6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION: ACUTE OTITIS EXTERNA

Efficacy and safety data were obtained from a randomized, evaluator-blinded comparison of Ciprofloxacin Otic Solution 0.2% to the otic solution containing Neomycin Sulfate and Polymyxin B Sulfate and Hydrocortisone in the treatment of acute diffuse otitis externa in children, adolescents, and adults.

6.1.1 Methods

The primary objective of this single trial was to determine whether the proportion of patients with clinical cure after 7 days of twice-daily treatment with ciprofloxacin otic solution 0.2% was non-inferior to the proportion with clinical cure after 7 days of three-times-daily treatment with neomycin sulfate and polymyxin B sulfate and hydrocortisone (PNH) otic solution in children, adolescents, and adults with acute diffuse otitis externa.
The secondary objectives were to determine whether the proportion of patients achieving each of the following endpoints after 7 days of twice-daily treatment with ciprofloxacin otic solution 0.2% was non-inferior to the proportion after 7 days of three-times-daily treatment with PNH otic solution:

- Clinical Cure at Visit 3 (EOT);
- Clinical Improvement at Visit 3 and at Visit 4 (Follow-up Visit);
- Resolution of otalgia at Visit 3 and at Visit 4;
- Improvement in otalgia at Visit 3 and at Visit 4;
- Clinical + Microbiological Cure at Visit 3 and at Visit 4; and
- Clinical + Microbiological Improvement at Visit 3 and at Visit 4;

and to assess safety, patient/caregiver and physician satisfaction, and patient compliance with ciprofloxacin and PNH otic therapy.

The diagnosis and criteria for inclusion: Male and female patients aged at least 2 years who had acute diffuse otitis externa (OE) of less than 3 weeks' duration. Consent for participation in the study was obtained from the patient or the caregiver for minors. Patients were excluded if they used prohibited concomitant medications (including other investigational treatments, other treatments for OE, or other antibiotics), or if they had a history of adverse reaction to any component of either study medication; had complicating conditions (including otic dermatitis, eardrum perforation, tympanostomy tubes, otomycosis, mastoid disease, diabetes, or immunodeficiency); were pregnant or breastfeeding; or had any other condition that might interfere with participation in the study.

6.1.2 General Discussion of Endpoints

The protocol for this study was submitted to the IND and reviewed by Dr. Tom Smith. A detailed protocol can be found in section 10 of this review.

The primary efficacy endpoints were the proportions of Clinical Per-Protocol (CPP) and Clinical Intent-to-Treat (CITT) patients with Clinical Cure at Visit 4.
The secondary efficacy endpoints were the proportions of patients with:

- 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 + Microbiological Cure at Visit 3 and at Visit 4; and
- Clinical + Microbiological Improvement at Visit 3 and at Visit 4.

Safety was assessed by adverse events (AEs) and physical examination findings (including vital signs).

6.1.3 Study Design

This was a randomized, parallel-group, evaluator-blinded, active-controlled, and multicenter study comparing ciprofloxacin otic solution 0.2% with PNH otic solution in the treatment of acute diffuse OE in children, adolescents, and adults.
Planned enrollment was 630 patients. Patients were stratified at enrollment so that approximately equal numbers of patients 12 years old or younger (had not reached their thirteenth birthday) would be treated with test drug or comparator.
The safety population contained 628 patients, 319 who received ciprofloxacin and 309 who received PNH. Of these patients, 276 (44%) were 12 years old or younger and 352 (56%) were over 12 years old.

6.1.4 Efficacy Findings

Medical Officer's Comments:

The data analyses presented in this review were performed by the applicant. The Medical Officer concurs with the results that are presented in this section.

Title of Study: 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: CIPROT III/ 03 1A 02

Phase of Development: 3

Study Period:

Date of first enrollment: 01 Jun 2004
Date of last completed: 23 Nov 2004

Investigators: Forty-seven investigators in the United States (US) and Spain participated in this study.

Study Centers: Patients were randomized at 47 study centers, 42 in the US and 5 in Spain.

