Clinical Cure at Visit 3: CITT Population

	Number (%) of Patients		Treatment difference (%)
	Ciprofloxacin (N=318)	PNH (N=309)	(PNH-ciprofloxacin) with 95% CI
Number of patients	318	309	
Clinical Cure	214 (67.3)	183 (59.2)	-8.1 (-15.6, -0.5)
Clinical Failure	104 (32.7)	126 (40.8)	
Clinical Improvement	69 (21.7)	81 (26.2)	
Indeterminate	13 (4.1)	9 (2.9)	

Comparators - Cipro® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension), Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension, and Neomycin Sulfate and Polymyxin B Sulfate and Hydrocortisone Otic Solution (PNH)

Although approved otic products, neither Cipro® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension), Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension, nor Neomycin Sulfate and Polymyxin B Sulfate and Hydrocortisone Otic Solution had approval based on the contribution of both their anti-infective and corticosteroid components. It was presumed that because the steroid components of Cipro® HC and Ciprodex® are not known to have antimicrobial properties that the anti-microbial effect of these products is related to the ciprofloxacin component alone.

In a systematic review and random effects meta-analysis of randomized controlled trials with parallel groups, Rosenfeld et al[3] examined topical antimicrobial therapy for acute otitis externa. Comparisons were made for the following: anti-microbial vs placebo, antiseptic vs antimicrobial, quinolone antibiotic vs non-quinolone antibiotic, steroid-anti-microbial vs anti-microbial, or anti-microbial-steroid vs steroid.

Rosenfeld et al performed a systematic review of topical antimicrobial therapy for AOE as part of a multidisciplinary, evidence-based, clinical practice guideline created by the American Academy of Otolaryngology--Head and Neck Surgery Foundation (AAO-HNSF). Their goal was to identify relevant randomized controlled trials (RCTs) and derive summary estimates of effect size by statistically pooling data from similar studies. Descriptive characteristics of 20 randomized trials included in the final data set are summarized in the following table. Year of publication ranged from 1967 to 2005, with 50% of studies published after 1994 and 25% in 2002 or later.

[3] Rosenfeld R, Singer M, Wasserman J, Stinnett S. Systematic review of topical antimirbial therapy for acute otitis externa. Otolaryngology 2006: 134S24-48.

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In the preceding table, topical quinolone antibiotic and topical non-quinolone antibiotic achieved comparable clinical cure rates for AOE at 3 to 4 days, 7 to 10 days, and 14 to 28 days. Quinolones used in the meta-analyses were ofloxacin (1 study), ciprofloxacin alone (3), or ciprofloxacin combined with dexamethasone (2) or hydrocortisone (1).

In the preceding table, topical antimicrobial/steroid and topical antimicrobial alone achieved comparable clinical and bacteriologic cure rates for AOE at 7 days. Most studies were single blind, of low quality, and performed aural toilet. Antimicrobial/steroid combinations used in the meta-analyses were ciprofloxacin/hydrocortisone, ciprofloxacin/ dexamethasone, and acetic acid/triamcinolone.

Comparable clinical outcomes occur with antiseptic vs antibiotic, quinolone vs nonquinolone antibiotic, and antimicrobial vs antimicrobial plus steroid; steroid alone had better outcomes than steroid plus antibiotic. The incidence of bacteriologic cure tends to exceed the clinical response, with about 80% to 95% bacteriologic efficacy at the test of cure visit. Quinolones have slightly better bacteriologic efficacy than nonquinolone antibiotics.

Ciprofloxacin otic preparations are shown to be highly effective for acute otitis externa, which supports the single clinical trial submitted in this application as well as the reliance on the on the FDA's previous findings of safety and effectiveness for Cipro® HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension) and Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension

Clinical Microbiology – Identification of Pathogens/Microbiological Efficacy

In Clinical Study CIPROT HV 03 IA 02, the Microbiological Per-Protocol (MPP) population[4], 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. The table below 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 percentages of patients infected with *P. aeruginosa* and *S. aureus* in the MITT population were similar to those in the MPP population.

