Other Efficacy Assessments:

- Otalgia in evaluable ear at Visits 1
- Edema in evaluable ear at Visits 1,3,4
- Otorrhea in evaluable ear at Visits 1,3,4
- Total Symptom score (otalgia score + edema score + otorrhea score) at Visits 1,3,4
- Clinical Cure of otalgia at Visit 3,4
- Improvement of otalgia at Visit 3,4
- Clinical Cure of edema at Visit 3,4
- Improvement of edema at Visit 3,4

3.1.4 Results and Conclusions

Efficacy Results

Table 5: Sponsor Assessment of Clinical Response at TOC, Number (%) of Subjects

	Ciprofloxacin	PNH	(Ciprofloxacin – PNH) with 95% CI
CPP Subjects at TOC	247	243	
Cure	214 (86.6)	197 (81.1)	5.6 (-0.9, 12.1)
Failure	33 (13.4)	46 (18.9)	
CITT Subjects at TOC	318	309	
Cure	259 (81.4)	237 (76.7)	4.7 (-1.6, 11.1)
Failure	59 (18.6)	72 (23.3)	

* Source: Sponsor Statistical Tables 7.1.1, 7.1.2

Statistical Reviewer Comments: *The non-inferiority of Ciprofloxacin therapy to PNH therapy is demonstrated since for both co-primary endpoints the lower limit of the 95% CI for the treatment difference is greater than -10%.*

Table 6: Sponsor Assessment of Microbiological Cure Rates at TOC, Number (%) in MPP and MITT Populations

	Ciprofloxacin	PNH	(Ciprofloxacin – PNH) with 95% CI
MPP Subjects at TOC	174	174	
Cure	157 (90.2)	152 (87.4)	2.9 (-3.9, 9.7)
Failure	17 (9.8)	22 (12.6)	
MITT Subjects at TOC	232	217	
Cure	197 (84.9)	182 (83.9)	1.0 (-5.7, 7.9)
Failure	35 (15.1)	35 (16.1)	

Cure= Eradication or Presumed Eradication, Failure= Persistence + Presumed Persistence + Indeterminate.
Source: Modified from Sponsor's Statistical Tables 21.1.1, 21.1.2

Statistical Reviewer Comments: *The microbiological cure rate at TOC in the Ciprofloxacin arm was non-inferior to the microbiological cure rate in PNH arm for both the MPP and MITT populations. Microbiological cure rates at TOC (Ciprofloxacin vs. PNH) were: 90.2% vs. 87.4%, a 2.9% (-3.9%, 9.7%) treatment difference (95% CI) in the MPP population and 84.9% vs. 83.9%, a 1.0% (-5.7%, 7.9%) treatment difference (95% CI) in the MITT population.*

Table 7: Sponsor Assessment of Clinical Cure at Visit 4 by Pathogen: Number (%) of Subjects in MPP and MITT Populations

	Number (%) of Subjects		
	Ciprofloxacin	PNH	(Ciprofloxacin – PNH) with 95% CI
MPP Population	**N=174**	**N=174**	
Pseudomonas aueruginosa			
Number of Subjects	152	154	
Clinical Cure	133 (87.5)	121 (78.6)	8.9 (0.5, 17.4)
Clinical Failure	19 (12.5)	33 (21.4)	
Staphylococcus aureas			
Number of Subjects	22	29	
Clinical Cure	16 (72.7)	22 (75.9)	-3.1 (-29.9, 22.5)*
Clinical Failure	6 (27.3)	7 (24.1)	
MITT Population	**N=232**	**N=227**	
Pseudomonas aueruginosa			
Number of Subjects	197	193	
Clinical Cure	160 (81.2)	147 (76.2)	5.1 (-3.1, 13.2)
Clinical Failure	37 (18.8)	46 (23.8)	
Staphylococcus aureas			
Number of Subjects	33	35	
Clinical Cure	21 (63.6)	23 (65.7)	-2.1 (-25.0, 21.1)*
Clinical Failure	12 (36.4)	12 (34.3)	

Source: Modified from Sponsor's Tables 8.1.1, 8.1.2 * Exact 95% CI computed, Pathogen isolated at Visit 1

