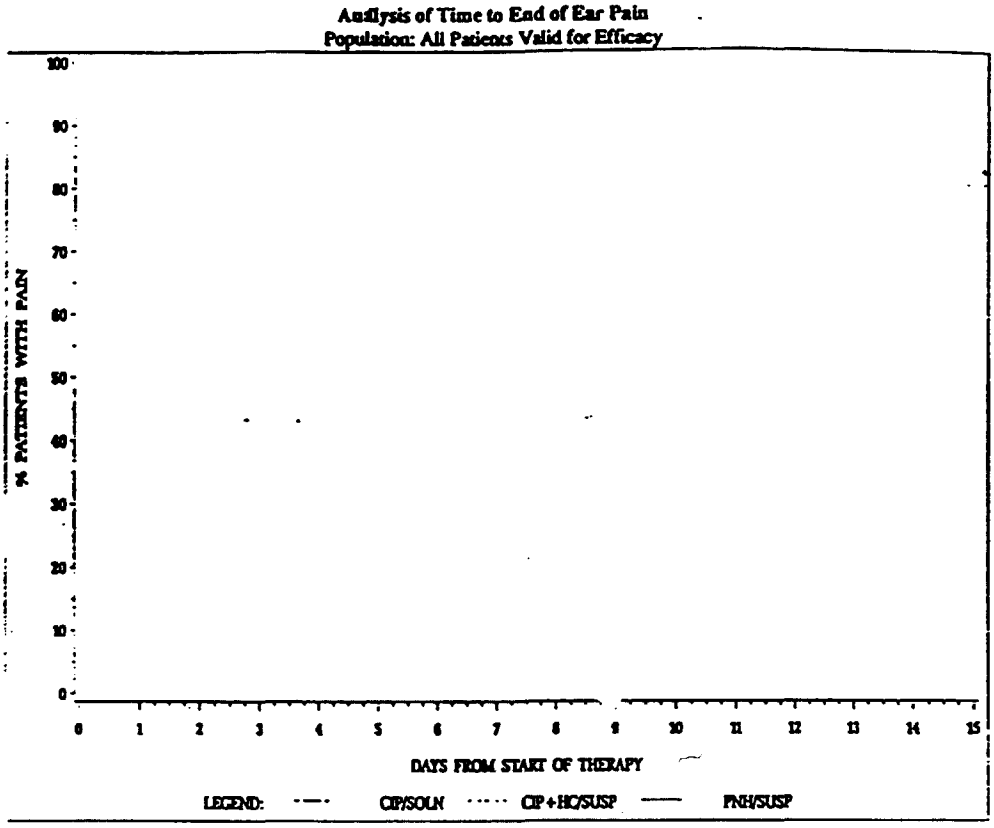
TABLE 13
BASELINE PAIN MEASUREMENT
POPULATION: ALL PATIENTS VALID FOR EFFICACY

RESULTS FOR POOLED DATA

	CIP/SOLN N=239			CIP+HC/SUSP N=236			PNH/SUSP N=228		
DISTRIBUTION (CM)	N	(%)	(CUM %)	N	(%)	(CUM %)	N	(%)	(CUM %)
MISSING	5	2.1	2.1	0	0.0	0.0	3	1.3	1.3
	9	3.8	5.9	9	3.8	3.8	3	1.3	2.6
	54	22.6	28.5	59	25.0	28.8	49	21.5	24.1
	68	28.5	56.9	59	25.0	53.8	65	28.5	52.6
	66	27.6	84.5	73	30.9	84.7	67	29.4	82.0
	37	15.5	100.0	36	15.3	100.0	41	18.0	100.0
MEAN		7.798			7.757			8.223	
MEDIAN		7.50			7.50			8.00	
STANDARD DEVIATION		3.893			4.039			3.729	
RANGE									

P-VALUES OF F STATISTICS USED TO TEST FOR EQUALITY OF MEANS FOR MAIN EFFECTS:
DRUG=0.3344 CENTER=0.0001
STATISTICS CALCULATED USING SS3 CRITERIA.

Table 14. Analysis of Time to End of Ear Pain
Population: All Patients Valid for New Clinical Efficacy Analysis Using +3 to +10 Window



Comparison	P-value (Log-Rank Test)
*CIP+HC/SUSP vs. CIP/SOLN**	*0.039*
CIP+HC/SUSP vs. PNH/SUSP	0.181
CIP/SOLN vs. PNH/SUSP	0.518

* Primary comparison for time to end of pain

Treatment Group	# Observations	# Censored Observations	Estimated Median Time (Days) to End of Ear Pain	95% Confidence Interval for Median	
				Lower Bound	Upper Bound
CIP/SOLN	239	34	4.67	4.031	4.885
CIP+HC/SUSP	236	30	3.79	3.389	4.104
PNH/SUSP	228	31	4.07	3.747	4.715

Note: The time to end of ear pain was obtained as follows. If the date and time of end of pain were entered in the fields at the top of page 8 in the patient's diary, they were used to calculate the duration of pain, the interval between the time of the first dose and the time of the end of pain. For such patient ears, the time to end of pain was observed and therefore was not censored. If the date/time field at the top of page 8 was blank, this indicated that pain did not end while the patient was under study observation and the observation was censored. The time value for such an censored observation was the duration of time when the patient was under observation, which is the time interval between the time of the first dose and the time of the last pain measurement entry in the patient's diary. For patients with bilateral infections both valid for efficacy, the time to end of pain for the patient was defined as follows:

1. If end of pain was observed (i.e., not censored) for both ears, the time to end of pain for the patient was the greater of the two time values and the observation was not censored.
2. If the time to end of pain was censored for at least one ear, the patient's time to end of pain was the greater of the time values and the observation was censored.

Safety

A total of 842 patients were considered valid for safety analysis: 285 Cipro SOLN, 282 Cipro HC, and 275 PNH patients. An overview of all adverse events, whether or not considered related to the study drug, are recorded in Table 14. The most commonly recorded event was headache (under the "Body as a Whole" category) in 15 Cipro SOLN patients (5%), 27 Cipro HC patients (10%), and 12 PNH patients (4%).

Summary of all events considered to be drug-related by the investigators is shown in Table 15. Adverse events were considered to be drug related if the relationship was assessed as "remote", "possible", or "probable" by the investigators. Five to six percent of patients in all groups reported drug-related adverse events. Again, the most common event reported was headache in 2% of Cipro SOLN and Cipro HC patients and 1% of PNH patients.

There were no deaths in the study. Dropouts due to adverse events (Table 16) numbered one in the Cipro SOLN group (<1%), 5 in the Cipro HC group (2%) and 3 in the PNH group (1%). Following review of the case report forms for these patients, the medical reviewer agreed with the investigator's assessment that these events had either no or only remote relationship to treatment with the study drug. Patient #31007 (Cipro HC group) developed otitis media during therapy which was classified as having possible relationship to the study drug. In the absence of a tympanic membrane perforation, however, this relationship seems unlikely.

Only one serious adverse event occurred during the study. Patient / (PNH group) sustained an accidental injury (compression fracture of T7,T8) requiring hospitalization; this accident was not considered treatment related.

MO Comment: Adverse events were generally mild, self-limited, and evenly distributed among the three treatment groups. Headache, the most commonly recorded adverse event, was likely related in most cases to the underlying ear infection rather than a direct effect of the study drug.

TABLE 14
ADVERSE EVENTS BY TREATMENT GROUP AND BODY SYSTEM
WITHOUT RELATIONSHIP TO STUDY DRUG

	CIP-SOLN (N=285)		CIP-HC-SUSP (N=282)		PNH-SUSP (N=275)	
	N	%	N	%	N	%
Any Body System						
Any event	66	23	70	25	55	20
Body As a Whole	26	9	40	14	22	8
Cardiovascular	3	1	1	0	1	0
Digestive	6	2	9	3	11	4
Hemic and Lymphatic	0	0	2	1	0	0
Musculoskeletal	3	1	0	0	2	1
Nervous	1	0	1	0	2	1
Respiratory	15	5	13	5	10	4
Skin and Appendages	11	4	7	2	6	2
Special Senses	15	5	13	5	14	5
Urogenital	1	0	1	0	2	1

TABLE 15

INCIDENCE RATES OF DRUG-RELATED ADVERSE EVENTS
BY BODY SYSTEM AND TREATMENT
FOR ALL PATIENTS VALID FOR SAFETY ANALYSIS

ADVERSE EVENT	CIP/SOLN	CIP+HC/SUSP	PNH/SUSP
ANY BODY SYSTEM			
ANY EVENT	18/285 (6%)	13/282 (5%)	14/275 (5%)
BODY AS A WHOLE			
ANY EVENT	7/285 (2%)	6/282 (2%)	3/275 (1%)
ABDOMINAL PAIN	1/285 (0%)	0/282 (0%)	0/275 (0%)
FEVER	1/285 (0%)	0/282 (0%)	0/275 (0%)
HEADACHE	5/285 (2%)	6/282 (2%)	3/275 (1%)
LEG PAIN	0/285 (0%)	0/282 (0%)	1/275 (0%)
CARDIOVASCULAR			
ANY EVENT	1/285 (0%)	1/282 (0%)	0/275 (0%)
MIGRAINE	0/285 (0%)	1/282 (0%)	0/275 (0%)
PERIPHERAL EDEMA	1/285 (0%)	0/282 (0%)	0/275 (0%)
DIGESTIVE			
ANY EVENT	1/285 (0%)	0/282 (0%)	5/275 (2%)
NAUSEA AND VOMITING	0/285 (0%)	0/282 (0%)	1/275 (0%)
NAUSEA	0/285 (0%)	0/282 (0%)	4/275 (1%)
VOMITING	1/285 (0%)	0/282 (0%)	1/275 (0%)
MUSCULOSKELETAL			
ANY EVENT	0/285 (0%)	0/282 (0%)	2/275 (1%)
ARTHRALGIA	0/285 (0%)	0/282 (0%)	2/275 (1%)
NERVOUS			
ANY EVENT	1/285 (0%)	1/282 (0%)	1/275 (0%)
DIZZINESS	1/285 (0%)	0/282 (0%)	1/275 (0%)
HYPESTHESIA	0/285 (0%)	1/282 (0%)	0/275 (0%)
SKIN AND APPENDAGES			
ANY EVENT	5/285 (2%)	2/282 (1%)	3/275 (1%)

NOTES: INCIDENCE RATE = # OF EVENTS / # AT RISK, WHERE:
OF EVENTS = # OF PATIENTS REPORTING A DRUG-RELATED EVENT.
ALL PATIENTS VALID FOR SAFETY ARE CONSIDERED AT RISK.
SIGNIFICANCE TESTING NOT PERFORMED.

TABLE 16
ADVERSE EVENTS CAUSING DISCONTINUATION OF STUDY DRUG

Study Drug	Patient #	Adverse Event Causing Discontinuation	Relation to Study Treatment
CIP/SOLN			
		Infection	None
CIP-HC-SUSP			
		Ear Pain	None
		Otitis Media	None
		Lymphadenopathy	None
		Diarrhea	None
		Nausea	None
		Vomiting	None
		Otitis Media	Possible
PNH-SUSP			
		Nausea	Remote
		Vomiting	Remote
		Otitis Media	None
		Headache	Remote
		Nausea	Remote

8.2.2. Trial #2: Study No. 1439 (European Study)

"Prospective, Controlled, Randomized, Non-Blinded, Multi-Center Clinical Study of Ciprofloxacin Otic Drops With or Without Hydrocortisone Versus Polymyxin B-Neomycin-Hydrocortisone Otic Drops in the Treatment of Acute Diffuse Bacterial External Otitis" (Volumes 32-48, NDA 20-805)

Objectives/Rationale

Please refer to the Objectives /Rationale section of the preceding clinical trial (Study D94-008).

Study Design

Please refer to the Study Design section of the preceding clinical trial (Study D94-008).