When pathogens were identified by country, *P. aeruginosa* and *S. aureus* were again the most prevalent isolates associated with otitis externa.

[4] The MPP population includes 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.

Table 3: Pre-Therapy Pathogens (MPP) by Country

	Cipro-	flexacin	(N=247)	PNH	(N=243)	
Pathogen	US	Spain	Total	US	Spain	Total
At least one pathogen	127 (88.3%)	47 (77%)	174 (70.4%)	124 (72.5%)	50 (89.4%)	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%)

A central laboratory tested the sensitivity of each isolate of *S. aureus* and *P. aeruginosa* to a standard panel of antibiotics based upon Clinical and Laboratory Standards Institute

(CLSI) breakpoint standards using an automated Vitek TM antibiotic microtiter panel. In addition, the central laboratory tested the sensitivity of each isolate to ciprofloxacin using a _____ series created specifically for this study (the ciprofloxacin-custom" series) to determine the MIC of ciprofloxacin for each isolate. These data were then used to determine the MIC50 and MIC90 of ciprofloxacin for *S. aureus* and *P. aeruginosa.*

The MIC_{50} and MIC_{90} of ciprofloxacin are shown in the table found below. There were no differences in MIC between isolates from patients in the ciprofloxacin group and isolates from patients in the PNH group. For *P. aeruginosa,* the MIC_{50} of ciprofloxacin was 0.12 µg/mL and the MIC_{90} was 0.50 µg/mL. For *S. aureus,* the MIC_{50} *was* 0.25 µg/mL and the MIC_{90} was 1 µg/mL.

Table 4: Ciprofloxacin MIC_{50} and MIC_{90} (µg/mL) for *P. aeruginosa* and *S. aureus* - MITT Population

		Ciprofloxacin	PNH	Total
P.aeruginosa	n	183	199	382
	MIC50	0.12	0.12	0.12
	MIC90	0.50	0.50	0.50
S. aureus	n	33	35	68
	MIC50	0.25	0.25	0.25
	MIC90	1.0	1.0	1.0

Source: Table 5, section 5.3.5.4.11, p26; Statistical Tables 4.1.1.1 and 4.1.2.1

Clinical Microbiology – Bacterial Eradication

Bacteriologic response is summarized in the table provided below. In the Microbiological Per Protocol population (MPP), at both the End-of-Treatment (EOT) visit and the Test-of-Cure visit, which occurred about one week after EOT, the bacteriologic response was Eradication or Presumed Eradication for the great majority of patients in both treatment groups. At the EOT visit, 96% of patients in the ciprofloxacin group and 93% in the PNH group had Eradication or Presumed Eradication.

Table 5: Bacteriologic Response

Visit		Microbiological per Protocol Population		Microbiological Intent to Treat Population	
		Cipro (N=174)	PNH (N=174)	Cipro (N=232)	PNH (N=217)
End of Treatment	Eradication	39 (22.4%)	46 (26.4%)	53 (22.8%)	56 (25.8%)
	Presumed Eradication	128 (73.6%)	115 (66.1%)	157 (67.7%)	139 (64.1%)
	Eradication or Presumed Eradication	167 (96%)	161 (92.5%)	210 (90.5%)	195 (89.9%)
	Persistence	1 (0.6%)	5 (2.9%)	3 (1.3%)	7 (3.2%)
	Presumed Persistence	5 (2.9%)	8 (4.6%)	8 (3.5%)	11 (5.1%)
	Superinfection	1 (0.6%)	0	1 (0.4%)	0
	Indeterminate	--	--	10 (4.3%)	4 (1.8%)
Test of Cure	Eradication	16 (9.2%)	22 (12.6%)	21 (9.1%)	27 (12.4%)
	Presumed Eradication	141 (81%)	130 (74.7%)	176 (75.9%)	155 (71.4%)
	Eradication or Presumed Eradication	157 (90.2%)	152 (87.4%)	197 (84.9%)	182 (83.9%)
	Persistence	1 (0.6%)	1 (0.6%)	1 (0.4%)	2 (0.9%)
	Presumed Persistence	16 (9.2%)	21 (12.1%)	24 (10.3%)	29 (13.4%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	10 (4.3%)	4 (1.8%)

Source: Table 7.1, section 5.3.5.4.12, p23; Statistical Tables 21.1.1 and 21.1.2 (Original submission)

8. Safety

For detailed safety information on Clinical Trial CIPROT III/ 03 IA 02, see the Medical Officer Review dated April 7, 2006.

