formulations of ciprofloxacin used at the recommended dosages. There were no reports of detection of circulating metabolites of ciprofloxacin. These results are consistent with preclinical assessments of ciprofloxacin absorption in animals, as discussed in Module 2.6 of this submission. Ciprofloxacin Otic Solution 0.2% is not likely to have any discernible pharmacologic effect when used in accordance with the proposed label directions for treatment of OE.

No Human Pharmacokinetics Studies were performed.

Pharmacodynamics

Primary Pharmacodynamics

The Applicant provides no explanation of primary pharmacodynamics in Section 4.2.1.1. In this section, the Applicant provides one reference from the literature [37]. The Applicant asserts that primary pharmacodynamics is supported by literature and by the Agency's findings supporting the development of ciprofloxacin for approved formulations and indications that are summarized in ciprofloxacin product labeling (Cipro® HC Otic Prescribing Information, Tab 4.3.2, Module 4, Volume 2, this submission).

Secondary Pharmacodynamics

As stated by the Applicant in Section 4.2.1.2 of this submission, no secondary pharmacodynamics studies were conducted. This section references back to the Agency's findings supporting the development of ciprofloxacin for approved formulations and indications that are summarized in ciprofloxacin's product labeling.

Pharmacodynamic Drug Interactions

As stated by the Applicant in Section 4.2.1.4 of this submission, no pharmacodynamic drug interaction studies were conducted. This section references back to the Agency's findings supporting the development of ciprofloxacin for approved formulations and indications that are summarized in ciprofloxacin's product labeling.

Product Development Rationale

The Applicant presents the rationale for the development of the product in Section 2.5.1 of this submission.

The Applicant is investigating the use of Ciprofloxacin Otic Solution 0.2% as a treatment for acute diffuse bacteria otitis externa (OE). Ciprofloxacin is a fluoroquinolone antibiotic with broad-spectrum antibacterial activity. It is a well-characterized compound that is used intravenously, orally, and topically to treat a variety of infections. Topical formulations containing ciprofloxacin in combination with hydrocortisone (HC) and with dexamethasone have been approved in the US for treatment of OE. Otic formulations containing ciprofloxacin alone have been approved outside the US.

The Applicant's clinical development program for Ciprofloxacin Otic Solution 0.2% includes one multicenter study (with study centers in the US and Spain) of safety and efficacy in adults, adolescents, and children (the Pivotal Study, CIPROT III/03 IA 02),

supported by publicly available information about ciprofloxacin in general and Ciprofloxacin Otic Solution 0.2% in particular. A particularly relevant study was published in 1999 by Pistorius et al. [38]; this was a randomized, non-blinded, active-controlled, multicenter study comparing the safety and efficacy of ciprofloxacin in 0.2% plus HC 1.0% with ciprofloxacin 0.2% and with neomycin/polymyxin B/hydrocortisone (PNH) in 842 patients in the US. This study plus the Pivotal Study are referred to as the Core Studies. The Sponsor conducted Study CIFLOT III/00-01, a randomized, parallel-group, double-blind, active-controlled, multicenter study comparing the safety and efficacy of ciprofloxacin otic solution 0.3% with ciprofloxacin 0.3% plus fluocinolone 0.025% (a combination product marketed in Spain as Cetraxal Plus®); this is referred to as the Supportive Study. Additional information is found in several Published Studies of ciprofloxacin otic solution at concentrations of 0.2%, 0.3%, and 0.5%. In accordance with 21 CRF§314.54, the Sponsor also relies on the Agency's previous findings of safety and effectiveness for ciprofloxacin in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

Representatives of the Applicant and the Contract Research Organization (CRO) met with representatives of the Agency on September 29, 2003 and again by teleconference on January 14, 2004 to discuss the clinical and regulatory development plan for Ciprofloxacin Otic Solution 0.2%. Meeting minutes are included in this submission. Based on the discussions at these meetings, the Agency agreed to consider a 505(b)(2) New Drug Application (NDA) incorporating published literature of ciprofloxacin, referencing the Agency's previous findings of safety and efficacy for ciprofloxacin, and including data from at least one clinical efficacy study to demonstrate non-inferiority of the proposed product. The Pivotal Study was performed in accordance with the recommendations made at these meetings and with Agency guidance documents for antimicrobial drugs [39] and for choice of control group and related issues in clinical studies [40].