Study Objectives:

Primary Objective: To determine whether the proportion of patients with Clinical Cure at Visit 4 after 7 days of twice-daily treatment with ciprofloxacin otic solution 0.2% was non-inferior to the proportion with Clinical Cure after 7 days of three-times-daily treatment with neomycin and polymyxin B sulfates and hydrocortisone (PNH) otic solution in children, adolescents, and adults with acute diffuse otitis externa.

Secondary Objectives: To determine whether the proportion of patients achieving each of the following endpoints after 7 days of twice-daily treatment with ciprofloxacin otic solution 0.2% was non-inferior to the proportion after 7 days of three-times-daily treatment with PNH otic solution 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 + Microbiological Cure at Visit 3 and at Visit 4; and
Clinical + Microbiological Improvement at Visit 3 and at Visit 4;
and to assess safety, patient/caregiver and physician satisfaction, and patient compliance with ciprofloxacin and PNH otic therapy.

Disposition of Patients

Disposition of patients is summarized in Table 6. Six hundred sixty-six patients were screened, of whom 630 entered the study and were randomized. Of the patients who did not enter the study, most were excluded because their otitis did not meet the protocol requirements for acute diffuse otitis externa. Study medication was distributed to 54 study centers, 48 in the US and 6 in Spain. Patients were randomized at 47 study centers, 42 in the US and 5 in Spain.
The large majority of patients, 95% of patients in both treatment groups, completed the study. Of patients who withdrew before completing the study, the largest proportion were lost to follow-up. Three patients in each treatment group were withdrawn because of adverse events. Consent was withdrawn by 1 patient in the ciprofloxacin group and

5 patients in the PNH group. Three patients in the ciprofloxacin group and 1 in the PNH group were withdrawn because of treatment failure.

Table 3: Enrollment and Disposition of Patients

Category	Number (%) of Patients		
	Ciprofloxacin	PNH	Total
Patients randomized*	318 (100.0)	312 (100.0)	630 (100.0)
Patients who completed the study*	302 (95.0)	296 (94.9)	598 (94.9)
Patients who withdrew before completion*	16 (5.0)	16 (5.1)	32 (5.1)
Reasons for withdrawal:#			
Lost to follow-up	9 (56.3)	6 (37.5)	15 (46.9)
Adverse event	3 (18.8)	3 (18.8)	6 (18.8)
Withdrawal of consent	1 (6.3)	5 (31.3)	6 (18.8)
Treatment failure	3 (18.8)	1 (6.3)	4 (12.5)
Death	0	0	0
Risk to the patient	0	0	0
Swimming	0	1 (6.3)	1 (3.1)

* Percentages based on the numbers of patients randomized.
# Percentages based on the numbers of patients who withdrew.

Protocol Deviations

Approximately 22% of patients in each treatment group had protocol violations that caused them to be excluded from the CPP and MPP populations. More than 1 deviation could be reported for an individual patient. The types of violations observed were very similar between treatment groups. The most common violations were non-compliance with study medication, use of prohibited concomitant medications, and occurrence of Visit 3 and/or Visit 4 outside the allowed time windows.

Table 4: Summary of Protocol Deviations

	Number (%) of Patients		
Category	**Ciprofloxacin**	**PNH**	**Total**
Patients with protocol violations	71 (22.3)	69 (22.1)	140 (22.2)
Type of violation: Non-compliant with study medication	26 (8.2)	26 (8.3)	52 (8.3)
Used prohibited concomitant medication	29 (9.1)	21 (6.7)	50 (7.9)
Visit 3 and/or Visit 4 outside window*	17 (5.3)	20 (6.4)	37 (5.9)
Did not complete Visit 3 and Visit 4#	14 (4.4)	13 (4.2)	27 (4.3)
Violation of inclusion or exclusion criteria	5 (1.6)	5 (1.6)	10 (1.6)
Other	0	2 (0.6)	2 (0.3)

*Permitted windows were 7 to 11 days after start of treatment for Visit 3 and 14 to 21 days after start of treatment for Visit 4.
Unless clinical response was assessed as Clinical Failure before Visit 4.

