Table 14: Common Pathogenic Organisms Isolated from Cultures at Baseline: MPP Population

	Number (%) of Patients with Pathogen	
	Ciprofloxacin (N=174)	PNH (N=174)
Number of patients with any pathogen*	174	174
Pseudomonas aeruginosa	152 (87.4)	154 (88.5)
Staphylococcus aureus	22 (12.6)	29 (16.7)
Enterobacter cloacae	10 (5.7)	3 (1.7)
Klebsiella pneumoniae	8 (4.6)	6 (3.4)
Escherichia coli	6 (3.4)	6 (3.4)
Klebsiella oxytoca	5 (2.9)	3 (1.7)

* There could be more than 1 pathogen from a single patient.

Table 15: Common Pathogenic Organisms Isolated from Cultures at Baseline: MITT Population

	Number (%) of Patients with Pathogen	
	Ciprofloxacin (N=232)	PNH (N=217)
Number of patients with any pathogen*	232	217
Pseudomonas aeruginosa	197 (84.9)	193 (88.9)
Staphylococcus aureus	33 (14.2)	35 (16.1)
Klebsiella pneumoniae	12 (5.2)	6 (2.8)
Enterobacter cloacae	12 (5.2)	5 (2.3)
Klebsiella oxytoca	8 (3.4)	5 (2.3)
Escherichia coli	7 (3.0)	6 (2.8)
Enterobacter aerogenes	5 (2.2)	3 (1.4)

* There could be more than 1 pathogen from a single patient.

Minimum Inhibitory Concentrations of Ciprofloxacin

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 1.00 µg/mL. The MIC_{50} and MIC_{90} values of ciprofloxacin for *P. aeruginosa* and *S. aureus* observed in this study were similar to those previously reported in published studies involving pseudomonal and staphylococcal isolates taken from a variety of other

body sites.

The distribution of MICs of ciprofloxacin is shown by treatment group in Figure 1 for isolates of *P. aeruginosa* and in Figure 2 for isolates of *S. aureus*. There were no substantial differences in susceptibility between isolates from patients in the different treatment groups. The MICs of ciprofloxacin for most isolates of *P. aeruginosa* were between 0.06 and 0.25 µg/mL, while MICs for most isolates of S. *aureus* were between 0.12 and 1.0 µg/mL.