ANIMAL THERAPEUTIC STUDIES

The Applicant presents no data from animal models of efficacy.

CLINICAL EFFICACY

CLINICAL LABORATORY SUSCEPTIBILITY TEST METHODS

Disk Content Studies

The Applicant states that disk content studies are not applicable since the subject drug of this application is not a newly developed antibiotic and the Applicant is not making any new claims regarding the *in vitro* activity of the active agent, ciprofloxacin, in their topical otic formulation.

MIC/Disk Diffusion Correlation Studies

MIC/Disk Diffusion correlation studies were not performed since new disks are not being developed. The Applicant again asserts that the subject drug of this application is not a newly developed antibiotic and therefore, these studies are not applicable.

QUALITY CONTROL STUDIES

The Applicant asserts that since disk development studies are not applicable, there are no Quality Control studies to submit regarding newly developed MIC testing.

Reviewer's comments: The Applicant does not provide MIC interpretive criteria for *S. aureus* or *P. aeruginosa* susceptibility to ciprofloxacin. However, the following MIC interpretive criteria are taken from the Cipro I.V. (Bayer) package insert and may be applied to the clinical microbiology studies performed in the application.

For *dilution techniques*, the following verbiage was taken from the package insert for Cipro I.V. (Bayer):

Qualitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*:

MIC (µg/ml)	Interpretation
≤ 1	susceptible (S)
2	intermediate (I)
≥ 4	resistant (R)

These interpretive standards are applicable only to broth microdilution susceptibility testes with streptococcus using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the following MIC values:

Organism	Strain	MIC (µg/ml)
P. aeruginosa	ATCC 27853	0.25–1.0
S. aureus	ATCC 29213	0.12–0.5

PHASE III PIVOTAL CLINICAL TRIAL

CIPROT III/03 IA 02, is a randomized, evaluator-blinded comparison of the efficacy and safety of ciprofloxacin otic solution 0.2% with neomycin and polymyxin B sulfates and hydrocortisone otic solution in the treatment of acute diffuse otitis externa in children, adolescents, and adults.

Study Objectives

The *primary objective* is to determine whether the proportion of patients with clinical cure after seven days of twice-daily treatment with Ciprofloxacin Otic Solution 0.2% is non-inferior to the proportion with clinical cure after seven days of three-times-daily treatment with PNH in children, adolescents, and adults with acute diffuse otitis externa. Clinical efficacy parameters are established as pain (otalgia), edema, and otorrhea.

Secondary objectives: To determine whether the proportion of patients achieving each of the following endpoints after seven days of twice daily treatment with the drug product is non-inferior to the proportion after seven days of three-times-daily treatment with PNH in children, adolescents, and adults with acute diffuse otitis externa:

- Clinical cure at Visit 3,
- Clinical improvement at Visit 3 and at Visit 4,
- Resolution of otalgia at Visit 3 and at Visit 4,
- Improvement in otalgia at Visit 3 and at Visit 4,
- Clinical and microbiological cure at Visit 3 and at Visit 4, and
- Clinical and microbiological improvement at Visit 3 and at Visit 4.

Patient Populations

There are five populations defined for this study: Clinical Per Protocol (CPP), Clinical Intent-To-Treat (CITT), Microbiological Intent-To-Treat (MITT), Microbiological Per Protocol (MPP), and Safety.

The CITT population included all patients who are randomized and receive any study medication. The CPP population is the primary population for efficacy analyses which is defined as those patients who:

- Satisfy all inclusion and exclusion criteria;
- Do not receive any prohibited concomitant medications;
- Do not have any other major protocol violations; Complete Visit 3 and Visit 4 (unless the subject is deemed a clinical failure at an earlier visit than Visit 4); and
- Have compliance rates between 80% and 120% as defined under Study Medication Compliance (patients who are deemed Clinical Failures are to be included if they had compliance rates between 80% and 120% during the first three days of study treatment).