Data Sets Analyzed

The sizes of specific analysis populations in this study are shown in Table 5. A total of 630 patients were randomized, 318 to the ciprofloxacin group and 312 to the PNH group. One patient randomized to the PNH group, Patient 105-020, did not sign a required document (the Health Insurance Portability and Accountability Act [HIPAA] form, required for patients in the US) and thus was included in the Safety population but not in any of the efficacy analysis populations. One patient, Patient 201-079, was randomized to the PNH group but instead received ciprofloxacin; thus, this patient is included in the ciprofloxacin group in the Safety population but in the PNH group in the ITT populations. In addition, 2 patients randomized to the PNH group did not receive any study medication. Thus, the Safety population included 319 patients in the ciprofloxacin group and 309 in the PNH group, while the CITT population included 318 patients in the ciprofloxacin group and 309 in the PNH group. Approximately 22% of patients in each treatment group were excluded from the CPP and MPP populations. Only patients for whom adequate microbiological data were available were included in the MITT and MPP populations.

Table 5: Summary of Analysis Populations: All Randomized Patients

Category	Number (%) of Patients		
	Ciprofloxacin (N=318)	PNH (N=312)	Total (N=630)
Safety population*	319 (100.3)	309 (99.0)	628 (99.7)
Clinical Intent-to-Treat population*	318 (100.0)	309 (99.0)	627 (99.5)
Clinical Per-Protocol population*	247 (77.7)	243 (77.9)	490 (77.8)
Microbiological Intent-to-Treat population#	232 (73.0)	217 (69.6)	449(71.3)
Microbiological Per-Protocol populations§	174 (54.7)	174 (55.8)	348 (55.2)

* Randomized patients who received at least 1 dose of study medication. Note: One patient randomized to receive PNH actually received ciprofloxacin otic suspension. This is the reason that the number of patients in the safety population for ciprofloxacin is one higher than the number of patients randomized to receive ciprofloxacin.
* Randomized patients who received 80%-120% of the doses of study medication and completed Visit 3 and Visit 4 (unless the patient's outcome was Clinical Failure at an earlier visit than Visit 4), excluding those patients who had any protocol deviations.
# CITT patients whose Visit 1 microbiological culture yielded 1 or more pathogens.
§ CPP patients who's Visit 1 microbiological culture yielded 1 or more pathogens and who had microbiological results from Visit 3 and for Visit 4.

Analysis of Efficacy

Primary Efficacy Endpoint: Clinical Cure at Visit 4

Results for the primary efficacy endpoint are shown in Table 6 for the CPP population and in Table 7 for the CITT population. In the CPP population, 214 (86.6%) patients in the ciprofloxacin group and 197 (81.1%) in the PNH group had Clinical Cure at Visit 4. The difference between treatment groups in proportion of patients with Clinical Cure (i.e., the proportion for PNH minus the proportion for ciprofloxacin) was -5.6% (95% CI -12.1%, 0.9%). The upper limit of the 95% CI, 0.9%, was smaller than the predefined limit of 10%; thus, ciprofloxacin was non-inferior to PNH in the CPP population. Compared with the PNH group, the proportion of patients in the ciprofloxacin group with Sustained Clinical Cure was greater (69% vs. 58%), and the proportion with Subsequent Clinical Cure was smaller (18% vs. 24%). The proportion of patients with Clinical Failure was smaller in the ciprofloxacin group (13%) than in the PNH group (19%). In the CITT population, proportions of patients with Clinical Cure were smaller than in the CPP population, but differences between treatment groups showed the same trends. Two hundred fifty-nine (81.4%) patients in the ciprofloxacin group and 237 (76.7%) in the PNH group had Clinical Cure at Visit 4. The difference between treatment groups in proportion of patients with Clinical Cure was 4.7 % (95% CI -11.1%, 1.6%). The upper limit of the 95% CI, 1.6%, was smaller than the predefined limit of 10%; thus, ciprofloxacin was non-inferior to PNH in the CITT population. Compared with the PNH group, the proportion of patients in the ciprofloxacin group with Sustained Clinical Cure was greater (65% vs. 55%), and the proportion with Subsequent Clinical Cure was smaller (16% vs. 21 %). The proportion of patients with Clinical Failure was smaller in

the ciprofloxacin group (19%) than in the PNH group (23%).