Protocol Overview

Please refer to the Protocol Overview section of the preceding clinical trial (Study D94-008). A notable difference between the two protocols involved the Time to End of Pain (TEOP) determination. In a response dated October 17, 1997, to the medical officer's request for clarification of how TEOP was calculated, the sponsor stated:

"In the European study SN 1439 Medical Research Report, the time to end of pain variable was based on the pain score measurements and the 'Time /Date Pain Ended' field and was determined on a patient by patient basis. If at a time point a patient recorded a pain score of zero and all pain measurements after this time point were zero, then this was considered to be the end of pain, although a few patients with positive but very low pain scores were also considered to have achieved end of pain. If a patient did not have a zero pain score and the 'Time/Date Pain Ended' field has a value later than all the pain score measurement times, then end of pain was considered to have occurred at the time entered in the 'Time /Date Pain Ended' field. The following was [sic] the guidelines for study SN 1439 in evaluating whether and when pain ended.

"1. If the 'Time/Date Pain Ended' field on page 8 of the patient's diary was not blank and pain measurements in the diary were never less than 0.01, then the time to end of pain was set to missing (a censored observation).
"2. If a pain measurement in the diary was zero, then the time to end of pain variable was set to correspond to the time of the zero pain measurement.
"3. If the pain measurements were not zero but were <= 0.25, and if the 'Date/Time Pain Ended' field in page 8 had a value later than the last pain measurement time within the diary, then the end of pain time was taken as that given by the field on page 8.

"In addition, censored observations were set to 15 days in the SN1439 MRR time to end of pain analysis."

MO Comment: The guidelines for determining when and if pain ended in the European study appear somewhat inconsistent and arbitrary compared to the guidelines used in the U.S. study. More emphasis was placed on the individual pain scores recorded by the patients in the European study, and the use of censoring was also quite different.

Statistical Considerations

Aside from the differences in analysis of TEOP scores listed above, the statistical plan for this protocol was identitical to that for study D94-008.

MO Comment: Since the original case report forms and patient diaries were not included with the NDA, a random sample of 5% of these documents from the intent-to-treat population was requested from the sponsor. These documents were used to audit the accuracy of transcription of the clinical and microbiological data to the data listings within the NDA. This audit revealed accurate and consistent capture of data from original case report forms and diaries by the sponsor's data listings with two exceptions: (1) early (during therapy) treatment failures were mistakenly not carried forward to the End of Therapy efficacy analyses, and (2) fungal isolates were incorrectly labeled as "superinfection" in certain instances. These errors in the study data base were recognized and corrected by the sponsor in a written response dated December 2, 1997.

The medical and statistical reviewers concluded that the integrity of the data base and the robustness of the clinical efficacy rates would permit a random sample of the intent to treat population to assess accuracy and consistency of clinical judgments concerning patient evaluability and efficacy/safety determinations. A 10% and a 20% random sample of the efficacy evaluable and efficacy non-evaluable patients, respectively, were performed. The medical officer agreed with the sponsor's determinations of patient evaluability and efficacy determination with one notable exception. By expanding the time window for the End of Therapy visit, the sponsor considered patients who were off study drug for less than three days to be evaluable for the primary efficacy determination. For the reasons outlined above in the Clinical Response Endpoints section of Study D94-008, the Division requested that the sponsor reanalyze the data using a 3-10 day post-therapy window for the primary efficacy determination. The revised data base and tables generated by the sponsor (dated December 2, 1997) were judged to be an accurate reflection of the results of this clinical trial by the statistical and medical reviewers. Thus, the sponsor's revised tables were used, with minor format modifications, in the presentation of the study results in the following section.

Study Results

Evaluability

A total of 842 patients were enrolled in 30 centers throughout Europe from May 1995 through March 1996 as shown in Table 1. Of the enrolled patients, 838 patients were considered evaluable for safety; 583 patients were considered evaluable for efficacy as follows: 185 Cipro SOLN patients, 207 Cipro HC patients, and 191 PNH patients. The reasons for exclusion from the efficacy population are listed in Table 2. The most common reasons for exclusion were: an End of Therapy visit outside the acceptable time window (n=112), patient noncompliance with the dosage regimen (n=52), or missing diary (n=29). The Curriculum Vitae of the principal investigator, Dr. Pierre Gehanno, was reviewed and found to be acceptable.

MO Comment: Poorer compliance with the dosage regimen, diary return, and End of Therapy visits resulted in a markedly lower percentage of evaluable patients from the intent to treat population in the European study (69%) compared to the U.S. study (83%). However, the number of patients excluded as well as their reasons for exclusion from the efficacy evaluable population were similar among the three treatment arms. Of note, two patients in the Cipro SOLN group and two patients in the PNH group were lost to follow-up immediately following the initial visit and were therefore not evaluable for safety or efficacy.

TABLE 1
PATIENT ENROLLMENT BY INVESTIGATOR SITE AND TREATMENT GROUP

	CIP/SOLN			CIP+HC/SUSP			PN+HC/SUSP		
	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED
BELGIUM									
9 (EGEDEM I)	2	5	7	3	2	5	6	4	10
SWITZERLAND									
8 (ZURICH)				1	0	1	1	0	1
GERMANY									
1 (HANNOVER)	2	1	3	2	1	3	0	1	1
3 (WUERZBURG)	9	2	11	11	1	12	8	4	12
4 (HAMBURG)	11	4	16	11	4	15	11	3	16
5 (WESTFALIA)	16	4	20	17	2	19	16	3	19
6 (ESSEN)	2	2	4	2	2	4	1	3	4
24 (MUNICH)	9	6	16	12	4	16	12	3	15
25 (WARBURG)	1	5	6	1	5	6	3	4	7
26 (HANN.MUEN.)	16	4	20	17	3	20	16	4	20
DENMARK									
15 (VEJLE)	4	0	4	6	1	7	3	4	7
SPAIN									
22 (GIRONA)	3	1	4	2	1	3	0	2	2
38 (BADALONA)	1	3	4	2	1	3	3	0	3

(continued)

TABLE 1 (continued)
PATIENT ENROLLMENT BY INVESTIGATOR SITE AND TREATMENT GROUP

	CIP/SOLN			CIP+HC/SUSP			PN+HC/SUSP		
	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED	VALID FOR EFFICACY AND SAFETY	VALID FOR SAFETY ONLY	PATIENTS ENROLLED
17 (PARIS I)	14	6	20	12	8	20	15	5	20
18 (PARIS II)	4	3	7	2	5	7	2	5	7
19 (TOULOUSE)	4	2	6	5	2	7	3	2	5
20 (BORDEAUX)	6	3	9	7	4	11	7	3	10
30 (LATTES)	10	2	12	10	2	12	5	7	12
31 (NICE I)	4	3	7	5	1	6	7	1	8
36 (NICE II)	2	3	5	4	3	7	1	5	6
37 (PARIS III)	19	5	24	19	5	24	16	6	22
39 (LA REUNION)	1	1	2	8	0	8	3	0	3
GREAT BRITAIN									
10 (3 CENTRES POOLED)	6	5	11	6	4	10	8	4	12
GREECE									
12 (THESSALONIKI I)	14	2	16	11	4	15	15	1	16
23 (THESSALONIKI II)	11	5	16	13	2	15	15	2	17
ISRAEL									
13 (BEER SHEVA)	13	11	24	14	6	20	11	11	22
14 (KFAR SABA)	1	3	4	4	0	4	3	1	4
28 (HAIFA)	0	1	1	0	2	2			
TOTAL PATIENTS	185	92	279	207	75	282	191	88	281

TABLE 2
REASONS FOR EXCLUSION FROM EFFICACY ANALYSIS (PATIENT INVALIDITY)
POPULATION: ALL PATIENTS ENROLLED

	CIP/SOLN N = 279		CIP+HC/SUSP N = 282		PN+HC/SUSP N = 281		PVALUE
	N	PERCENT	N	PERCENT	N	PERCENT	
TOTAL INVALID FOR EFFICACY	94	33.7	75	26.6	90	32.0	0.162
INADEQUATE DURATION OF TREATMENT	4	1.4	4	1.4	3	1.1	
CONCOMITANT ANTIMICROBIAL THERAPY	0	0.0	0	0.0	2	0.7	
NONCOMPLIANCE WITH DOSAGE REGIMEN	16	5.7	16	5.7	20	7.1	
LOST TO FOLLOW-UP	7	2.5	0	0.0	7	2.5	
PT ON MEDICATION FOR <7 FULL DAYS	0	0.0	0	0.0	1	0.4	
EXCLUSION/INCLUSION CRITERIA VIOLATION	6	2.2	4	1.4	9	3.2	
NO POST-TREATMENT ASSESSMENT	0	0.0	1	0.4	0	0.0	
ANTIMICROBIAL THERAPY W/IN PRE-RX WINDOW	0	0.0	1	0.4	0	0.0	
NO END OF THERAPY EVALUATION	5	1.8	4	1.4	2	0.7	
DIARY MISSING	9	3.2	11	3.9	9	3.2	
OUTSIDE TIME WINDOW	45	16.1	32	11.3	35	12.5	
> 1 DOSE ANALGESIC (ANTIINFLAMM. PROPER.)	1	0.4	0	0.0	0	0.0	
TOPICAL STEROID	1	0.4	0	0.0	0	0.0	
USE OF PENICILLIN DUE TO AE	0	0.0	1	0.4	0	0.0	
CONCOM. ANTIMIC. THERAPY	0	0.0	0	0.0	1	0.4	
NO VISIT DAY 3-7	0	0.0	1	0.4	0	0.0	
NSAID	0	0.0	0	0.0	1	0.4	

PERCENT IS OF TOTAL POPULATION (N IN HEADING)

THE P-VALUE IS CALCULATED USING A CHI-SQUARE TEST

Demographics

Demographic characteristics for the three treatment arms are depicted in Table 3 and Table 4 for the intent-to-treat (ITT) population. Tables 5 and 6 show these characteristics for the clinically evaluable population. The three treatment arms were well-balanced with respect to sex, race, general status of health, and age distribution in both the ITT and evaluable populations.

MO Comment: The ITT and clinically evaluable populations share similar demographic characteristics as do the three treatment arms in each study. Of note, pediatric experience in this trial was very limited (approximately 5% of evaluable patients) compared with the U. S. Study. The increased use of aural debridement and ear wicks in the management of otitis externa in this trial reflects the greater percentage of otolaryngologists involved in the care of these patients compared to the U.S. study.

Baseline characteristics of otitis externa were very similar across treatment groups with respect to duration of the present episode and the number of prior episodes in the past twelve months as demonstrated in Tables 7 and 8 (Volume 32, pp. 65-67) of the sponsor's study summary report in the NDA submission (not shown here).

TABLE 3

CATEGORICAL DEMOGRAPHIC, TREATMENT AND BASELINE MEDICAL CHARACTERISTICS
RESULTS FOR POOLED DATA

POPULATION: ALL PATIENTS VALID FOR SAFETY

VARIABLE (P-VALUE)		CIP/SOLN (N=277)		CIP+HC/SUSP (N=282)		PN+HC/SUSP (N=279)	
		N	PCT	N	PCT	N	PCT
SEX (P=0.272)	FEMALE	102	36.8	112	39.7	122	43.7
	MALE	175	63.2	170	60.3	157	56.3
RACE (P=0.541)	ASIAN	4	1.4	3	1.1	3	1.1
	BLACK	2	0.7	5	1.8	3	1.1
	OTHER	0	0	4	1.4	3	1.1
	WHITE	271	97.8	270	95.7	270	96.8
GENERAL STATUS OF HEALTH (P=0.444)	EXCELLENT	186	67.1	200	70.9	191	68.5
	GOOD	86	31.0	74	26.2	85	30.5
	FAIR	5	1.8	7	2.5	2	0.7
	POOR	0	0	1	0.4	1	0.4
LOCATION OF INFECTION (P=0.809)	BILATERAL	17	6.1	19	6.7	24	8.6
	LEFT	120	43.3	126	44.7	117	41.9
	RIGHT	140	50.5	137	48.6	138	49.5
DEBRIDEMENT OF THE EAR? (P=0.545)	NO	207	74.7	200	70.9	200	71.9
	YES	70	25.3	82	29.1	78	28.1
USE OF AN EAR WICK? (P=0.984)	NO	216	78.0	219	77.7	217	77.8
	YES	61	22.0	63	22.3	62	22.2

TABLE 4

DEMOGRAPHICS - AGE
POPULATION: ALL PATIENTS VALID FOR SAFETY

RESULTS FOR POOLED DATA

	CIP/SOLN N=277			CIP+HC/SUSP N=282			PN+HC/SUSP N=279		
DISTRIBUTION (YRS)	N	(%)	(CUM %)	N	(%)	(CUM %)	N	(%)	(CUM %)
MISSING	0	0	0.0	2	0.7	0.7	0	0	0.0
	0	0	0.0	3	1.1	1.8	0	0	0.0
	6	2.2	2.2	6	2.1	3.9	8	2.9	2.9
	3	1.1	3.3	4	1.4	5.3	11	3.9	6.8
	268	96.8	100.1	267	94.7	100.0	260	93.2	100.0
MEAN		38.9			37.7			36.2	
MEDIAN		37.0			36.0			35.0	
STANDARD DEVIATION		16.0			14.0			14.5	
RANGE									

P-VALUES OF F-STATISTICS USED TO TEST FOR EQUALITY OF MEANS FOR MAIN EFFECTS:
DRUG=0.3191 CENTRE=0.0224
STATISTICS CALCULATED USING SS3 CRITERIA

TABLE 5
CATEGORICAL DEMOGRAPHIC, TREATMENT AND BASELINE MEDICAL CHARACTERISTICS
RESULTS FOR POOLED DATA (EFFICACY EVALUABLE PATIENTS)

VARIABLE (P-VALUE)		CIP/SOLN (N=185)		CIP+HC/SUSP (N=207)		PN+HC/SUSP (N=191)	
		N	PCT	N	PCT	N	PCT
SEX (P=0.291)	FEMALE	68	36.8	85	41.1	86	45.0
	MALE	117	63.2	122	58.9	105	55.0
RACE (P=0.379)	ASIAN	3	1.6	2	1.0	1	0.5
	BLACK	1	0.5	4	1.9	2	1.0
	OTHER	0	0	4	1.9	3	1.6
	WHITE	181	97.8	197	95.2	185	96.9
GENERAL STATUS OF HEALTH (P=0.429)	EXCELLENT	127	68.6	144	69.6	134	70.2
	GOOD	53	28.6	57	27.5	55	28.8
	FAIR	5	2.7	6	2.9	1	0.5
	POOR	0	0	0	0	1	0.5
LOCATION OF INFECTION (P=0.857)	BILATERAL	13	7.0	16	7.7	18	9.4
	LEFT	75	40.5	89	43.0	83	43.5
	RIGHT	97	52.4	102	49.3	90	47.1
DEBRIDEMENT OF THE EAR? (P=0.604)	NO	142	76.8	149	72.0	142	74.3
	YES	43	23.2	58	28.0	49	25.7
USE OF AN EAR WICK? (P=0.831)	NO	146	78.9	164	79.2	148	77.5
	YES	39	21.1	43	20.8	43	22.5

P-VALUES WERE CALCULATED USING MANTEL-HAENSZEL STATISTICS CONTROLLING FOR CENTRE

TABLE 6
DEMOGRAPHICS - AGE
POPULATION; ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

RESULTS FOR POOLED DATA

	CIP/SOLN N=185		CIP+HC/SUSP N=207		PN+HC/SUSP N=191	
DISTRIBUTION (YRS)	N	(%)	N	(%)	N	(%)
MISSING	0	0	2	1.0	0	0
	0	0	2	1.0	0	0
	5	2.7	5	2.4	6	3.1
	2	1.1	4	1.9	6	3.1
	178	96.2	194	93.7	179	93.7
MEAN	40.8		37.1		35.7	
MEDIAN	39.0		35.0		35.0	
STANDARD DEVIATION	16.9		13.7		14.5	
RANGE						

P-VALUES OF F-STATISTICS USED TO TEST FOR EQUALITY OF MEANS FOR MAIN EFFECTS:
DRUG=0.0830 CENTRE=0.1137
STATISTICS CALCULATED USING SS3 CRITERIA

Clinical Efficacy

Clinical Response at End of Therapy and Followup

From the ITT population, a total of 583 patients (69%) were evaluable for clinical efficacy: 185 Cipro SOLN patients, 207 Cipro HC patients, 191 PNH patients. Approximately 7-9 % of patients in the treatment groups had bilateral infections; the clinical response was recorded at the patient level using the worse faring ear in these cases.

Table 7 summarizes the clinical efficacy results at the End of Therapy (primary efficacy variable). The clinical success rates for the three treatment arms (defined as "resolution + improvement") were as follows: 85.9% for Cipro SOLN, 92.7% for Cipro HC, and 89.6% for PNH.

The 2-tailed 95% confidence interval for the Mantel-Haenszel weighted estimate of differences in efficacy rates between treatment arms is shown at the bottom of Table 7. For clinical success defined as resolution + improvement, the estimated difference in efficacy rates between Cipro HC and PNH was 0.0316 at the End of Therapy visit. Since the lower bound of the 95% confidence interval was -0.0246, the Division's criteria for therapeutic equivalence (greater than -0.10) of the two drugs is met. If success is defined as resolution only, the estimated difference in efficacy rates was 0.0485. Since an equivalence delta of 0.20 is used for efficacy rates less than 80%, the lower bound of the confidence interval of this difference (-0.0326) also meets the criteria for therapeutic equivalence.

Clinical efficacy data for the Follow-up Visit (Day 11-30 post-therapy) was available for 168 Cipro SOLN patients, 189 Cipro HC patients, and 175 PNH patient as shown in Table 8, representing 91%, 91% and 92% of the efficacy evaluable patients in the three groups, respectively. Similar rates of continued resolution, relapse, and failures (carried forward from the End of Therapy Visit), were noted for the three groups.

MO Comment: Therapeutic equivalence of Cipro HC with the FDA-approved comparator for this indication is demonstrated when success is defined as either "resolution + improvement" or "resolution" at the primary efficacy endpoint. Low rates of relapse (<4%) are noted for all three groups at the Follow-up visit which supports the use of "resolution+improvement" as the definition of a successful outcome in the primary efficacy analysis, as in the U.S. study.

TABLE 7
SUMMARY OF PATIENT CLINICAL RESPONSES AT END OF THERAPY
RESULTS FOR POOLED DATA

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

VARIABLE		CIP/SOLN (N=185)		CIP+HC/SUSP (N=207)		PN+HC/SUSP (N=191)	
		N	PCT	N	PCT	N	PCT
CLINICAL RESPONSE AT END OF THERAPY	RESOLUTION	136	73.5	164	79.2	143	74.9
	IMPROVEMENT	23	12.4	28	13.5	28	14.7
	FAILURE	26	14.1	15	7.2	20	10.5

Mantel-Haenszel Estimate of Difference in Rates

Variable	Drug Group	Rate	Contrast	Estimate	95% Conf. Interval
Patient Clin Resp EOT (1)	CIP/SOLN	159/185 = 85.95%	CIP/SOLN - PN+HC/SUSP:	-.0348	(-.1010, 0.0315)
	CIP+HC/SUSP	192/207 = 92.75%	CIP+HC/SUSP - PN+HC/SUSP:	0.0316	(-.0246, 0.0878)
	PN+HC/SUSP	171/191 = 89.53%			
Patient Clin Resp EOT (2)	CIP/SOLN	136/185 = 73.51%	CIP/SOLN - PN+HC/SUSP:	-.0088	(-.0969, 0.0792)
	CIP+HC/SUSP	164/207 = 79.23%	CIP+HC/SUSP - PN+HC/SUSP:	0.0485	(-.0326, 0.1296)
	PN+HC/SUSP	143/191 = 74.87%			

(1) RESOLUTION + IMPROVEMENT vs FAILURE.
(2) RESOLUTION vs IMPROVEMENT + FAILURE.

TABLE 8
SUMMARY OF PATIENT CLINICAL RESPONSES AT FOLLOW-UP
RESULTS FOR POOLED DATA

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

VARIABLE		CIP/SOLN (N=168)		CIP+HC/SUSP (N=189)		PN+HC/SUSP (N=175)	
		N	PCT	N	PCT	N	PCT
FOLLOW-UP	CONTINUED RESOLUTION	140	83.3	171	90.5	149	85.1
	RELAPSE	2	1.2	3	1.6	6	3.4
	FAILURE	26	15.5	15	7.9	20	11.5

FOR PATIENTS WITH BILATERAL INFECTIONS, RESPONSE IS THE WORSE OF THE TWO

Follow-up Clinical Response of Patients Rated as "Improvement" at End of Therapy

As in the review of the U.S. study results, follow-up on all patients classified as "Improvement" was requested from the sponsor to ensure that these patients did not subsequently have a relapse of their infection. In a written response dated September 18, 1997, the sponsor identified a total of 80 patients with a clinical response of "Improvement" at the End of Therapy visit for whom a follow-up clinical response was available: 24 Cipro SOLN patients, 29 Cipro HC patients, and 27 PNH patients. A total of 10 patients (2 Cipro SOLN, 3 Cipro HC, and 5 PNH patients) subsequently developed a relapse of their infection. All remaining patients were rated as "Continued Resolution."

MO Comment: Again, the relatively low incidence of relapse in patients rated as "Improvement" at the End of Therapy visit supports the validity of combining the "Improvement" and "Resolution" populations as the primary clinical efficacy definition of a successful outcome. The highest rate of relapse in the subgroup of patients rated as "Improvement" at the End of Therapy visit was noted in the approved comparator arm (5/27 patients or 18.5%).

Note: Follow-up on patients with a rating of "Improvement" at the End of Therapy visit was requested from the sponsor before the final adjustments in patient evaluability were made in the study data base as described in the Protocol Overview section. Therefore, slight discrepancies are noted in the number of patients rated as "Improvement" in the sponsor's written reply compared to Table 7 (generated from the finalized data base).

Clinical Response by Age Group

Table 9 summarizes the clinical response at the End of Therapy by age group. As in the U.S. study, adult patients (≥17 years) in all treatment arms appeared to have a somewhat higher rate of clinical failure when compared to the pediatric population (most pronounced in the Cipro SOLN and Cipro HC groups), although the very small number of pediatric patients precludes a meaningful comparison.

MO Comment: All three otic preparations demonstrated clinical efficacy rates in a small population of pediatric patients which appeared to equal or exceed efficacy rates in adults.

TABLE 9
SUMMARY OF CLINICAL RESPONSE AT END OF THERAPY BY AGE GROUP

POPULATION: ALL PATIENTS VALID FOR EFFICACY

		CIP/SOLN (N=185)		CIP+HC/SUSP (N=207)		PNH/SUSP (N=191)	
		N	%	N	%	N	%
AGE GROUP	CLINICAL RESPONSE EOT						
YEARS	RESOLUTION	7	100	11	85.0	8	66.7
	IMPROVEMENT	0	0	2	15.0	3	25.0
	FAILURE	0	0	0	0	1	8.3
YEARS	RESOLUTION	129	72.5	153	78.9	135	75.4
	IMPROVEMENT	23	12.9	26	13.4	25	14.0
	FAILURE	26	14.6	15	7.7	19	10.6
ALL PATIENTS	RESOLUTION	136	73.5	164	79.2	143	74.9
	IMPROVEMENT	23	12.4	28	13.5	28	14.7
	FAILURE	26	14.1	15	7.2	20	10.5

Bacteriological Efficacy

Bacteriologic Response by Patient -

The percentage of patients from the efficacy evaluable population in each group who had one or more causative organisms isolated from a valid ear at pretreatment *and* had a valid bacteriologic efficacy response (i.e., "eradication", "presumed eradication", "persistence", or "superinfection") at the End of Therapy visit were as follows: 48.6% in the Cipro SOLN group (90/185), 58% in the Cipro HC group (120/207), and 49.2% of the PNH group (94/191). As shown in Table 10, rates of eradication, presumed eradication, persistence, and superinfection were similar among the three groups. The rate of "eradication + presumed eradication" for the microbiologically evaluable patients in treatment arms is as follows: 88.9% for Cipro SOLN, 85.8% for Cipro HC, and 75.5% for PNH.

MO Comment: As in the U.S. study, some patients with a valid pre-treatment pathogen had either "indeterminate" or "missing" bacteriological responses at the End of Therapy visit. These patients were not included in Table 10.

The overall bacteriological response rates and the difference of response rates between groups appear at the bottom of Table 10. The two-sided 95% confidence interval for the difference between Cipro HC and PNH was (0.0031, 0.2197).

MO Comment: Both Cipro SOLN and Cipro HC groups demonstrated at least equivalent bacteriological efficacy compared to the approved comparator at the End of Therapy visit. As in the U.S. study, the confidence interval of the difference between the Cipro HC and PNH groups suggests possible superiority of Cipro HC, although the trial was not designed to demonstrate a superiority claim.

In the efficacy evaluable patients with a documented bacteriological response at the Follow-up visit (Day 11-30 post-therapy), the percentage of patients with "eradication" remained high for all groups: 100% for Cipro SOLN (16/16), 96% for Cipro HC (25/26), and 95% (19/20) for PNH (refer to Table 18 in Volume 32, p.90 of the NDA submission).

MO Comment: The bacteriological response rates at the Follow-up visit are based on those patients with a successful bacteriological response at the End of Therapy visit who returned for the Follow-up visit and were assigned a valid bacteriological response. In this population, none of the patients in the Cipro SOLN arm and only 4% of patients in the Cipro HC arm developed a relapse or reinfection. However, since bacteriological failures from the End of Therapy visit were not carried forward, the response rates at the Follow-up visit are inflated.

TABLE 10
SUMMARY OF PATIENT BACT. RESPONSE AT END OF THERAPY
RESULTS FOR POOLED DATA

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

VARIABLE		CIP/SOLN (N=90)		CIP+HC/SUSP (N=120)		PN+HC/SUSP (N=94)	
		N	PCT	N	PCT	N	PCT
BACT. RESPONSE AT END OF THERAPY	ERADICATION	77	85.6	93	77.5	69	73.4
	PRESUMED ERADICATION	3	3.3	10	8.3	2	2.1
	PERSISTENCE	6	6.7	11	9.2	18	19.2
	SUPERINFECTION	4	4.4	6	5.0	5	5.3

Patient Bact Resp EOT (1)	CIP/SOLN	80/ 90 = 88.89%	CIP/SOLN - PN+HC/SUSP:	0.1350	(0.0233, 0.2466)	
	CIP+HC/SUSP	103/120 = 85.83%	CIP+HC/SUSP - PN+HC/SUSP:	0.1105	(0.0031, 0.2179)	
	PN+HC/SUSP	71/ 94 = 75.53%				

(1) ERADICATION + PRESUMED ERADICATION vs PERSISTENCE + SUPERINFECTION.

Bacteriologic Response by Pathogen

Bacteriological response for selected organism species for the three treatment arms is shown in Table 11. (A complete listing of bacteriologic response by organism at the End of Therapy visit appears in Appendix II of this review.) A total of 419 organisms was isolated from pre-treatment cultures for all groups. In accordance with previous bacteriology studies in otitis externa (including the preceding U.S. clinical trial), the two most common isolates (total of all three arms) were *Pseudomonas aeruginosa* (n=247) and *Staphylococcus aureus* (n=51). For *Pseudomonas aeruginosa,* the rates of eradication + presumed eradication for the Cipro SOLN, Cipro HC, and PNH groups were 90.3%, 91.7%, and 78.5%, respectively. For *Staphylococcus aureus,* the rates of eradication + presumed eradication for the Cipro SOLN, Cipro HC, and PNH groups were 100%, 87.5%, and 91.7%, respectively. Excellent activity (100% eradication) was also noted against a small number of *Proteus mirabilis* isolates in the Cipro SOLN (n=1) and the Cipro HC (n=5) groups. Good activity was also noted against *Enterococcus faecalis* in all three groups (90-100% eradication rates). Rates of persistence of the major pathogens were generally very low, although *Pseudomonas aeruginosa* persisted in 17/79 (approximately 20%) of cases in PNH-treated patients (see Appendix II).

MO Comment: The results in this trial closely parallel those seen in the U.S. trial with respect to bacteriologic response by organism. Generally good rates of eradication were demonstrated by all three treatment regimens against the two major pathogens encountered in otitis externa, although a slightly higher failure rate with *P. aeruginosa* was noted in the approved comparator, PNH.

TABLE 11
BACTERIOLOGIC RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

ALL EARS VALID FOR EFFICACY

ORGANISM	TREATMENT GROUP								
	CIP/SOLN			CIP+HC/SUSP			PNH/SUSP		
	n	# erad*	% erad	n	# erad*	% erad	n	# erad*	% erad
PSEUDOMONAS AERUGINOSA	72	65	90.3	96	88	91.7	79	62	78.5
STAPHYLOCOCCUS AUREUS	15	15	100	24	21	87.5	12	11	91.7
ENTEROCOCCUS FAECALIS	9	9	100	12	11	91.7	3	3	100
PROTEUS MIRABILIS	1	1	100	5	5	100	1	1	100

* Eradication numbers and rates include patients with "eradication + presumed eradication" of the bacterial pathogens. The denominator includes all evaluable patients with the causative organism isolated pre-therapy including indeterminate and missing responses

Untoward Microbiologic Events

Superinfections

Table 12 lists the superinfecting organisms by treatment group at the End of Therapy visit. A total of 30 superinfecting organisms were isolated as follows: 8 from the Cipro SOLN group, 7 from the Cipro HC group, and 15 from the PNH group. By far the most common superinfecting organisms were *P. aeruginosa* (n=11) and *S. aureus* (n=8).

MO Comment: As in the U.S. study, the overall rate of superinfections was low for all groups. Unlike the U.S. study, however, the majority of isolates labeled as "superinfection" in this trial were the two major pathogens in otitis externa. Since most of these isolates were from patients with negative pre-treatment cultures, it is possible that they actually could represent "persistent" organisms in cases where the pre-treatment culture was falsely negative.

Fungal Isolates

For the efficacy evaluable population, 101 patients had fungal isolates in a valid ear at pre-treatment: 29 Cipro SOLN, 51 Cipro HC, and 21 PNH isolates. Of these patients, 83% (24/29) of Cipro SOLN patients had persistent fungal isolates at the End of Therapy visit although only five were labeled as clinical failures. Among Cipro HC patients, 47 of 51(92%) patients remained culture positive for fungus at the End of Therapy visit with only 4 of the patients with a clinical efficacy determination of "failure." Sixteen of the 21 patients (76%) with baseline fungal isolates in the PNH group remained culture positive at the End of Therapy but only one of these patients was considered a clinical failure. An additional three patients (one per group), who were culture negative for fungus at baseline, developed positive fungal cultures at End of Therapy visit.

MO Comment: The majority of patients with a positive fungal culture at baseline remained positive for fungus at the End of Therapy visit. Despite positive fungal cultures at the End of Therapy, however, a large majority (80-90%) of patients were evaluated as clinical successes. Unlike the U.S. study, the persistent fungal cultures were nearly as frequent in the comparator arm as in the Cipro SOLN and Cipro HC groups. The possibility of the fungus playing a role in patients with persistent symptoms should still be considered.

TABLE 12
SUPERINFECTING ORGANISMS

ALL EARS VALID FOR NEW CLIN EFFICACY ANALYSIS

	# OF EARS IN WHICH ORGANISM WAS ISOLATED									
	CIP/SOLN			CIP+HC/SUSP			PN+HC/SUSP			
ORGANISM	PRE-RX CULTURE NEGATIVE	PRE-RX CULTURE POSITIVE	TOTAL	PRE-RX CULTURE NEGATIVE	PRE-RX CULTURE POSITIVE	TOTAL	PRE-RX CULTURE NEGATIVE	PRE-RX CULTURE POSITIVE	TOTAL	TOTAL
ALC. FAECALIS	0	0	0	0	0	0	1	0	1	1
BETA HEMOLYTIC GROUP B	0	0	0	0	0	0	1	0	1	1
CLOSTRIDIUM SP.	0	0	0	2	0	2	0	0	0	2
ENTERO. FAECALIS	0	0	0	0	1	1	1	0	1	2
P. MIRABILIS	0	1	1	0	0	0	2	0	2	3
PEPTOSTREPT. SP.	0	0	0	0	0	0	1	0	1	1
PS. AERUGINOSA	4	0	4	1	1	2	5	0	5	11
PSEUDOMONAS SP.	0	0	0	0	0	0	0	1	1	1
STAPH. AUREUS	0	3	3	1	1	2	2	1	3	8
TOTAL	4	4	8	4	3	7	13	2	15	30

Time to End of Pain Analysis

As in the U.S. study, the sponsor studied the time to end of pain (TEOP) as a means of demonstrating the clinical superiority of Cipro HC over Cipro SOLN. Baseline pain measurements were not significantly different among treatment groups (p=0.6613) as shown in Table 13. The majority of patients in all groups had baseline scores on a visual analog scale above 5, corresponding clinically to moderate to severe pain according to the sponsor (0= no pain, 15= most severe pain).

A total of 583 patients were included in the TEOP analysis: 185 Cipro, 207 Cipro HC, and 191 PNH patients. The original analysis of the TEOP variable from the NDA submission is shown in Table 14. Although the estimated median TEOP was lower in the Cipro HC group than in the Cipro SOLN group by 0.2 days, this difference did not achieve statistical significance (p=0.14). The sponsor concluded that while not achieving statistical significance, the lower estimated median TEOP of Cipro HC was supportive of the significant results observed in the U.S. study.

The discrepant results of the U.S. and European trials for TEOP were of concern to the FDA reviewers. Although the population of the European study had a higher percentage of adult patients, the patient populations of the two studies were otherwise similar in demographics, in the baseline severity of pain scores, and in the bacterial pathogens isolated from the external ear canal. Of note, both the use of censoring and the harmonization of the pain scale measurements with the "Time/Date Pain Ended" field in the patient pain diaries differed in the statistical analysis of the two studies. To facilitate meaningful comparisons of the two studies, the Division requested that the European data base be re-analyzed, using the U.S. study guidelines and statistical methods, to determine and compare the "Time to End of Pain" measurements for the three treatment groups. This follow-up analysis was provided by the sponsor in a written response from December 2, 1997, and is shown in Table 15. Survival functions for the TEOP using the Kaplan-Meier product limit method again demonstrated a lower median TEOP value for the Cipro HC group compared to the Cipro SOLN group (a difference of 0.59 days). However, a statistically significant difference in TEOP between the two groups was not demonstrated (p=0.334). The increased p-value for this follow-up analysis compared to original analysis is in part related to the lower numbers of evaluable patients (resulting from the revised time window for the End of Therapy visit as described in the Protocol Overview section of this study review).

In reviewing the TEOP raw data, a significant percentage of patients in the European study were noted to achieve very low (<1) pain scores, but did not achieve a score of zero in their diaries. In discussions with the sponsor, it was unclear in many cases if the pain did not completely resolve or if the patient merely failed to place their mark directly over the "zero" on the visual analog scale. As a post-hoc exploratory analysis, patients with a baseline pain score of greater than six were followed until they achieved a pain score of less than one. Comparison of survival curves for the Cipro SOLN and Cipro HC groups (Table 16) demonstrated an estimated median difference of 0.54 days for time to pain less than 1. Again, the difference was not statistically significant (p=0.164), due at least in part to the smaller patient numbers in this subset of evaluable patients.

MO Comment: Although the estimated median TEOP in all analyses of the data was less in the Cipro HC group compared to the Cipro SOLN group, the difference did not achieve statistical significance. Thus, the superiority of Cipro HC compared to Cipro SOLN with respect to TEOP was not demonstrated in this study as it was in the U.S. study. The lower number of evaluable patients in the treatment groups and the higher percentage of adult patients in the European study may have been factors accounting for the observed differences in outcome compared to the U.S. study.

TABLE 13
BASELINE PAIN MEASUREMENT
POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

RESULTS FOR POOLED DATA

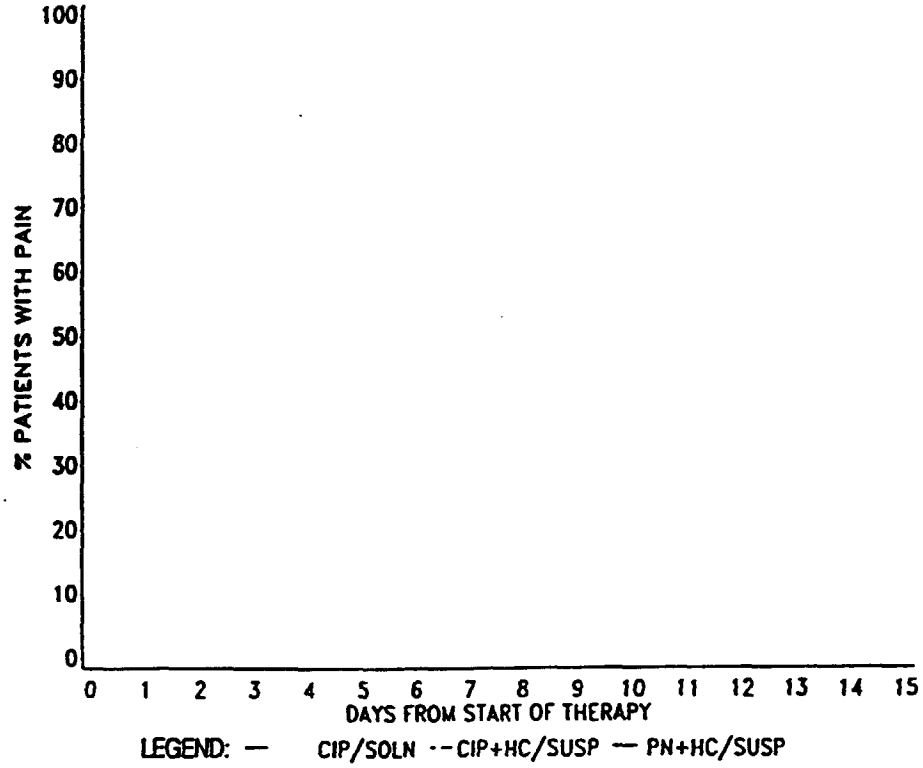
	CIP/SOLN N=185			CIP+HC/SUSP N=207			PN+HC/SUSP N=191		
DISTRIBUTION (CM)	N	(%)	(CUM %)	N	(%)	(CUM %)	N	(%)	(CUM %)
MISSING	35	18.9	18.9	38	18.4	18.4	29	15.2	15.2
	4	2.2	21.1	4	1.9	20.3	5	2.6	17.8
	25	13.5	34.6	24	11.6	31.9	29	15.2	33.0
	28	15.1	49.7	32	15.5	47.4	37	19.4	52.4
	61	33.0	82.7	62	30.0	77.4	55	28.8	81.2
	32	17.3	100.0	47	22.7	100.1	36	18.8	100.0
MEAN		8.991			9.330			8.785	
MEDIAN		10.00			9.75			9.00	
STANDARD DEVIATION		3.751			3.860			3.843	
RANGE									

P-VALUES OF F-STATISTICS USED TO TEST FOR EQUALITY OF MEANS FOR MAIN EFFECTS:
DRUG=0.6613 CENTRE=0.0000
STATISTICS CALCULATED USING SS3 CRITERIA

TABLE 14

Analysis of Time to End of Ear Pain

Population: All Patients Valid For Efficacy
Results For Pooled Data



Comparison	P-Value (Log-Rank Test)
CIP+HC/SUSP vs. CIP/SOLN*	0.140
CIP+HC/SUSP vs. PN+HC/SUSP	0.624
CIP/SOLN vs. PN+HC/SUSP	0.315

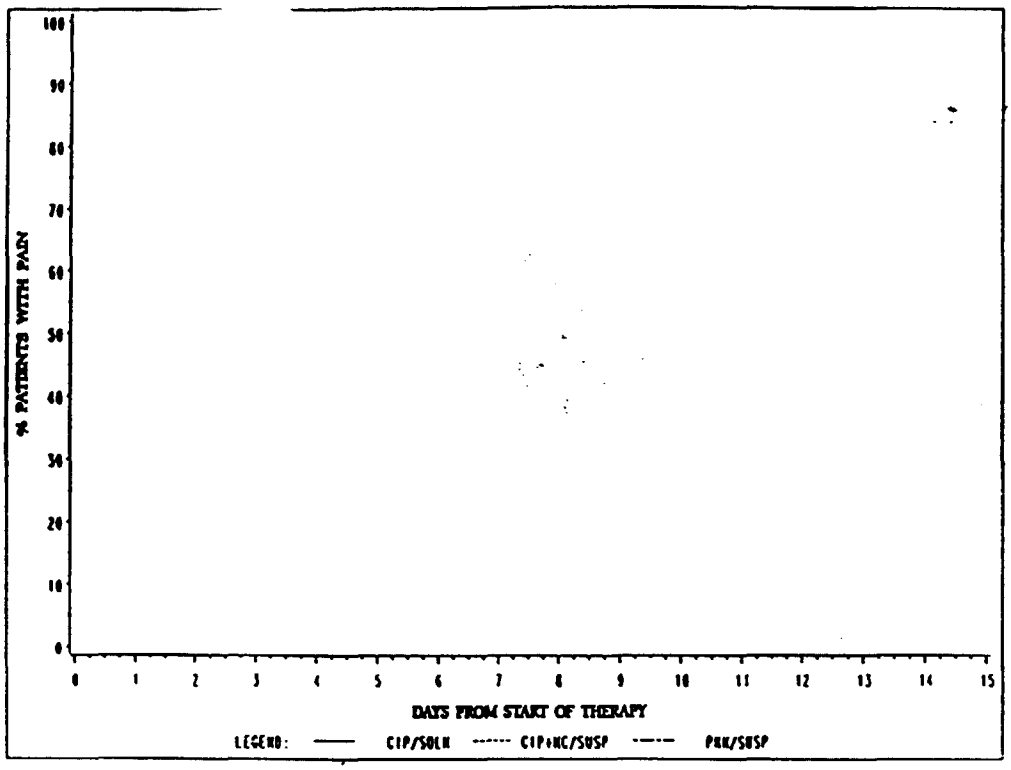
* Primary comparison for time to end of pain

Treatment Group	# Observations	# Censored Observations	Estimated Median Time (Days) to End of Ear Pain	95% Confidence Interval for Median	
				Lower Bound	Upper Bound
CIP/SOLN	225	60	5.00	4.70	5.80
CIP+HC/SUSP	235	51	4.80	4.30	5.30
PN+HC/SUSP	222	57	4.60	4.00	5.10

Note: For patients with bilateral infections both valid for efficacy, the time to end of pain is defined as follows:

1. If end of pain is observed (i.e., not censored) for both ears, the time to end of pain for the patient is the greater of the two time values and the observation is uncensored.
2. If the time to end of pain is censored for at least one ear, the patient's time to end of pain is the greater of the time values and the observation is censored.

Table 15
Analysis of Original Time to End of Ear Pain Data
Population: All Patients Valid for Revised Clinical Efficacy Analysis Using +3 to +10 Window



Comparison	P-value (Log-Rank Test)
*CIP+HC/SUSP vs. CIP/SOLN**	*0.344*
CIP+HC/SUSP vs. PNH/SUSP	0.829
CIP/SOLN vs. PNH/SUSP	0.420

* Primary comparison for time to end of pain

Treatment Group	# Observations	# Censored Observations	Estimated Median Time (Days) to End of Ear Pain	95% Confidence Interval for Median	
				Lower Bound	Upper Bound
CIP/SOLN	184	40	4.59	4.063	4.951
CIP+HC/SUSP	205	34	4.00	3.563	4.688
PNH/SUSP	189	38	4.06	3.833	4.538

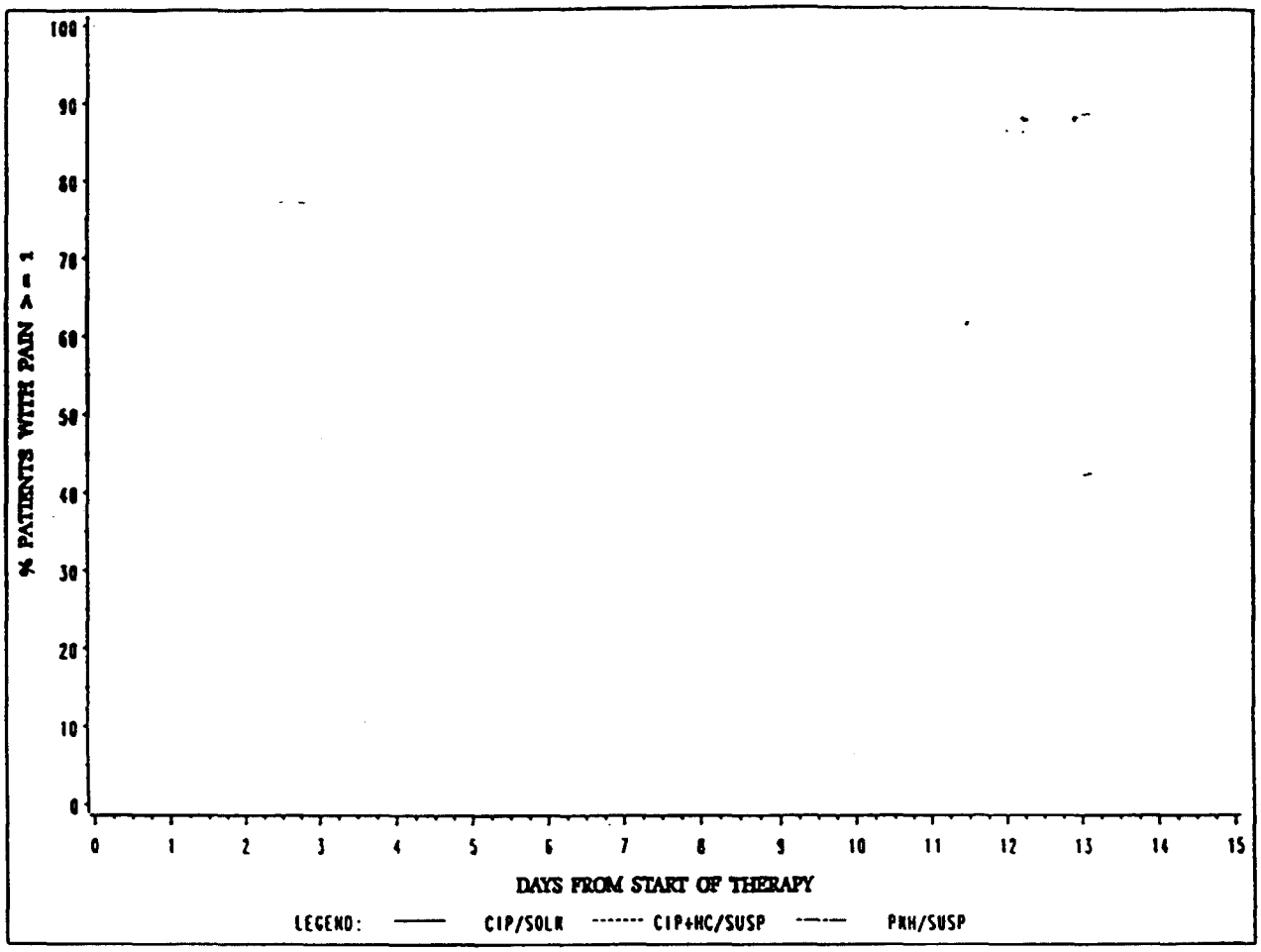
Note: The time to end of ear pain was obtained as follows. If the date and time of end of pain were entered in the fields at the top of page 8 in the patient's diary, they were used to calculate the duration of pain, the interval between the time of the first dose and the time of the end of pain. For such patient ears, the time to end of pain was observed and therefore was not censored. If the date/time field at the top of page 8 was blank, this indicated that pain did not end while the patient was under study observation and the observation was censored. The time value for such an censored observation was the duration of time when the patient was under observation, which is the time interval between the time of the first dose and the time of the last pain measurement entry in the patient's diary. For patients with bilateral infections both valid for efficacy, the time to end of pain for the patient was defined as follows:

1. If end of pain was observed (i.e., not censored) for both ears, the time to end of pain for the patient was the greater of the two time values and the observation was not censored.
2. If the time to end of pain was censored for at least one ear, the patient's time to end of pain was the greater of the time values and the observation was censored.

TABLE 16

A. An Exploratory Analysis of Time to Pain Measurement < 1

Population: All Patients Valid for Revised Clinical Efficacy Analysis Using +3 to +10 Window with *Baseline Pain Measurement Greater Than 6*



Comparison	P-value (Log-Rank Test)
CIP+HC/SUSP vs. CIP/SOLN	*0.164*
CIP+HC/SUSP vs. PNH/SUSP	0.171
CIP/SOLN vs. PNH/SUSP	0.958

Treatment Group	# Observations	# Censored Observations	Estimated Median Time (Days) to End of Ear Pain	95% Confidence Interval for Median	
				Lower Bound	Upper Bound
CIP/SOLN	131	24	4.00	3.54	4.48
CIP+HC/SUSP	152	14	3.46	3.01	3.84
PNH/SUSP	142	25	3.83	3.51	4.28

Note: The time to ear pain measurement of less than 1 was based on pain measurement data from patient's diary. If the last pain measurement had a value greater than or equal to 1, this observation was censored and pain intensity did not go below 1 (permanently). The time value for such an censored observation was the duration of time when the patient was under observation, which was the time interval between the time of the first dose and the time of the last pain measurement entry in the patient's diary. If the last pain measurement was less than 1, the patient achieved a pain intensity < 1 (permanently). The time value was the time to the first pain measurement of less than 1 such that there was no measurement ≥ 1 thereafter. For patients with bilateral infections both valid for efficacy, the time value for the patient was defined as follows:

1. If the time value was observed (i.e., not censored) for both ears, the time for the patient was the greater of the two time values and the observation was not censored.
2. If the time value was censored for at least one ear, the patient's time was the greater of the time values and the observation was censored.

Safety

A total of 838 patients out of the 842 patients enrolled were considered valid for safety analysis: 277 Cipro SOLN, 282 Cipro HC, and 279 PNH patients. An overview of all adverse events, whether or not considered related to the study drug are recorded in Table 17. The most commonly recorded events were otitis externa in the non-treated ear (n=13), moniliasis (n = 6), headache (n = 6), pruritus (n = 5), and otitis media (n = 5).

Summary of all events considered to be drug-related by the investigators is shown in Table 18. Adverse events were considered to be drug-related if the relationship was assessed as "remote", "possible", or "probable" by the investigators. Only 2% of Cipro HC- and Cipro SOLN-treated patients and 4% of PNH-treated patients experienced drug-related adverse events. Most commonly reported were an unspecified "ear disorder" in 4 patients (one each in Cipro SOLN and Cipro HC groups, 2 in PNH group) and headache in 3 patients (one per group).

There were no deaths in the study. Study medication was discontinued due to adverse events in none of the Cipro SOLN group, in one patient with pruritus in the Cipro HC group, and for one patient with moniliasis and abdominal pain in the PNH group.

Serious adverse events occurred in 4 patients requiring their hospitalization. Upon review of the case report forms and requesting additional information from the sponsor regarding patient the medical officer agreed that the events did not appear to be causally related to the study drug. The cases are summarized below:

- Patient (Cipro HC) experienced perichondritis of the external canal following 2 days of therapy. Study drug was discontinued and the condition resolved with i.v. clindamycin for 5 days.
- Patient (PNH), an 83 year old woman was hospitalized for treatment of erysipelas and poorly controlled diabetes mellitus two days after being designated as an early treatment failure on study drug. She responded well to i.v. penicillin and medical management of her diabetes.
- Patient (Cipro SOLN) was a 55 year old woman who developed tinnitus and subjective hearing loss in the treated ear seven days following therapy for otitis externa. Audiogram showed a bilateral high frequency sensorineural hearing loss. Rheological therapy (Trental, steroid taper, aspirin, low subcutaneous heparin) was apparently administered for 10 days with subjective improvement in her hearing. Electronystagmography (ENG), and auditory brainstem response testing were unremarkable.
- Patient (PNH) experienced increased tinnitus 19 days following completion of study drug and was treated with rheological therapy as above. Longterm follow-up on this patient was unavailable.

MO Comment: Adverse events were generally uncommon, mild, self-limited, and evenly distributed among the three treatment groups. Any association of tinnitus and/or hearing loss with use of a topical otic preparation is highly unlikely in patients with an intact tympanic membrane due to very limited systemic absorption.

TABLE 17
ADVERSE EVENTS BY TREATMENT GROUP AND BODY SYSTEM
WITHOUT RELATIONSHIP TO STUDY DRUG

All adverse events	CIP/SOLN (N=277)		CIP+HC/SUSP (N=282)		PN+HC/SUSP (N=279)	
	N	%	N	%	N	%
Body System						
Body as a whole	10	4	9	3	8	3
Cardiovascular	0	0	2	1	1	0
Digestive	0	0	1	0	4	1
Endocrine	0	0	0	0	1	0
Musculoskeletal	2	1	2	1	1	0
Nervous	1	0	1	0	5	2
Respiratory	4	1	5	2	3	1
Skin and Appendices	1	0	7	2	6	2
Special Senses	7	3	11	4	10	4
Total no. of patients with AE's	24	9	31	11	29	10

TABLE 18
INCIDENCE RATES OF DRUG-RELATED ADVERSE EVENTS
BY BODY SYSTEM AND TREATMENT
FOR ALL PATIENTS VALID FOR SAFETY ANALYSIS

ADVERSE EVENT	CIP/SOLN	CIP+HC/SUSP	PN+HC/SUSP
ANY BODY SYSTEM			
ANY EVENT	6/277 (2%)	7/282 (2%)	10/279 (4%)
BODY AS A WHOLE			
ANY EVENT	2/277 (1%)	1/282 (0%)	3/279 (1%)
ABDOMINAL PAIN	0/277 (0%)	0/282 (0%)	1/279 (0%)
INFECTION	1/277 (0%)	0/282 (0%)	1/279 (0%)
HEADACHE	1/277 (0%)	1/282 (0%)	1/279 (0%)
DIGESTIVE			
ANY EVENT	0/277 (0%)	0/282 (0%)	2/279 (1%)
NAUSEA	0/277 (0%)	0/282 (0%)	1/279 (0%)
VOMITING	0/277 (0%)	0/282 (0%)	1/279 (0%)
MUSCULOSKELETAL			
ANY EVENT	1/277 (0%)	0/282 (0%)	0/279 (0%)
BONE DISORDER	1/277 (0%)	0/282 (0%)	0/279 (0%)
NERVOUS			
ANY EVENT	0/277 (0%)	1/282 (0%)	4/279 (1%)
VERTIGO	0/277 (0%)	0/282 (0%)	2/279 (1%)
HYPESTHESIA	0/277 (0%)	0/282 (0%)	1/279 (0%)
TWITCHING	0/277 (0%)	0/282 (0%)	1/279 (0%)
PARESTHESIA	0/277 (0%)	1/282 (0%)	0/279 (0%)
RESPIRATORY			
ANY EVENT	0/277 (0%)	1/282 (0%)	0/279 (0%)
COUGH INCREASED	0/277 (0%)	1/282 (0%)	0/279 (0%)
SKIN AND APPENDAGES			
ANY EVENT	0/277 (0%)	4/282 (1%)	2/279 (1%)
RASH	0/277 (0%)	1/282 (0%)	1/279 (0%)
URTICARIA	0/277 (0%)	1/282 (0%)	0/279 (0%)
PRURITUS	0/277 (0%)	1/282 (0%)	1/279 (0%)
ALOPECIA	0/277 (0%)	1/282 (0%)	0/279 (0%)
SPECIAL SENSES			
ANY EVENT	4/277 (1%)	1/282 (0%)	3/279 (1%)
EAR DISORDER	1/277 (0%)	1/282 (0%)	2/279 (1%)
OTITIS EXTERNA	2/277 (1%)	0/282 (0%)	1/279 (0%)
CONJUNCTIVITIS	1/277 (0%)	0/282 (0%)	0/279 (0%)

9. Overview of Efficacy

Studies D94-008 (U.S. Study) and 1439 (European Study) provide convincing evidence of the efficacy of Cipro HC Otic Suspension in the treatment of acute, diffuse otitis externa due to *Pseudomonas aeruginosa* and *Staphylococcus aureus.*

Both studies were performed under nearly identical protocols in a total of 60 centers across the United States and Europe. In both studies, Cipro HC applied topically to the ear canal (three drops twice daily for seven days) was statistically equivalent to the approved comparator for this indication, PNH (3-4 drops applied three times daily for seven days), with respect to clinical success at the End of Therapy (3-10 days post-therapy). Specifically, the clinical response rates (defined as resolution + improvement) for the Cipro HC and PNH groups in the U.S. study were 90.1% and 87.2%, respectively, with a 95% confidence interval of (-0.0339, 0.0793) for the difference between response rates; for the European study, the clinical response rates for Cipro HC and PNH were 92.75% and 89.5%, respectively, with a 95% confidence interval of (-0.0246, 0.0878) for the difference between the response rates. High rates of continued resolution of infection were also observed in Cipro HC-treated patients at the Follow-up visit (11-30 days post-therapy) in both studies.

Experience with Cipro HC in 118 pediatric patients (age years) in the U.S. demonstrated that it is effective and well-tolerated in this population. The rate of resolution of the infection in Cipro HC-treated patients was actually almost 20% greater in this population at the End of Therapy visit than in the adult population. Since the bacterial pathogenesis of the infection is thought to be similar in adult and pediatric populations and there are no safety concerns specific to younger pediatric patients, it is felt that the labeling indication could be extended to patients one year of age and older by the Pediatric Rule. In patients less than one year of age, the small diameter of the ear canal might complicate the ability of the clinician to rule out a tympanic membrane perforation, which should be done prior to use of this nonsterile product. Furthermore, in patients less than 3 months of age, gram negative organisms (e.g., coliforms) may play an etiologic role in the infection, and the sponsor has not presented data to support the product's effectiveness in such infections.