The mean duration of exposure in Clinical Trial CIPROT III/ 03 IA 02 is found in the table provided below. In the ciprofloxacin group, the majority (58%) of patients used study medication for 7 days as specified in the protocol. In the PNH group, the majority of patients (64%) used study medication for 8 days.

Table 6: Extent of Exposure to Study Medication: Safety Population

	Ciprofloxacin (N=319)	PHB (N=[illegible])
Duration of treatment (days)		
Number of patients	304	302
Mean	7.3	7.6
Median	7	8
Number of days	Number (%) of patients taking study medication for this number of days	
1	0	3 (1.0)
2	1 (0.3)	0
3	2 (0.7)	5 (1.7)
4	2 (0.7)	2 (0.7)
5	0	1 (0.3)
6	5 (1.6)	5 (1.7)
7	176 (57.9)	83 (27.5)
8	113 (37.2)	192 (63.6)
>8	5 (1.6)	11 (3.6)

In the table provided below, the most common treatment-emergent adverse reactions in Clinical Trial CIPROT III/ 03 IA 02 in ciprofloxacin treated subjects were fungal otitis externa (otomycosis) and headache, both at 3%. Other common adverse reactions seen in 2% of ciprofloxacin treated subjects were nasopharyngitis, ear pruritis, and ear pain.

Table 7: Common Treatment-Emergent Adverse Events: Safety Population Events Occurring in at Least 2% of Patients in Either Treatment Group, by Systems and Preferred Term

	Number (%) of Patients Experiencing Event	
	Ciprofloxacin (N=319)	PHB (N=[illegible])
Any adverse event	98 (30.8)	96 (31.1)
Infections and Infestations	52 (16.3)	30 (9.7)
Otitis externa	18 (5.6)	9 (2.9)
Nasopharyngitis	7 (2.2)	5 (1.6)
Otitis externa fungal	8 (2.5)	1 (0.3)
Ear and Labyrinth Disorders	17 (5.3)	29 (9.4)
Ear pruritus	7 (2.2)	11 (3.6)
Ear pain	5 (1.6)	10 (3.3)
Nervous System Disorders	14 (4.4)	12 (3.9)
Headache	10 (3.1)	6 (1.9)
Dizziness	1 (0.3)	7 (2.3)
General Disorders and Administration Site Conditions	8 (2.5)	11 (3.6)
Pyrexia	3 (0.9)	7 (2.3)
Musculoskeletal and Connective Tissue Disorders*	7 (2.2)	9 (2.9)
Gastrointestinal Disorders*	3 (0.9)	11 (3.6)
Respiratory, Thoracic and Mediastinal Disorders*	3 (0.9)	9 (2.9)

In the table provided below, treatment-emergent adverse reactions leading to premature discontinuation occurred in 5 (1.6%) patients in the ciprofloxacin group and 4 (1.3%) patients in the PNH group in Clinical Trial CIPROT III/ 03 IA 02. Most of the treatment-emergent adverse reactions leading to discontinuation in the ciprofloxacin group were adverse reactions involving the ear.