Table 6: Clinical Cure at Visit 4: CPP Population

	Number (%) of Patients		Treatment difference
	Ciprofloxacin (N=247)	PNH (N=243)	(PNH-ciprofloxacin) with 95% CI
Number of patients	247	243	
Clinical Cure	214 (86.6)	197 (81.1)	-5.6 (-12.1,0.9)*
Sustained Clinical Cure	170 (68.8)	140 (57.6)	
Subsequent Clinical Cure	44 (17.8)	57 (23.5)	
Clinical Failure	33 (13.4)	46 (18.9)	

*Meets the protocol criteria for non-inferiority.

Table 7: Clinical Cure at Visit 4: 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	259 (81.4)	237 (76.7)	-4.7 (-11.1, 1.6)*
Sustained Clinical Cure	208 (65.4)	171 (55.3)	
Subsequent Clinical Cure	51 (16.0)	66 (21.4)	
Clinical Failure	59 (18.6)	72 (23.3)	
Indeterminate	14 (4.4)	11 (3.6)	

* Meets the protocol criteria for non-inferiority.

Results showed similar trends as in the CPP and CITT populations.

Clinical Cure at Visit 3

Results for the secondary endpoint of Clinical Cure at Visit 3 are summarized in Table 8 for the CPP population and in Table 9 for the CITT population. As expected, fewer patients had Clinical Cure at Visit 3 than at Visit 4, the Test-of-Cure visit. There was a substantial difference between treatment groups in proportions of patients with Clinical Cure at Visit 3. In the CPP population, the proportions were 70% for the ciprofloxacin group and 61% for the PNH group; in the CITT population, the proportions were 67% and 59%. The proportions of patients with Clinical Failure were greater in the PNH group

than in the ciprofloxacin group. In this analysis, patients with Clinical Improvement were included in the group with Clinical Failure, and most of the outcomes classified as Clinical Failure were Clinical Improvements. In the CITT population, approximately 3% to 4% of patients had results assessed as Indeterminate

Table 8: Clinical Cure at Visit 3: CPP Population

	Number (%) of Patients		Treatment difference (%)
	Ciprofloxacin (N=247)	PNH (N=243)	(PNH-ciprofloxacin) with 95% CI
Number of patients	247	243	
Clinical Cure	173 (70.0)	147 (60.5)	-9.5 (-17.9, -1.2)
Clinical Failure	74 (30.0)	96 (39.5)	
Clinical Improvement	56 (22.7)	68 (28.0)	

Table 9: 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)	

Clinical Improvement at Visit 3 and Visit 4

Results for the secondary endpoints of Clinical Improvement at Visit 3 and Clinical Improvement at Visit 4 are summarized in Table 10 for the CPP population and in Table 11 for the CITT population. In both populations, the large majority of patients assessed at both visits had Clinical Improvement (in this analysis, patients with Clinical Cure were included in the group with Clinical Improvement). The proportions of patients with Clinical Improvement in the ciprofloxacin group were greater than in the PNH group by approximately 4 percentage points at Visit 3 and 6 percentage points at Visit 4.