With respect to bacteriological efficacy, statistical equivalence to the approved comparator was clearly shown in both trials. In fact, the confidence interval of the difference between Cipro HC and PNH did not cross zero in either study suggesting possible superiority of Cipro HC (although the study was not designed to demonstrate superiority). Good antimicrobial activity of both Cipro HC and Cipro SOLN against both major pathogens, *Pseudomonas aeruginosa* and *Staphylococcus aureus,* was observed in both trials. There is no evidence from the observed clinical or bacteriologic response rates that the addition of hydrocortisone to the ciprofloxacin preparation in any way impairs its antimicrobial activity. Therefore, in determining justification for labeling of the product for the various pathogens, the isolates from the Cipro HC and the Cipro SOLN groups were combined. The eradication rates for the most commonly encountered pathogens in the study (combined Cipro HC and Cipro SOLN isolates) are summarized in Table 1 below:

TABLE 1
BACTERIOLOGICAL RESPONSE BY ORGANISM (BOTH TRIALS)

ORGANISM	STUDY POPULATION								
	U.S.			European			U.S. + European		
	n	# erad*	% erad	n	# erad*	% erad	n	# erad*	% erad
PSEUDOMONAS AERUGINOSA	285	259	90.9	168	153	91.1	453	412	90.9
STAPHYLOCOCCUS AUREUS	32	29	90.6	39	36	92.3	71	65	91.5
STENOTROPHOMONAS MALTOPHILIA	14	11	78.6	0	-	-	14	11	78.6
ACINETOBACTER ANITRATUS	15	15	100	0	-	-	15	15	100
PROTEUS MIRABILIS	9	9	100	6	6	100	15	15	100
ENTEROCOCCUS FAECALIS	0	-	-	21	20	95.2	21	20	95.2

* Eradication numbers and rates include patients with "eradication + presumed eradication" of the bacterial pathogens. The denominator includes all evaluable patients with the causative organism isolated pre-therapy including indeterminate and missing responses in both the Cipro SOLN and Cipro HC treatment groups.

A total of 493 patients from both clinical trials were evaluable for bacteriological efficacy. The Points to Consider document recommends that only those pathogens which comprise at least 10% of the evaluable cases and are successfully treated with the study drug be included in the **INDICATIONS AND USAGE** section of the product label. Based on the number of isolates and the observed eradication rates, labeling for *Pseudomonas aeruginosa* and *Staphylococcus aureus* is clearly justifiable. *Proteus mirabilis,* while present in only 3% of evaluable cases, represents a generally accepted pathogen in otitis externa and was seen in a percentage of cases that was consistent with other published studies (Cassisi et al., *Ann Otol Rhinol Laryngol Suppl* 1977; 86:1-16). Both Cipro HC and Cipro SOLN demonstrated excellent antimicrobial activity against isolates of this organism. In this situation, the Points to Consider document would support a labeling indication for *Proteus mirabilis*. However, the organisms *Acinetobacter anitratus, Stenotrophomonas maltophilia,* and *Enterococcus faecalis* were isolated in less than 10% evaluable cases and their role as pathogens in otitis externa has not been well established. Furthermore, *Enterococcus faecalis* was only isolated in the European study and does not appear to be a clinically relevant pathogen in the U.S. population. Thus, the labeling recommendation for this indication should include the following three organisms: *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Proteus mirabilis.*

The rate of superinfection was similar in the Cipro HC and PNH groups. However, the development of positive fungal cultures appeared to be more frequent in the Cipro SOLN and Cipro HC groups compared to the PNH group, particularly in the U.S. study. The significance of positive fungal cultures remains unclear since fungus is frequently a colonizing organism in the normal, healthy ear canal and a large majority of patients with positive fungal cultures were rated as clinical successes based on the End of Therapy clinical assessment. However, it would seem prudent to consider fungal superinfection in patients with persistent symptoms during and following therapy.

As outlined above, the sponsor clearly demonstrated in two large, well-controlled, multi-center trials that the clinical and bacteriological efficacy rates for Cipro HC were equivalent to the approved comparator drug for this indication, PNH. However, the Combination Rule (21 CFR section 300.50) also requires the sponsor to demonstrate that the addition of hydrocortisone to the preparation results in a clinically significant contribution to the overall effectiveness of the combined product. From a scientific rationale standpoint, topical steroids are currently used as an effective treatment for a wide array of inflammatory skin conditions. Since acute otitis externa is typically characterized by significant inflammation of the ear canal skin in response to infection, the addition of hydrocortisone to the otic formulation might be expected to aid in the resolution of this inflammation. The general acceptance of this rationale in the past is evidenced by the presence of 1% hydrocortisone in five currently approved combination otic formulations for the indication of acute otitis externa: Cortisporin Suspension, Cortisporin Solution, Vosol HC Otic Solution, Pediotic Suspension, and Colymycin S Otic. [However, the FDA approval of these products predated the implementation of the Combination Rule, and the sponsors were not required to specifically demonstrate a clinical benefit from the addition of hydrocortisone to the product.] Although no direct evidence regarding the effects of hydrocortisone in acute otitis externa exists, the approved use of decadron ophthalmic solution for this indication supports a role for a topical steroid as a single agent in relieving inflammation associated with this condition.

The Time to End of Pain (TEOP) variable was studied by the sponsor as a means to demonstrate clinical benefit from the addition of hydrocortisone (Cipro HC) compared to ciprofloxacin solution alone (Cipro SOLN) in the two clinical trials. The superiority of the combination product with respect to TEOP was demonstrated with statistical significance in the U.S. study in both the intent-to-treat ($p=0.041$) and clinically evaluable ($p=0.039$) patient populations (FDA analysis). The estimated difference in median TEOP between the Cipro HC and Cipro SOLN evaluable patient populations was nearly one day (21 hours). This difference in TEOP between groups was consistent across all age groups above six years old. While the European study showed the estimated median TEOP in the Cipro HC group was over 12 hours less than the Cipro SOLN group of evaluable patients, the difference failed to achieve statistical

significance. An excessively high number of missing values for TEOP in both treatment arms apparently resulted from both poor patient compliance in returning pain score diaries and from incomplete recordings in the diaries. The medical and statistical reviewers agreed that the largely incomplete TEOP data base from this study precludes any meaningful comparison of the Cipro SOLN and Cipro HC treatment groups with respect to this variable. Thus, only the U.S. trial TEOP analyses were considered adequate to assess the clinical benefit from the addition of hydrocortisone to the product.

Given (1) the scientific rationale for use of steroids in this condition (including a currently approved indication for a steroid alone product for acute otitis externa), (2) the long record of safe and effective use of five combination otic products containing 1% hydrocortisone for acute otitis externa, and (3) the significant reduction in TEOP in the U.S. patient population when the Cipro HC group was compared to the Cipro SOLN group, the medical reviewers conclude that the data from the U.S. study provide sufficient data to support the conclusion that hydrocortisone contributes to the overall effectiveness of Cipro HC.

10. Overview of Safety

Review of adverse events for the two pivotal trials in this NDA submission indicate that Cipro HC Otic Suspension is safe for topical use in patients with acute, diffuse otitis externa. The incidence of drug-related adverse events in both studies was quite low. These events were typically uncommon, mild, self-limited and occurred with a frequency similar to the approved comparator. The most commonly reported drug-related events for the two studies were headache and unspecified "ear disorder", both of which occurred in only 1-2% of patients in both studies. No drug-related serious adverse events and no deaths were reported in either trial.

11. Labeling Recommendations

The following is the recommended package insert for use with Cipro HC Otic Suspension:

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

12. Overall Conclusions/Recommendations

Cipro HC Otic Suspension is recommended for approval for the indication of acute diffuse bacterial external otitis in adult and pediatric patients, one year and older, caused by organisms susceptible to the action of ciprofloxacin, including *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Proteus mirabilis.* Insufficient numbers of isolates of the organisms *Enterococcus faecalis, Acinetobacter anitratus (baumannii)* and *Stenotrophomonas maltophilia* were obtained in the U.S. clinical trial to justify their inclusion in the labeling for this indication as proposed by the sponsor. Furthermore, the role of these organisms as bacterial pathogens in otitis externa has not been clearly established. In two adequate and well-controlled clinical trials, Cipro HC Otic Suspension was demonstrated to be at least as safe and effective as the FDA-approved comparator for this indication, PNH, with clinical efficacy rates (defined as resolution + improvement) exceeding 90% in both trials at the End of Therapy (3-10 days post-therapy) visit. Results from both trials suggest that an underlying fungal infection should be considered in patients who have persistent symptoms following a full course of therapy. Since the product is non-sterile and its animal ototoxicity data base is incomplete, labeling should recommend against use in patients with known or suspected perforation of the tympanic membrane.

/S/

Eric A. Mann, MD, PhD
Medical Officer, HFD-520

cc: Orig NDA
HFD-340
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/EMann
HFD-520/Pharm/AEllis
HFD-520Micro/PDionne
HFD-520/Chem/DMateka
HFD-520/CSO/KRoche

Concurrence Only:
HFD-520/DivDir/GChikami 2/6/98
HFD-520/SMO/RRoberts RR 2/5/98

APPENDIX I
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY
POPULATION: PATIENTS VALID FOR EFFICACY

TREATMENT GROUP: CIP/SOLN	Causative Organism Response at EOT										TOTAL	
	ERADICATION		PRESUMED ERADICATED		PERSISTENCE		INDETERMINATE		MISSING			
	N	%	N	%	N	%	N	%	N	%	N	%
ORGANISM												
PS. AERUGINOSA	116	78.4	20	13.5	2	1.4	7	4.7	3	2.0	148	100.0
STAPH. AUREUS	13	92.9							1	7.1	14	100.0
STENOTROPH MALTOPHILIA	6	66.7			1	11.1			2	22.2	9	100.0
ACIN. ANITRATUS	6	100.0									6	100.0
ENT. AEROGENES	4	100.0									4	100.0
P. MIRABILIS	2	66.7	1	33.3							3	100.0
ENT. CLOACAE	2	66.7	1	33.3							3	100.0
SER. MARCESCENS	1	50.0					1	50.0			2	100.0
KLEBSIELLA SP.	2	66.7					1	33.3			3	100.0
E. COLI	2	100.0									2	100.0
K. PNEUMONIAE	1	100.0									1	100.0
PS. STUTZERI	1	33.3	2	66.7							3	100.0
CITROBACTER KOSERII	4	100.0									4	100.0
PS. FLUOR/PUTIDA/MENDOCIN	2	100.0									2	100.0

(CONTINUED)

APPENDIX I (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY
POPULATION: PATIENTS VALID FOR EFFICACY

TREATMENT GROUP: CIP/SOLN	Causative Organism Response at EOT										TOTAL	
	ERADICATION		PRESUMED ERADICATED		PERSISTENCE		INDETERMINATE		MISSING			
	N	%	N	%	N	%	N	%	N	%	N	%
ORGANISM												
CIT. FREUNDII	2	100.0									2	100.0
ACIN. LWOFFI	1	100.0									1	100.0
FLAVIMONAS ORYZIHABITANS	1	100.0									1	100.0
STREPT. GP A(PYOGENES)	1	100.0									1	100.0
STREPT. GP B(AGALACT)	1	100.0									1	100.0
AEROMONAS SP.	2	100.0									2	100.0
ACHR. XYLOSOXIDANS	1	100.0									1	100.0
ENTEROBACTER SP.	1	100.0									1	100.0
SER. LIQUEFACIENS	1	100.0									1	100.0
PROV. RETTGERI	1	100.0									1	100.0
ALC. FAECALIS	1	100.0									1	100.0
PS. FLUORESCENS	1	100.0									1	100.0
ACHROMOBACTER SP.	1	100.0									1	100.0
ALCALIGENES SP.	1	100.0									1	100.0

(CONTINUED)

APPENDIX I (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY
POPULATION: PATIENTS VALID FOR EFFICACY

TREATMENT GROUP: CIP/SOLN	Causative Organism Response at EOT											
	ERADICATION		PRESUMED ERADICATED		PERSISTENCE		INDETERMINATE		MISSING		TOTAL	
	N	%	N	%	N	%	N	%	N	%	N	%
ORGANISM												
AER. HYDROPHILA			1	100.0							1	100.0
TOTAL	178	80.5	25	11.3	3	1.4	9	4.1	6	2.7	221	100.0

PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
TABLE ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX I (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY
POPULATION: PATIENTS VALID FOR EFFICACY