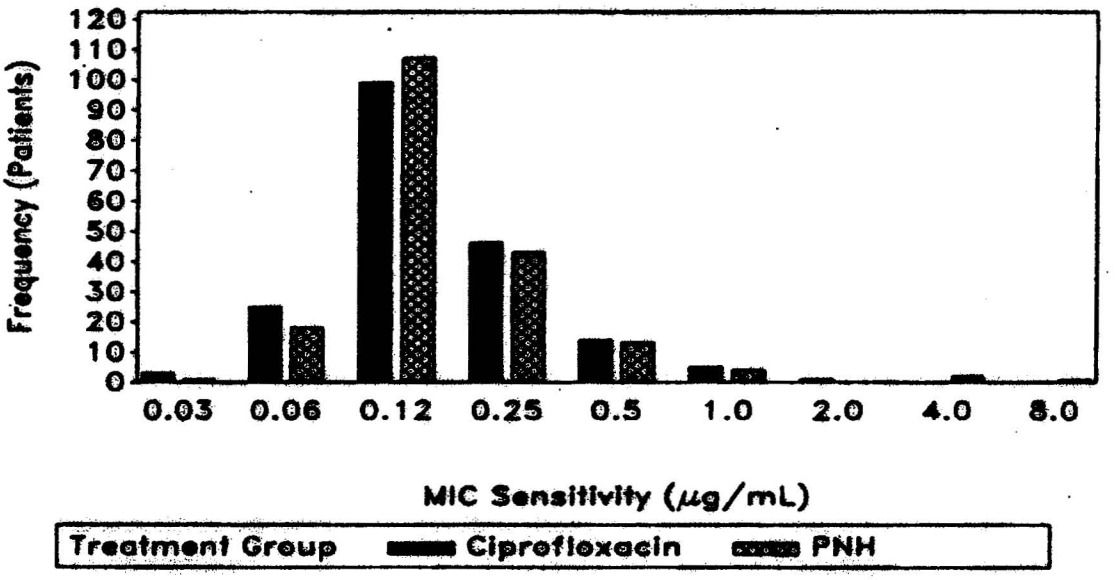

Figure 1: MICs of Ciprofloxacin for Isolates of *Pseudomonas aeruginosa*

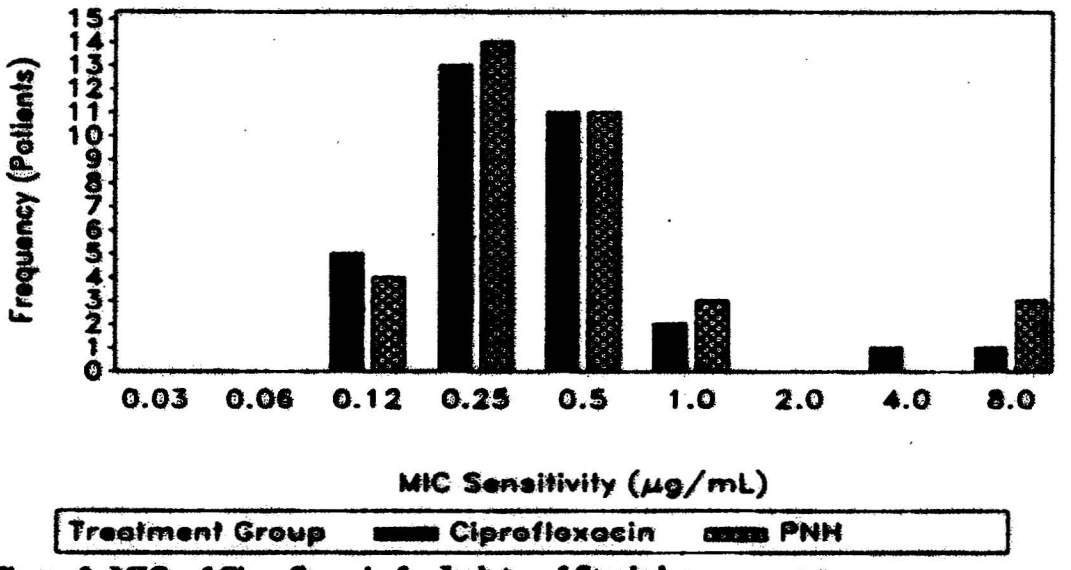

Figure 2: MICs of Ciprofloxacin for Isolates of *Staphylococcus aureus*

Bacteriologic Response

Bacteriologic response is summarized in Table 16 for the MPP population and in Table 17 for the MITT population. In the MPP population, at both Visit 3 and Visit 4, the bacteriologic response was Eradication or Presumed Eradication for the great majority of patients in both treatment groups. At Visit 3, 96% of patients in the ciprofloxacin group and 93% in the PNH group had Eradication or Presumed Eradication. At Visit 4, Eradication or Presumed Eradication was reported for 90% of patients in the ciprofloxacin group and 87% in the PNH group. In the MITT population, trends were generally similar to those in the MPP population, and several patients (4% in the ciprofloxacin group and 2% in the PNH group) had responses assessed as Indeterminate.

Table 16: Bacteriologic Response: MPP Population

		Number (%) of Patients	
		Ciprofloxacin (N=174)	PNH (N=174)
Visit 3	Number of patients	174	174
	Eradication	39 (22.4)	46 (26.4)
	Presumed Eradication	128 (73.6)	1 15 (66.1)
	Eradication or Presumed Eradication	167 (96.0)	161 (92.5)
	Persistence	1 (0.6)	5 (2.9)
	Presumed Persistence	5 (2.9)	8 (4.6)
	Superinfection	1 (0.6)	0
Visit 4	Number of patients	174	174
	Eradication	16 (9.2)	22 (12.6)
	Presumed Eradication	141 (81.0)	130 (74.7)
	Eradication or Presumed Eradication	157 (90.2)	152 (87.4)
	Persistence	1 (0.6)	1 (0.6)
	Presumed Persistence	16 (9.2)	21 (12.1)
	Superinfection	0	0

Table 17: Bacteriologic Response: MITT Population

		Number (%) of Patients	
		Ciprofloxacin (N=232)	PNH (N=217)
Visit 3	Number of patients	232	217
	Eradication	53 (22.8)	56 (25.8)
	Presumed Eradication	157 (67.7)	139 (64.1)
	Eradication or Presumed Eradication	2 10 (90.5)	195 (89.9)
	Persistence	3 (1.3)	7 (3.2)
	Presumed Persistence	8 (3.4)	11 (5.1)
	Superinfection	1 (0.4)	0
	Indeterminate	10 (4.3)	4 (1.8)
Visit 4	Number of patients	232	217
	Eradication	2 1 (9.1)	27 (12.4)
	Presumed Eradication	176 (75.9)	155 (71.4)
	Eradication or Presumed Eradication	197 (84.9)	182 (83.9)
	Persistence	1 (0.4)	2 (0.9)
	Presumed Persistence	24 (10.3)	29 (13.4)
	Superinfection	0	0
	Indeterminate	10 (4.3)	4 (1.8)

Efficacy Results by Pathogen

The numbers of patients infected with pathogens other than *P. aeruginosa* and *S. aureus* were too small to allow trends to be observed. Therefore, the discussions below are limited to *P. aeruginosa* and *S. aureus*.

Clinical Cure at Visit 4 by Pathogen

Incidence of Clinical Cure at Visit 4 by pathogen is summarized for the MPP population in Table 18 and for the MITT population in Table 19.

In both treatment groups, incidence of Clinical Cure was higher in patients infected with *P. aeruginosa* than in patients infected with S. aureus. In patients infected with *P. aeruginosa*, incidence of Clinical Cure was higher in the ciprofloxacin group than in the PNH group. In patients infected with *S. aureus*, incidence of Sustained Clinical Cure was higher in the PNH group, while incidence of Subsequent Clinical Cure was higher in the ciprofloxacin group.

Table 18: Clinical Cure at Visit 4 by Pathogen: MPP Population

	Number (%) of Patients	
Pathogen isolated at Visit 1	**Ciprofloxacin (N=174)**	**PNH (N=174)**
Pseudomonas aeruginosa		
Number of patients	152	154
Clinical Cure	133 (87.5)	121 (78.6)
Sustained Clinical Cure	104 (68.4)	85 (55.2)
Subsequent Clinical Cure	29 (19.1)	36 (23.4)
Clinical Failure	19 (12.5)	33 (21.4)
Staphylococcus aureus		
Number of patients	22	29
Clinical Cure	16 (72.7)	22 (75.9)
Sustained Clinical Cure	11 (50.0)	20 (69.0)
Subsequent Clinical Cure	5 (22.7)	2 (6.9)
Clinical Failure	6 (27.3)	7 (24.1)

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Table 19: Clinical Cure at Visit 4 by Pathogen: MITT Population

	Number (%) of Patients	
Pathogen isolated at Visit 1	Ciprofloxacin (N=232)	PNH (N=217)
Pseudomonas aeruginosa		
Number of patients	197	193
Clinical Cure	160 (81.2)	147 (76.2)
Sustained Clinical Cure	125 (63.5)	106 (54.9)
Subsequent Clinical Cure	35 (17.8)	41 (21.2)
Clinical Failure	37 (18.8)	46 (23.8)
Indeterminate	9 (4.6)	4 (2.1)
Staphylococcus aureus		
Number of patients	33	35
Clinical Cure	21 (63.6)	23 (65.7)
Sustained Clinical Cure	15 (45.5)	20 (57.1)
Subsequent Clinical Cure	6 (18.2)	3 (8.6)
Clinical Failure	12 (36.4)	12 (34.3)
Indeterminate	3 (9.1)	1 (2.9)

Clinical & Microbiological Results

Clinical & microbiological outcome is summarized in Table 20 for the MPP population and in Table 21 for the MITT population. Clinical & Microbiological Cure and Clinical & Microbiological Improvement at Visit 3 and at Visit 4 were secondary efficacy endpoints in this study.

In the MPP population, at Visit 3, 70% of patients in the ciprofloxacin group and 60% in the PNH group had Clinical & Microbiological Cure. Clinical & Microbiological Improvement was assessed in 21% of patients in the ciprofloxacin group and 26% in the PNH group. At Visit 4, the proportions of patients with Clinical & Microbiological Cure had increased to 85% in the ciprofloxacin group and 78% in the PNH group. The proportions of patients with Clinical & Microbiological Improvement had decreased to 3% in the ciprofloxacin group and 2% in the PNH group.

In the MITT population, results were generally similar to those in the MPP population, but differences between treatments were less pronounced. At Visit 3, 66% of patients in the ciprofloxacin group and 59% in the PNH group had Clinical & Microbiological Cure, and 21% and 24%, respectively, had Clinical & Microbiological Improvement. At Visit 4, the proportions of patients with Clinical & Microbiological Cure had increased to 79% in

the ciprofloxacin group and 75% in the PNH group, and the proportions with Clinical & Microbiological Improvement had decreased to 3% in the ciprofloxacin group and 2% in the PNH group.

Table 20: Overall Clinical & Microbiological Outcome at Visit 3 and at Visit 4: MPP Population

	Number (%) of Patients		Treatment difference
	Ciprofloxacin (N=174)	PNH (N=174)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Number of patients	174	174	
Cure	121 (69.5)	104 (59.8)	-9.8 (-19.8, 0.2)
Improvement	37 (21.3)	45 (25.9)	
Failure	16 (9.2)	25 (14.4)	
Visit 4			
Number of patients	174	174	
Cure	148 (85.1)	136 (78.2)	-6.9 (-15.0, 1.2)
Improvement	5 (2.9)	3 (1.7)	
Failure	21 (12.1)	35 (20.1)	

Table 21: Overall Clinical + Microbiological Outcome at Visit 3 and at Visit 4: MITT Population

	Number (%) of Patients		Treatment difference (%)
	Ciprofloxacin (N=232)	PNH (N=217)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Number of patients	232	217	
Cure	153 (65.9)	129 (59.4)	-6.5 (-15.4, 2.4)
Improvement	48 (20.7)	53 (24.4)	
Failure	31 (13.4)	35 (16.1)	
Visit 4			
Number of patients	232	217	
Cure	184 (79.3)	163 (75.1)	-4.2 (-12.0, 3.6)
Improvement	8 (3.4)	5 (2.3)	
Failure	40 (17.2)	49 (22.6)	

Efficacy Results by Age Group
Certain efficacy evaluations were performed by age group. Analyses were performed for patients 12 years old or younger (had not reached their thirteenth birthday) and patients over 12 years old (had reached their thirteenth birthday).
Additional analyses were performed using a different set of age categories. These analyses were performed for patients under 18 years old and patients 18 years old or older.

Clinical Cure at Visit 4 by Age Group

12 Years Old or Younger vs. Over 12 Years Old

Analysis of the primary efficacy endpoint by age group (12 years old or younger vs. over 12 years old) is shown in Table 22 for the CPP population and in Table 23 for the CITT population. Some differences between age groups were observed. In the CPP population, in the younger group, 94% of patients in the ciprofloxacin group and 78% in the PNH group had Clinical Cure at Visit 4. The proportion of patients achieving Subsequent Clinical Cure was similar between treatment groups, but the proportion achieving Sustained Clinical Cure was considerably greater in the ciprofloxacin group (71%) than in the PNH group (52%). The contrast between treatments was notably different in the older group, in which Clinical Cure was achieved by 79% of patients in the ciprofloxacin group and 84% in the PNH group. Sustained Clinical Cure was

achieved by more patients in the ciprofloxacin group (67%) than in the PNH group (61%), but Subsequent Clinical Cure was achieved by substantially more patients in the PNH group (22%) than in the ciprofloxacin group (12%). Trends were similar in the CITT population.