The MITT population includes all CITT patients whose Visit 1 microbiological culture yielded one or more pathogens. The MPP population will include all CPP patients whose Visit 1 microbiological culture yields one or more pathogens and who have microbiological results (Eradication, Presumed Eradication, Persistence, or Superinfection) from Visit 3 and/or Visit 4.

Clinical Efficacy

CIPROT III/03 IA 02 compares the Applicant's proposed corticosteroid-free ciprofloxacin otic solution drug product with an approved otic drug product, PNH for clinical cure at Visit 4. Three clinical efficacy parameters included otalgia, edema, and otorrhea that were scored as absent (0+), mild (1+), moderate (2+), and severe (3+). A total symptom score is obtained by adding all three evaluation scores together. The overall clinical outcomes were categorized as clinical cure, clinical improvement, clinical failure, and indeterminate. Clinical cure is defined as resolution of otalgia, edema, and otorrhea. A sustained clinical cure is noted if a clinical cure is seen at both Visit 3 and Visit 4. A subsequent clinical cure is noted if clinical improvement is seen at Visit 3 and clinical cure is recorded at Visit 4. The primary efficacy endpoint for this study is

clinical cure at Visit 4 for the total population. For purposes of the primary analysis patients who had a clinical outcome recorded as clinical improvement at Visit 4 are combined with the patients who have a clinical outcome recorded as clinical failure (at Visit 3 or Visit 4) to form an overall clinical failure group.

Microbiological Efficacy

Microbiological cultures of ear discharge are taken at Visits 1, 3, and 4 except when no discharge is present. After processing at the central laboratory, species identification and bacterial abundance is assessed. Bacterial abundance is assessed on a scale of 1+ to 4+ per standard laboratory grading. To be considered a pathogen, the cultured organism must have been present at a level of 2+ or higher.

Identification of Pathogens in the Clinical Study CIPROT III/ 03 IA 02

In the pivotal CIPROT IIV 03 IA 02 study, the Microbiological Per-Protocol (MPP) population, 174 patients in each treatment group (70% and 72% of the Clinical Per-Protocol [CPP] populations for ciprofloxacin and polymyxin B/neomycin/ hydrocortisone [PNH] groups respectively) had at least one pathogen at pre-therapy. Table 9 lists all of the pre-therapy pathogens identified in the MPP population. *Pseudomonas aeruginosa* was isolated from a majority of these patients (87% in the ciprofloxacin group and 89% in the PNH group). *Staphylococcus aureus* was isolated from 13% of patients in the ciprofloxacin group and 17% in the PNH group. The Microbiological Intent-to-Treat (MITT) population included 232 patients in the ciprofloxacin group (73% of the Clinical Intent-to-Treat [CITT population) and 217 patients in the PNH group (70% of the CITT population). The percentages of patients infected with *P. aeruginosa* and *S. aureus* in the MITT population were similar to those in the MPP population. Table 10 lists the pathogens identified in the MITT population.

When pathogens were identified by country, *P. aeruginosa* and *S. aureus* were again the most prevalent isolates associated with OE. Tables 9 and 10 show the comparison between the US and Spanish MPP and MITT populations from which at least one pathogen was identified at pre-therapy in the CIPROT study.

Table 9. Pre-Therapy Pathogens (MPP) by Country.

	Cipro-	floxacin	(N=247)	PNH	(N=243)	
Pathogen	US	Spain	Total	US	Spain	Total
At least one pathogen	127 (68.3%)	47 (77%)	174 (70.4%)	124 (72.5%)	50 (68.4%)	174 (71.6%)
Pseudomonas aeruginosa	110 (86.6%)	42 (89.4%)	152 (87.4%)	112 (90.3%)	42 (84%)	154 (88.5%)
Staphylococcus aureus	17 (13.4%)	5 (10.6%)	22 (12.6%)	17 (13.7%)	12 (24%)	29 (16.7%)
Enterobacter cloacae	9 (7.1%)	1 (2.1%)	10 (5.7%)	2 (1.6%)	1 (2%)	3 (1.7%)
Klebsiella pneumoniae	7 (5.5%)	1 (2.1%)	8 (4.6%)	3 (2.4%)	3 (6%)	6 (3.4%)
Escherichia coli	4 (3.1%)	2 (4.3%)	6 (3.4%)	4 (3.2%)	2 (4.0%)	6 (3.4%)
Klebsiella oxytoca	2 (1.6%)	3 (6.4%)	5 (2.9%)	1 (0.8%)	2 (4.0%)	3 (1.7%)