Statistical Reviewer Comments: *Clinical cure rates at TOC for subjects with Pseudomonas aueruginosa isolated at visit 1 were higher in the Ciprofloxacin arm than in the PNH arm at 87.5% vs. 78.6%, an 8.9% (0.5%, 17.4%) treatment difference (95% CI) and 81.2% vs. 76.2%, a 5.1% (-3.1%, 13.2%) treatment difference (95% CI) in the MPP and MITT populations respectively. Clinical cure rates at TOC for subjects with Staphylococcus aureas isolated at visit 1 were lower in the Ciprofloxacin arm for both the MPP and MITT populations at 72.7% vs. 75.9% and 63.6% vs. 65.7% respectively. The estimates for Staphylococcus aureas were highly variable due to limited sample sizes.*

3.4 Evaluation of Safety

3.4.1 Evaluation of Safety

Table 8: Overview of Adverse Events: Safety Population

	Number (%) of Subjects Experiencing Event	
Category	Ciprofloxacin (N = 319)	PNH (N = 309)
Any treatment adverse event	92 (28.8)	96 (31.1)
Treatment-related adverse events	16 (5.0)	11 (3.6)
Severe adverse events	3 (0.9)	6 (1.9)
Serious adverse events	2 (0.6)	0
Deaths	0	0
Adverse events causing discontinuation	5 (1.6)	4 (1.3)

Source: Sponsor's Statistical Tables 28, 29, 30, 34, 35

Statistical Reviewer Comments: *Adverse events were similar between the Ciprofloxacin and PNH groups.*

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Table 9: Sponsor Assessment of Clinical Cure Rates at TOC by Gender, Age, Race in the CPP and CITT Populations

	Number Cured / Number of Subjects (%)		
	Ciprofloxacin N = 318	PNH N = 309	(Ciprofloxacin – PNH) with 95% CI
CPP Population			
Gender			
MALE	115/132 (87.1)	90/113 (79.6)	7.5% (-1.9%, 16.8%)
FEMALE	99/115 (86.1)	107/130 (82.3)	2.3% (-6.7%, 11.3%)
Age (years)			
≤ 12 YEARS	115/122 (94.3)	80/103 (77.7)	16.6% (7.6%, 25.6%)
> 12 YEARS	99/125 (79.2)	117/140 (83.6)	-4.4% (-13.8%, 5.0%)
< 18 YEARS	138/147 (93.9)	100/127 (78.7)	15.1% (7.0%, 23.2%)
≥ 18 YEARS	76 /100 (76.0)	97/116 (83.6)	-7.6% (-18.4%, 3.1%)
Race			
CAUCASIAN	185/213 (86.9)	174/212 (82.1)	4.8% (-2.1%, 11.7%)
NON-CAUCASIAN	29/34 (85.3)	23/31 (74.2)	11.1% (-8.4%, 30.6%)
CITT Population			
Gender			
MALE	144/175 (82.3)	105/140 (75.0)	7.3% (-1.8%, 16.4%)
FEMALE	115/143 (80.4)	132/169 (78.1)	2.3% (-6.7%, 11.3%)
Age (years)			
≤ 12 YEARS	131/145 (90.3)	99/131 (75.6)	14.8% (6.0%, 23.6%)
> 12 YEARS	128/173 (74.0)	138/178 (77.5)	-3.5% (-12.5%, 5.4%)
< 18 YEARS	157/175 (89.7)	121/161 (75.2)	14.6% (6.5%, 22.6%)
≥ 18 YEARS	102/143 (71.3)	116/148 (78.4)	-7.1%* (-17.0%, 2.9%)
Race			
CAUCASIAN	228/280 (81.4)	208/266 (78.2)	3.2% (-3.5%, 10.0%)
NON-CAUCASIAN	31/38 (81.6)	29/43 (67.4)	14.1% (-4.5%, 32.8%)

Source: Modified from Sponsor's Tables 7.2.1,7.2.2, 7.3.1, 7.3.2, 7.4.1,7.4.2, 7.5.1,7.5.2
* Rounded from -7.05 to -7.1. Differed from Sponsor's estimate of -7.0.

Statistical Reviewer Comments: *Overall, there were no remarkable differences in clinical cure rates by gender or race in the CPP or CITT populations. There were, however, differences in treatment by age category. In the ≤ 12 years and < 18 years categories, cure rates were higher in the Ciprofloxacin arm. Note that for subjects receiving PNH therapy, clinical cure rates were higher in adult subjects (≥ 18 years of age).*

It should be noted that clinical cure rates in adolescent patients (ages 12-17) were similar to rates in children under 12 years of age. However, cure rates were significantly lower in patients ≥ 18 vs. patients < 18 receiving Ciprofloxacin therapy. A *post-hoc* analysis was conducted by the Statistical Reviewer to compare Ciprofloxacin treatment efficacy between the < 18 years and ≥

18 year age groups in the CPP and CITT populations. Ciprofloxacin therapy was found to be significantly less effective for subjects ≥ 18 years of age (p-value < .0001) in both the CPP and CITT populations.

Table 10: Comparisons of Sponsor Assessed Clinical Cure Rates at TOC, Number (%) (Subjects < 18 years of age vs. Subjects ≥ 18 years of age)

	< 18 years	**≥ 18 years**	**' < 18 years' – ' ≥ 18 years') with 95% CI**
CPP Subjects	**(N=247)**	**(N=243)**	
Ciprofloxacin	147	100	
Cure	138 (93.9)	76 (76.0)	*17.9 (9.2, 27.7)
Failure	9 (6.1)	24 (24.0)	
PNH	127	116	
Cure	100 (78.7)	97 (83.6)	-4.9 (-14.7, 5.1)
Failure	27 (21.3)	19 (16.4)	
CITT Subjects	**(N=318)**	**(N=309)**	
Ciprofloxacin	175	143	
Cure	157 (89.7)	102 (71.3)	*18.4 (9.9, 27.2)
Failure	18 (10.3)	41 (28.7)	
PNH	161	148	
Cure	121 (75.2)	116 (78.4)	-3.7 (-13.1, 5.8)
Failure	41 (28.7)	32 (21.6)	

Source: FDA Table, * - Indicates significantly larger than 0 (p-value <.0001)

Statistical Reviewer Comments: *In the Ciprofloxacin arm clinical cure rates for subjects < 18 years of age vs. subjects ≥ 18 years of age were: 138/147 (93.9%) vs. 76/100 (76.0%), a 17.9% (9.2%, 27.7%) treatment difference (95% CI) in the CPP population and 157/175 (89.7%) vs. 102/143 (71.3%), an 18.4% (9.9%, 27.2%) treatment difference (95% CI) in the CITT population. These results indicate lower clinical cure rates in subjects ≥ 18 years of age compared with subjects < 18 years of age. Results were statistically significant (p-value < .0001).*

Statistical Reviewer Comments: *The above findings suggest that the outcome of Ciprofloxacin therapy is unlikely to follow a common distribution across age groups but rather separate distributions in adults and in non-adults. Therefore, results should be interpreted separately for subjects < 18 years of age and for subjects ≥ 18 years of age.*

Table 11: Sponsor Assessment of Clinical Cure Rates at TOC, Number (%) in CPP and CITT Populations by Age Group: (<18 years, ≥ 18 years)

	Ciprofloxacin	PNH	(Ciprofloxacin – PNH) with 95% CI
CPP Subjects	**(N=247)**	**(N=243)**	
< 18 years	147	127	
Cure	138 (93.9)	100 (78.7)	15.1 (7.0, 23.2)
Failure	9 (6.1)	27 (21.3)	
≥ 18 years	100	116	
Cure	76 (76.0)	97 (83.6)	-7.6 (-18.4, 3.1)
Failure	24 (24.0)	19 (16.4)	
CITT Subjects	**(N=318)**	**(N=309)**	
< 18 years	175	161	
Cure	157 (89.7)	121 (75.2)	14.6 (6.5, 22.6)
Failure	18 (10.3)	40 (24.8)	
≥ 18 years	143	148	
Cure	102 (71.3)	116 (78.4)	-7.1*(-17.0, 2.9)
Failure	41 (28.7)	32 (21.6)	

Source: Modified from Sponsor's Tables 7.5.1, 7.5.2
* Rounded from -7.05 to -7.1. Differed from Sponsor's estimate of -7.0.

Statistical Reviewer Comments: *In the <18 year age group, there is strong evidence regarding the efficacy of Ciprofloxacin versus PNH. In the ≥ 18 year age group, however, there is no statistical evidence to suggest that Ciprofloxacin would be effective therapy and/or non-inferior to PNH therapy. The lower limit of the 95% CI for the treatment difference is considerably below -10% in the CPP and CITT populations at -18.4% and -17.0% respectively.*

Statistical Reviewer Comments: *It is unlikely the lack of statistical evidence of non-inferiority (within a 10% non-inferiority margin) was due to the limited sample size of the adult subgroup given the magnitudes of the treatment differences (Ciprofloxacin – PNH) of -7.6% in the CPP population and -7.1% in the CITT population. Note that the smallest possible treatment difference (Ciprofloxacin – PNH) in demonstrating non-inferiority (within a 10% margin) in Study CIPROT III/03 IA with all subjects included would be approximately -3.5% in both the CPP and CITT populations.*

Table 12: Sponsor Assessment of Microbiological Cure Rates at TOC, Number (%) in MPP and MITT Populations by Age Group: (<18 years, ≥ 18 years)

	Ciprofloxacin	PNH	(Ciprofloxacin – PNH) with 95% CI
MPP Subjects	**(N=174)**	**(N=174)**	
< 18 years	103	93	
Cure	94 (91.3)	71 (76.3)	14.9 (4.7, 25.1)
Failure	9 (9.8)	22 (24.0)	
≥ 18 years	71	81	
Cure	54 (76.1)	65 (80.2)	-4.2 (-17.4, 9.0)
Failure	17 (23.9)	16 (19.8)	
MITT Subjects	**(N=232)**	**(N=217)**	
< 18 years	127	117	
Cure	109 (85.8)	87 (74.4)	11.5(-1.5, 21.4)
Failure	21 (14.2)	30 (25.6)	
≥ 18 years	105	100	
Cure	75 (71.4)	76 (76.0)	-4.6 (-16.6, 7.5)
Failure	30 (28.6)	24 (24.0)	

Cure= Eradication or Presumed Eradication, Failure= Persistence+ Presumed Persistence+Indeterminate.
Source: Modified from Sponsor's Statistical Tables 7.5.3, 7.5.4

Statistical Reviewer Comments: *Microbiological cure rates at Test of Cure (TOC) with Ciprofloxacin vs. PNH in subjects less than 18 years of age, were: 91.3% vs. 76.3%, a 14.9% (4.7%, 25.1%) treatment difference (95% CI) in the MPP population and 85.8% vs. 74.4%, a 11.5% (-1.5%, 21.4%) treatment difference (95% CI) in the MITT population. These results provide strong evidence of non-inferiority.*

Microbiological cure rates at Test of Cure (TOC) with Ciprofloxacin vs. PNH in subjects 18 years of age or greater were: 76.1% vs. 80.2%, a -4.2% (-17.4%, 9.0%) treatment difference (95% CI) in the MPP population and 71.4% vs. 76.0%, a -4.6% (-16.6%, 7.5%) treatment difference (95% CI) in the MITT population. These results do not provide evidence of non-inferiority.

Statistical Reviewer Comments: *Clinical cure rates and/or microbiological cure rates at TOC were significantly lower in subjects 18 years or older treated with Ciprofloxacin in the MPP and MITT analysis populations as well as the CPP and CITT analysis populations. Treatment differences (Ciprofloxacin – PNH) were less extreme in the MPP and MITT populations vs. the CPP and CITT populations at -4.2%, -4.6% vs. -7.1% , -7.6% respectively.*

5. SUMMARY AND CONCLUSIONS

This study demonstrated the non-inferiority (within a 10% margin) of Ciprofloxacin Otic Solution 0.2% therapy to comparator therapy (PNH) for the treatment of otitis externa (OE) in both the CITT and CPP populations. Comparisons of clinical cure rates at Test of Cure (TOC) with Ciprofloxacin vs. PNH were: 86.6% vs. 81.1%, a 5.6% (-0.9%, 12.1%) treatment difference (95% CI) in the CPP population and 81.4% vs. 76.7%, a 4.7% (-1.6%, 11.1%) treatment difference (95% CI) in the CITT population (Table 5).

Secondary analyses in the overall population were generally consistent with the primary analysis and show Ciprofloxacin Otic Solution 0.2% therapy as non-inferior (within a 10% margin) to PNH therapy for endpoints which include: proportions of subjects with Clinical Cure at Visit 3, Clinical Improvement at Visit 4, Clinical + Microbiological Cure at Visit 3 and at Visit 4. Proportions of subjects with resolution of otalgia and improvement in otalgia at Visit 3 and at Visit 4 were generally similar between Ciprofloxacin and PNH.

This study failed to provide substantial evidence that Ciprofloxacin is non-inferior (within a 10% margin) to PNH in an adult population (18 years or older). Firstly, statistical inferences from the primary analysis across all patient age groups could not be made since patient outcomes did not follow a common independent approximately normal distribution as assumed in the statistical methodology. Patient outcomes instead followed separate distributions for the adult and non-adult patient subgroups. Evidence of separate distributions for adults and non-adults is also supported by several studies included in the Sponsor's submission. A 'Core Study' by Pistorius et al. 1999[1] suggested lower efficacy rates for adult subjects in both the Ciprofloxacin and PNH treatment arms. A 'Published Study' by Jones et al. 1997[2] suggested lower efficacy rates for adult patients in the ofloxacin (a drug in the same class as Ciprofloxacin) and PNH arms. The FDA's previous findings of effectiveness for Cipro HC otic, the RLD, also showed lower efficacy rates in adult patients for both the Cipro HC and PNH.

Due to these inconsistencies an FDA *post-hoc* analysis was conducted to compare efficacy rates between adults and non-adults for each of the Ciprofloxacin and PNH treatment arms. Results in the Ciprofloxacin arm were highly significant in both the CPP and CITT populations (two-sided p-value $< .0001$). Clinical cure rates (< 18 years of age vs. ≥ 18 years of age) were 138/147 (93.9%) vs. 76/100 (76.0%), a 17.9% (9.2%, 27.7%) treatment difference (95% CI) in the CPP population and 157/175 (89.7%) vs. 102/143 (71.3%), an 18.4% (9.9%, 27.2%) treatment difference (95% CI) in the CITT population (Table 10).

Another *post-hoc* analysis compared efficacy rates between Ciprofloxacin and PNH for a given age group. Clinical cure rates (Ciprofloxacin vs. PNH) in adults were 76/100 (76.0%) vs. 97/116 (83.6%), a -7.6% (-18.4%, 3.1%) treatment difference (95% CI) in the CPP population and 102/143 (71.3%) vs. 116/148 (78.4%), a -7.1% (-17.0%, -2.9%) treatment difference (95% CI) in the CITT population (Table 11).

The later FDA *post-hoc* analysis failed to provide statistical evidence that Ciprofloxacin would be effective and non-inferior (within a 10% margin) to PNH therapy in an adult population.

Given the magnitude of the treatment difference (Ciprofloxacin – PNH), it is also unlikely this lack of statistical evidence of non-inferiority was due to the limited sample size of the adult subgroup. Treatment differences observed in the *post-hoc* analysis of adult subjects were -7.1% and -7.6% in the CPP and CITT populations. Note that the smallest possible treatment difference (Ciprofloxacin – PNH) in demonstrating non-inferiority (within a 10% margin) in Study CIPROT III/03 IA with all subjects included would be approximately -3.5% in both the CPP and CITT populations.

It is important to note that *post-hoc* analyses may have limitations especially if used inappropriately. As previously noted, these *post-hoc* analyses were based on findings from several studies which showed separate distributions of clinical cures for adult and non-adult patients. These *post-hoc* analyses were also conducted as part of subgroup analyses of gender, age, and racial subgroups required under NDA regulation 21 CFR 314.50(d)(5)(v).

In conclusion, Pivotal Study CIPROT III/03 IA 02 provides substantial evidence that Ciprofloxacin Otic Solution 0.2% administered twice daily (bid) for 7 days is non-inferior (within a 10% margin) to PNH administered 3 times daily (tid) for the treatment of OE in children and adolescents. However, this study raises doubts about the efficacy of Ciprofloxacin otic in the treatment of adults for OE. As required by 21 CFR 314.50(d)(5)(v), *post-hoc* analyses were conducted by gender, age, and racial subgroups. For non-adults, the comparison of clinical cure rates at TOC with Ciprofloxacin vs. PNH were: 93.9% vs. 78.7%, a treatment difference (95% CI) of 15.1% (7.0, 23.2) in the CPP population. This contrasts with results for adults with 76.0% vs. 83.6%, a -7.6% (-18.4%, 3.1%) treatment difference (95% CI). See Table 9 which shows consistent results in the CITT population. Additional sensitivity analyses are included in Section 4. Separate comparisons for adults and non-adults are highly relevant due to results from two previous studies included in the Sponsor's submission which suggested lower efficacy rates in adults treated with PNH, Ciprofloxacin, Cipro HC or ofloxacin. The FDA's previous findings of effectiveness for Cipro HC otic, the RLD, also showed lower efficacy rates in adult patients for both the Cipro HC and PNH treatment arms. Based on the clear differences in adult and non-adult populations and the magnitude of treatment differences found in favor of PNH therapy, both inferential evidence and direct evidence of non-inferiority of Ciprofloxacin therapy in an adult population were not considered to be substantial. The Statistical Reviewer feels that the difference in results for non-adults and adults warrant mention in the label even though the clinical relevance is unclear.

References

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2. Jones RN, Milazzo J, Seindlin M. Ofloxacin otic solution for treatment of oisis externa in children and adults. *Arch Otolaryngol Head Neck Surg*1997;123:1193-1200

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