Table 22: Clinical Cure at Visit 4 by Age Group: CPP Population

	Number (%) of Patients		Treatment difference (%)
	Ciprofloxacin (N=247)	PNH (N=243)	(PNH-ciprofloxacin) with 95% CI
Age Group: ≤12 years			
Number of patients	122	103	
Clinical Cure	115 (94.3)	80 (77.7)	-16.6 (-25.6, -7.6)
Sustained Clinical Cure	86 (70.5)	54 (52.4)	
Subsequent Clinical Cure	29 (23.8)	26 (25.2)	
Clinical Failure	7 (5.7)	23 (22.3)	
Age Group: >12 years			
Number of patients	125	140	
Clinical Cure	99 (79.2)	117 (83.6)	4.4 (-5.0, 13.8)
Sustained Clinical Cure	84 (67.2)	86 (61.4)	
Subsequent Clinical Cure	15 (12.0)	31 (22.1)	
Clinical Failure	26 (20.8)	23 (16.4)	

Table 23: Clinical Cure at Visit 4 by Age Group: CITT Population

	Number (%) of Patients		Treatment difference (%)
	Ciprofloxacin (N=318)	PNH (N=309)	(PNH-ciprofloxacin) with 95% CI
Age Group: ≤12 years			
Number of patients	145	131	
Clinical Cure	131 (90.3)	99 (75.6)	-14.8 (-23.6, -6.0)
Sustained Clinical Cure	99 (68.3)	67 (51.1)	
Subsequent Clinical Cure	32 (22.1)	32 (24.4)	
Clinical Failure	14 (9.7)	32 (24.4)	
Indeterminate	3 (2.1)	2 (1.5)	
Age Group: >12 years			
Number of patients	173	178	
Clinical Cure	128 (74.0)	138 (77.5)	3.5 (-5.4, 12.5)
Sustained Clinical Cure	109 (63.0)	104 (58.4)	
Subsequent Clinical Cure	19 (11.0)	34 (19.1)	
Clinical Failure	45 (26.0)	40 (22.5)	
Indeterminate	11 (6.4)	9 (5.1)	

Medical Officer's Comments:

The applicant has a clinical study section in the proposed labeling for this NDA where only clinical outcome table for patients less than and equal to 12 years is proposed. The Medical Officer suggests that both tables for CPP population (≤ 12 yrs. and > 12yrs.) should be placed in the labeling. This will be addressed in the section 9.4.

Concomitant medications

The most frequently used concomitant medication was paracetamol (acetaminophen), the analgesic recommended in the protocol for treatment of otalgia, which was used by approximately 27.7% of patients in the ciprofloxacin group and 34% of patients in the PNH group. Analgesic medications containing codeine, which were permitted by the protocol for treatment of otalgia, were used by 4.3% of patients in the ciprofloxacin group and 2.4% in the PNH group. Ibuprofen was used by 11.3% of patients in the ciprofloxacin group and 9.7% in the PNH group. Other medications used were anthistamines (about 6%) in both groups. Antibacterials for systemic use were used by 4.4% of patients win the ciprofloxacin group and 5.2% in the PNH group.

6.1.5 Clinical Microbiology

Topical fluoroquinolone preparations are the preferred treatment for otitis externa because they are generally effective against both *P. aeruginosa* and *S. aureus*, the main pathogens of acute otitis externa, are rarely associated with contact hypersensitivity, and are unlikely to have ototoxic effects. In the clinical trial, the sponsor demonstrated similar outcomes between ciprofloxacin otic solution and PNH in patients with otitis externa and baseline cultures that grew these pathogens.
The bacteriologic results have been discussed as part of the efficacy review in section 6.1.4. For detailed microbiology review, please refer to Dr. Peter Coderre's review.

6.1.6 Efficacy Conclusions

In both the CPP population and the CITT population, the proportion of patients with Clinical Cure at Visit 4 was larger in the ciprofloxacin group than in the PNH group, and the predefined criteria for non-inferiority were met.

Results in the ciprofloxacin group were as good as or better than results in the PNH group for the following secondary efficacy criteria:

- 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.

Efficacy Results by Pathogen: Conclusions

Analyses by pathogen showed differences between patients infected with *P. aeruginosa* and patients infected with *S. aureus*. Patients infected with *P. aeruginosa* tended to have better outcomes than patients infected with *S. aureus*. Patients infected with *P. aeruginosa* had better clinical and bacteriological results with ciprofloxacin than with PNH, while in patients infected with *S. aureus*, outcomes tended to be similar between treatment groups or to be slightly better with PNH than with ciprofloxacin.