Serratia marcescens	2 (1.6%)	3 (6.4%)	5 (2.9%)	1 (0.8%)	0	1 (0.6%)
Citrobacter diversus	1 (0.8%)	3 (6.4%)	4 (2.3%)	1 (0.8%)	0	1 (0.6%)
Proteus mirabilis	1 (0.8%)	3 (6.4%)	4 (2.3%)	0	1 (2.0%)	1 (0.6%)
Beta-hemolytic streptococci, Group B	0	2 (4.3%)	2 (1.1%)	2 (1.6%)	2 (4.0%)	4 (2.3%)
Enterobacter aerogenes	1 (0.8%)	1 (2.1%)	2 (1.1%)	0	1 (2.0%)	1 (0.6%)
Agrobacterium radiobacter/ Tumefaciens	1 (0.8%)	0	1 (0.6%)	1 (0.8%)	0	1 (0.6%)
Enterobacter species	1 (0.8%)	0	1 (0.6%)	1 (0.8%)	0	1 (0.6%)
Pseudomonas stutzeri	0	1 (2.1%)	1 (0.6%)	1 (0.8%)	0	1 (0.6%)
Aeromonas hydrophila	1 (0.8%)	0	1 (0.6%)	0	0	0
Beta-hemolytic streptococci, Group A	0	1 (2.1%)	1 (0.6%)	0	0	0
Beta-hemolytic streptococcus, Group G	1 (0.8%)	0	1 (0.6%)	0	0	0
Pantoea agglomerans	1 (0.8%)	0	1 (0.6%)\	0	0	0
Serratia rubidaea	0	1 (2.1%)	1 (0.6%)	0	0	0
Stenotrophomonas maltophilia	0	0	0	5 (4.0%)	0	5 (2.9%)
Citrobacter freundii	0	0	0	1 (0.8%)	1 (2.0%)	2 (1.1%)
Enterobacter sakazakii	0	0	0	2 (1.6%)	0	2 (1.1%)
Citrobacter species	0	0	0	0	1 (2.0%)	1 (0.6%)

Note: N is the total number of patients in the PP population.
Note: Bacterial abundance is assessed on a scale of 1+ to 4+, per standard laboratory grading (0 if the culture is sterile).
To be considered a pathogen, the cultured organism must be present at a level of 2+ or higher.
Patient may have more than one pathogen.
Percentages for 'Any pathogen' are calculated using the PP population as the denominator. All other percentages are calculated using the MPP population as the denominator.
Percentages for US and Spain are calculated using the number of patients in that country in the appropriate population as the denominator.
Source: Table 4.1, section 5.3.5.4.10, p18: Statistical Table 4.2.1.1

Table 10. Pre-Therapy Pathogens (MITT) by Country.

	Cipro flozacin (N=318)			PNH (N=355)		
Pathogen	**US**	**Spain**	**Total**	**US**	**Spain**	**Total**
At least one pathogen	167 (71.7%)	65 (76.5%)	232 (73%)	156 (70.6%)	61 (88.3%)	217 (70.2%)
Pseudomonas aeruginosa	142 (85%)	55 (84.6%)	197 (84.9%)	142 (91%)	51 (83.6%)	193 (88.9%)
Staphylococcus aureus	27 (16.2%)	6 (9.2%)	33 (14.2%)	22 (14.1%)	13 (21.3%)	35 (16.1%)
Klebsiella pneumoniae	9 (5.4%)	3 (4.6%)	12 (5.2%)	3 (1.9%)	3 (4.9%)	6 (2.8%)
Enterobacter cloacae	10 (6.0%)	2 (3.1%)	12 (5.2%)	3 (1.9%)	2 (3.3%)	5 (2.3%)
Klebsiella oxytoca	5	3	8	2	3	5