Table 10: Clinical Improvement at Visit 3 and at Visit 4: CPP Population

	Number (%) of Patients		Treatment difference
	Ciprofloxacin (N=247)	PNH (N=243)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Number of patients	247	243	
Clinical Improvement	229 (92.7)	215 (88.5)	-4.2 (-9.4,0.9)
Clinical Failure	18 (7.3)	28 (11.5)	
Visit 4			
Number of patients	247	243	
Clinical Improvement	221 (89.5)	202 (83.1)	-6.3 (-12.4, -0.3)
Clinical Failure	26 (10.5)	41 (16.9)	

Table 11: Clinical Improvement at Visit 3 and at Visit 4: CITT Population

	Number (%) of Patients		Treatment difference
	Ciprofloxacin (N=318)	PNH (N=309)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Number of patients	318	309	
Clinical Improvement	283 (89.0)	264 (85.4)	-3.6 (-8.8, 1.7)
Clinical Failure	35 (11.0)	45 (14.6)	
Indeterminate	13 (4.1)	9 (2.9)	
Visit 4			
Number of patients	318	309	
Clinical Improvement	269 (84.6)	244 (79.0)	-5.6 (-11.7, 0.4)
Clinical Failure	49 (15.4)	65 (21.0)	
Indeterminate	14 (4.4)	11 (3.6)	

Resolution and Improvement in Otalgia at Visit 3 and Visit 4

Resolution of otalgia and improvement in otalgia at Visit 3 and at Visit 4 were secondary endpoints in this study. Clinical outcome for otalgia at Visit 3 and at Visit 4 is summarized in Table 12 for the CPP population and in Table 13 for the CITT population. In the CPP population, 87% of patients in the ciprofloxacin group and 88% in the PNH group reported resolution of otalgia at Visit 3, and 96% in the ciprofloxacin group and

97% in the PNH group reported resolution or improvement. Differences between the treatment groups were very small (less than 1 percentage point). At Visit 4, 96% of patients in the ciprofloxacin group and 97% in the PNH group reported resolution of otalgia, and almost all (98% in the ciprofloxacin group and 99% in the PNH group) reported resolution or improvement. Differences between treatment groups continued to be very small and in favor of PNH. Results in the CITT population were similar to those in the CPP population.

Table 12: Clinical Outcome of Otalgia at Visit 3 and at Visit 4: CPP Population

	Number (%) of Patients		Treatment difference (PNH-ciprofloxacin) with 95% CI
	Ciprofloxacin (N=247)	PNH (N=243)	
Visit 3			
Number of patients	247	243	
Resolved	216 (87.4)	214 (88.1)	0.6 (-5.2, 6.4)
Improved	22 (8.9)	22 (9.1)	
Resolved or improved	238 (96.4)	236 (97.1)	0.8 (-2.4,3.9)
Not resolved or improved	9 (3.6)	7 (2.9)	
Visit 4			
Number of patients	247	242	
Resolved	237 (96.0)	235 (97.1)	1.2 (-2.1,4.4)
Improved	5 (2.0)	4 (1.7)	
Resolved or improved	242 (98.0)	239 (98.8)	0.8 (-1.5,3.0)
Not resolved or improved	5 (2.0)	3 (1.2)	

Table 13: Clinical Outcome of Otalgia at Visit 3 and at Visit 4: CITT Population

	Number (%) of Patients		Treatment difference
	Ciprofloxacin (N=318)	PNH (N=309)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Number of patients	306	301	
Resolved	271 (88.6)	260 (86.4)	-2.2 (-7.4, 3.1)
Improved	24 (7.8)	27 (9.0)	
Resolved or improved	295 (96.4)	287 (95.3)	-1.1 (-4.2, 2.1)
Not resolved or improved	11 (3.6)	14 (4.7)	
Visit 4			
Number of patients	305	300	
Resolved	294 (96.4)	289 (96.3)	-0.1 (-3.0, 2.9)
Improved	6 (2.0)	6 (2.0)	
Resolved or improved	300 (98.4)	295 (98.3)	0.0 (-2.1, 2.0)
Not resolved or improved	5 (1.6)	5 (1.7)	

Microbiological Results

The most common pathogens identified in this study are shown in Table 14 for the MPP population and in Table 15 for the MITT population. In the MPP population, 174 patients in each treatment group had at least 1 pathogen at Visit 1. *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. In the MITT population, the percentages of patients infected with *P. aeruginosa* and *S. aureus* were similar to those in the MPP population.