TREATMENT GROUP: CIP+HC/SUSP	Causative Organism Response at EOT											
	ERADICATION		PRESUMED ERADICATED		PERSISTENCE		INDETERMINATE		MISSING		TOTAL	
	N	%	N	%	N	%	N	%	N	%	N	%
ORGANISM												
PS. AERUGINOSA	104	75.9	19	13.9	2	1.5	11	8.0	1	0.7	137	100.0
STAPH. AUREUS	12	66.7	4	22.2	1	5.6	1	5.6			18	100.0
STENOTROPH MALTOPHILIA	5	100.0									5	100.0
ACIN. ANITRATUS	9	100.0									9	100.0
ENT. AEROGENES	3	100.0									3	100.0
P. MIRABILIS	3	50.0	3	50.0							6	100.0
ENT. CLOACAE	3	60.0	1	20.0			1	20.0			5	100.0
SER. MARCESCENS	3	100.0									3	100.0
KLEBSIELLA SP.	4	100.0									4	100.0
E. COLI	2	50.0	1	25.0			1	25.0			4	100.0
K. PNEUMONIAE	1	25.0	3	75.0							4	100.0
PS. STUTZERI	1	100.0									1	100.0
CIT. FREUNDII	1	100.0									1	100.0
ACIN. LWOFFI	1	100.0									1	100.0

(CONTINUED)

APPENDIX I (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

POPULATION: PATIENTS VALID FOR EFFICACY

TREATMENT GROUP: CIP+HC/SUSP	Causative Organism Response at EOT										TOTAL	
	ERADICATION		PRESUMED ERADICATED		PERSISTENCE		INDETERMINATE		MISSING			
	N	%	N	%	N	%	N	%	N	%	N	%
ORGANISM												
FLAVIMONAS ORYZIHABITANS			1	100.0							1	100.0
CHRYSEOMONAS LUTEOLA			1	100.0							1	100.0
STREPT. GP A(PYOGENES)			1	100.0							1	100.0
PSEUDOMONAS SP.	1	100.0									1	100.0
WEEKSELLA ZOOHELCUM	1	100.0									1	100.0
TOTAL	154	74.8	34	16.5	3	1.5	14	6.8	1	0.5	206	100.0

PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX I (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY
POPULATION: PATIENTS VALID FOR EFFICACY

TREATMENT GROUP: PNH/SUSP	Causative Organism Response at EOT											
	ERADICATION		PRESUMED ERADICATED		PERSISTENCE		INDETERMINATE		MISSING		TOTAL	
	N	%	N	%	N	%	N	%	N	%	N	%
ORGANISM												
PS. AERUGINOSA	96	71.1	20	14.8	11	8.1	5	3.7	3	2.2	135	100.0
STAPH. AUREUS	11	91.7	1	8.3							12	100.0
STENOTROPH MALTOPHILIA	4	66.7	2	33.3							6	100.0
ACIN. ANITRATUS	4	80.0			1	20.0					5	100.0
ENT. AEROGENES	6	85.7			1	14.3					7	100.0
P. MIRABILIS	3	75.0			1	25.0					4	100.0
ENT. CLOACAE	2	50.0	2	50.0							4	100.0
SER. MARCESCENS	4	80.0	1	20.0							5	100.0
KLEBSIELLA SP.	2	66.7	1	33.3							3	100.0
E. COLI	1	50.0	1	50.0							2	100.0
K. PNEUMONIAE	1	100.0									1	100.0
PS. STUTZERI	2	100.0									2	100.0
CITROBACTER KOSERII									1	100.0	1	100.0
PS. FLUOR/PUTIDA/MENDOCIN	1	33.3	1	33.3					1	33.3	3	100.0

(CONTINUED)

APPENDIX I (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY
POPULATION: PATIENTS VALID FOR EFFICACY

TREATMENT GROUP: PNH/SUSP	Causative Organism Response at EOT										TOTAL	
	ERADICATION		PRESUMED ERADICATED		PERSISTENCE		INDETERMINATE		MISSING			
	N	%	N	%	N	%	N	%	N	%	N	%
ORGANISM												
CIT. FREUNDII	1	100.0									1	100.0
ACIN. LWOFFI	2	100.0									2	100.0
FLAVIMONAS ORYZIHABITANS	1	100.0									1	100.0
CHRYSEOMONAS LUTEOLA	2	100.0									2	100.0
K. OXYTOCA	2	100.0									2	100.0
STREPT. GP B(AGALACT)	1	100.0									1	100.0
ACHR. XYLOSOXIDANS	1	100.0									1	100.0
ENTEROBACTER SP.	1	100.0									1	100.0
TOTAL	148	73.6	29	14.4	14	7.0	5	2.5	5	2.5	201	100.0

PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX II
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

TREATMENT GROUP: CIP/SOLN	CAUSATIVE ORGANISM RESPONSE AT EOT								TOTAL	
	ERADICATION		PERSISTENCE		INDETERMINATE		PRESUMED ERADICATED			
	N	PCT	N	PCT	N	PCT	N	PCT	N	PCT
ORGANISM										
BETA HEMOLYTIC GROUP B	2	100.0	0	0	0	0	0	0	2	100.0
E. COLI	0	0	0	0	0	0	1	100.0	1	100.0
ENTERO. FAECALIS	9	90.0	0	0	1	10.0	0	0	10	100.0
ENTEROCOCCUS SP.	1	100.0	0	0	0	0	0	0	1	100.0
K. OXYTOCA	1	100.0	0	0	0	0	0	0	1	100.0
P. MIRABILIS	1	100.0	0	0	0	0	0	0	1	100.0
PEPTOSTREPT. SP.	5	100.0	0	0	0	0	0	0	5	100.0
PS. AERUGINOSA	63	76.8	7	8.5	10	12.2	2	2.4	82	100.0
PS. STUTZERI	0	0	0	0	1	100.0	0	0	1	100.0
PSEUDOMONAS SP.	1	100.0	0	0	0	0	0	0	1	100.0
SER. MARCESCENS	1	100.0	0	0	0	0	0	0	1	100.0

(CONTINUED)

NOTE: PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS.
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX II (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

TREATMENT GROUP: CIP/SOLN	CAUSATIVE ORGANISM RESPONSE AT EOT								TOTAL	
	ERADICATION		PERSISTENCE		INDETERMINATE		PRESUMED ERADICATED			
	N	PCT	N	PCT	N	PCT	N	PCT	N	PCT
ORGANISM										
STAPH. AUREUS	15	93.8	0	0	1	6.3	0	0	16	100.0
STREPT. GP A(PYOGENES)	1	100.0	0	0	0	0	0	0	1	100.0
STREPT. GP C	2	100.0	0	0	0	0	0	0	2	100.0
STREPT. GP G	2	100.0	0	0	0	0	0	0	2	100.0
STREPT. PNEUMONIAE	1	100.0	0	0	0	0	0	0	1	100.0
TOTAL	105	82.0	7	5.5	13	10.2	3	2.3	128	100.0

NOTE: PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS.
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX II (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

TREATMENT GROUP: CIP+HC/SUSP	CAUSATIVE ORGANISM RESPONSE AT EOT									
	ERADICATION		PERSISTENCE		INDETERMINATE		PRESUMED ERADICATED		TOTAL	
	N	PCT	N	PCT	N	PCT	N	PCT	N	PCT
ORGANISM										
BACT. FRAGILIS	3	100.0	0	0	0	0	0	0	3	100.0
BETA HEMOLYTIC GROUP B	3	100.0	0	0	0	0	0	0	3	100.0
E. COLI	0	0	0	0	0	0	1	100.0	1	100.0
ENTERO. FAECALIS	10	76.9	1	7.7	1	7.7	1	7.7	13	100.0
ENTEROCOCCUS SP.	3	75.0	0	0	0	0	1	25.0	4	100.0
K. OXYTOCA	3	100.0	0	0	0	0	0	0	3	100.0
KLEBSIELLA SP.	0	0	0	0	1	100.0	0	0	1	100.0
P. MIRABILIS	5	100.0	0	0	0	0	0	0	5	100.0
PEPTOSTREPT. SP.	2	100.0	0	0	0	0	0	0	2	100.0
PS. AERUGINOSA	81	78.6	8	7.8	7	6.8	7	6.8	103	100.0
PSEUDOMONAS SP.	2	100.0	0	0	0	0	0	0	2	100.0

(CONTINUED)

NOTE: PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS.
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX II (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

TREATMENT GROUP: CIP+HC/SUSP	CAUSATIVE ORGANISM RESPONSE AT EOT								TOTAL	
	ERADICATION		PERSISTENCE		INDETERMINATE		PRESUMED ERADICATED			
	N	PCT	N	PCT	N	PCT	N	PCT	N	PCT
ORGANISM										
STAPH. AUREUS	19	76.0	3	12.0	1	4.0	2	8.0	25	100.0
STAPH. EPIDERMIDIS	0	0	0	0	1	100.0	0	0	1	100.0
STREPT. GP A(PYOGENES)	1	100.0	0	0	0	0	0	0	1	100.0
STREPT. GP C	0	0	0	0	1	100.0	0	0	1	100.0
STREPT. GP G	1	100.0	0	0	0	0	0	0	1	100.0
TOTAL	133	78.7	12	7.1	12	7.1	12	7.1	169	100.0

NOTE: PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS.
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX II (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

TREATMENT GROUP: PN+HC/SUSP	CAUSATIVE ORGANISM RESPONSE AT EOT								TOTAL	
	ERADICATION		PERSISTENCE		INDETERMINATE		PRESUMED ERADICATED			
	N	PCT	N	PCT	N	PCT	N	PCT	N	PCT
ORGANISM										
BACTEROIDES SP.	1	100.0	0	0	0	0	0	0	1	100.0
BETA HEMOLYTIC GROUP B	1	50.0	0	0	1	50.0	0	0	2	100.0
E. COLI	1	100.0	0	0	0	0	0	0	1	100.0
ENTERO. FAECALIS	3	75.0	0	0	1	25.0	0	0	4	100.0
ENTEROBACTER SP.	1	100.0	0	0	0	0	0	0	1	100.0
ENTEROCOCCUS SP.	3	100.0	0	0	0	0	0	0	3	100.0
K. OXYTOCA	2	100.0	0	0	0	0	0	0	2	100.0
P. MIRABILIS	1	100.0	0	0	0	0	0	0	1	100.0
PS. AERUGINOSA	59	67.0	17	19.3	9	10.2	3	3.4	88	100.0
PS. FLUOR/PUTIDA/MENDOCIN	1	100.0	0	0	0	0	0	0	1	100.0
PSEUDOMONAS SP.	2	100.0	0	0	0	0	0	0	2	100.0

(CONTINUED)

NOTE: PATIENT MAY HAVE MULTIPLE CAUSATIVE ORGANISMS.
ONE SPECIES MAY BE ISOLATED IN BOTH EARS FOR PTS WITH BILATERAL INFECTIONS.
ONLY VALID EARS ARE INCLUDED IN THIS TABLE.

APPENDIX II (continued)
BACTERIOLOGICAL RESPONSE BY CAUSATIVE ORGANISM AT END OF THERAPY

POPULATION: ALL PATIENTS VALID FOR NEW CLIN EFFICACY ANALYSIS

TREATMENT GROUP: PN+HC/SUSP	CAUSATIVE ORGANISM RESPONSE AT EOT								TOTAL	
	ERADICATION		PERSISTENCE		INDETERMINATE		PRESUMED ERADICATED			
	N	PCT	N	PCT	N	PCT	N	PCT	N	PCT
ORGANISM										
STAPH. AUREUS	11	84.6	1	7.7	1	7.7	0	0	13	100.0
STREPT. GP F	1	100.0	0	0	0	0	0	0	1	100.0
STREPT. GP G	2	100.0	0	0	0	0	0	0	2	100.0
TOTAL	89	73.0	18	14.8	12	9.8	3	2.5	122	100.0