Table 8: Summary of Treatment-Emergent AEs Leading to Premature Discontinuation of Study Treatment: Safety Population

	Number (%) of Patients Experiencing Event	
	Ciprofloxacin (N=319)	PNH (N=309)
Any TEAE leading to discontinuation	5 (1.6)	4 (1.3)
Infections and Infestations	3 (0.9)	3 (1.0)
Otitis externa	1 (0.3)	1 (0.3)
Otitis media	1 (0.3)	1 (0.3)
Carbuncle	1 (0.3)	0
External ear cellulitis	0	1 (0.3)
Ear and Labyrinth Disorders	0	2 (0.6)
Ear pain	0	1 (0.3)
Tympanic membrane perforation	0	1 (0.3)
Injury, Poisoning, and Procedural Complications	1 (0.3)	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.3)	0
Tracheal edema	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders	0	1 (0.3)
Erythema	0	1 (0.3)

The adverse reactions identified in Clinical Trial CIPROT III/ 03 IA 02 and found in the product labeling are taken from this review, Table 7: Common Treatment-Emergent Adverse Events: Safety Population Events Occurring in at Least 2% of Patients in Either Treatment Group, by Systems and Preferred Term.

9. Advisory Committee Meeting

No Advisory Committee was convened for Cetraxal (ciprofloxacin otic solution) 0.2%.

10. Pediatrics

The safety and effectiveness of Cetraxal in infants below one year of age have not been established. The efficacy of Cetraxal in treating otitis externa in pediatric patients one year or older has been demonstrated in a controlled clinical trial.

There is no evidence that the otic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested.

Per the DSI review dated February 1, 2006:

The Review Division requested a routine data audit inspection of two study sites that conducted study Protocol #CIPROT III IA 02 and from which data was submitted in support of NDA#21-918.

Name	City, State	Country	Protocol	Insp. Date	Classification
Gary Goldstein	Palm Harbor, FL	USA	CIPROT III	12/5 to 8/2005	NAI
John Champlin	Carmichael, CA	USA	CIPROT III	11/15 to 18/2005	VAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

Based on the results of the inspections it appears that the data submitted in support of this application from Dr. Goldstein's study site is acceptable.

Regarding the data from Dr. Champlin's study site, the following unreported protocol deviations and adverse events were noted:

a. Protocol deviations that were not reported by the clinical investigator to the sponsor:
   i. Subject #001 was enrolled on 6/21/04 but took Advil on 6/20-22/04.
   ii. Subject #005 missed 3 consecutive doses (afternoon and evening of July 1, 2004 and morning of July 2). The clinical research coordinator (CRC) instructed the subject to make up 3 doses on day 8, July 6, 2004.

iii. Subject #022 swam between Visit 3 and Visit 4.
iv. Subject #024 had a discharge from the ear at Visit 3 ( ) but the CRC forgot to collect lab sample. b(6)
v. Subject #026 was taking Sudafed 3x/day for ear ache and pressure up to time of study entry on 9/10/04.

b. Three (3) adverse events (AEs) were not reported:
   i Subject #022, experienced worsening of OE and reported to sub-investigator (sub-I) by phone on or about 8/22/04. Sub-I examined and treated the subject at Visit 3 on 8/23/04 and started subject on Keflex 250mg PO TID.
   ii. Subject #024, experienced increased pain and discharge in the affected right ear on 9/1/04 (between Visit 1 & Visit 2). Worsening of symptoms was not reported as an AE.
   iii. Subject #030 reported experiences of increased pain and discharge in the affected ear at Visit 4 (10/11/04).

The observations noted above for the data from Dr. Champlin's study site are based on the Form FDA 483, and communications from field investigator. Per DSI, the data from Dr. Champlin's study site may be deemed acceptable if the review division medical officer determines that the above mentioned issues are not significant enough to adversely impact the overall study data; in this medical officer's opinion, the unreported protocol deviations and adverse events are not significant enough to adversely impact the overall study data.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. None of the listed investigators had financial information to disclose.

There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA/DDMAC

The proposed name, Cetraxal was previously reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in 2005 and re-reviewed this cycle in order to rule out any objections to the proposed proprietary name since the signature date of the previous DMEPA review. The Proprietary Name Risk Assessment findings indicate that the proposed name, Cetraxal, is not vulnerable to name confusion that could lead to medication errors. Thus, DMEPA) has no objection to the proprietary name, Cetraxal, for this product at this time. Additionally, DDMAC does not object to the proposed name, Cetraxal, from a promotional perspective.

Per the DMEPA review dated March 31, 2009: