

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-799

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEC 8 1997

NDA: 20-799 FLOXIN® Otic (Ofloxacin Otic Solution) 0.3%
Generic Drug Name: Ofloxacin
Drug Trade Name: FLOXIN® Otic
Formulation: Otic solution
Drug Class: 1-S
Applicant: Daiichi Pharmaceutical Corporation.

Indications:

1. Otitis externa in adults and children
2. Chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane
3. Acute otitis media in children with tympanostomy tubes

Documents Reviewed: NDA volumes 1.1, 1.113 - 1.192 dated December 18, 1996
Type of Review: Clinical

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Review's Note: Reviewer's comments are given in italics throughout the review.

I. OTITIS EXTERNA IN ADULTS AND CHILDREN

I.A. INTRODUCTION

The Applicant submitted two controlled studies, PRT-002 and PRT-003, as evidence to support oral ofloxacin regarding this indication for adults and pediatric subjects, respectively. The general designs of the studies are as follows:

Study PRT-002 was a multicenter, randomized, parallel group, evaluator-blind, comparative trial which compared the safety and efficacy of ofloxacin otic solution (0.5 ml b.i.d.) versus cortisporin otic solution (0.2 ml q.i.d.), administered orally for 10 days for the treatment of subjects 12 years of age and older with acute otitis externa. It was initiated on July 19, 1994 and completed on November 11, 1994.

Study PRT-003 was a multicenter, randomized, parallel group, evaluator-blind, comparative trial which compared the safety and efficacy of ofloxacin otic solution (0.25 ml b.i.d.) versus cortisporin otic solution (0.15 ml q.i.d.), administered orally for 10 days for the treatment of subjects under 12 years of age (1 through 11) with acute otitis externa. It was initiated on July 16, 1994 and completed on June 9, 1995.

I.B. STUDY PRT-002

I.B.1. METHODS

Approximately 270 subjects 12 years of age and older were collectively enrolled to ensure clinically evaluable data from a minimum of 224 subjects (112 subjects per treatment group). Subjects with a clinical diagnosis of acute otitis externa (current episode < 2 weeks) of presumed bacterial origin were eligible for enrollment, and were randomized to one of the two treatment groups in a 1:1 ratio to either ofloxacin otic solution 0.5 ml twice daily or cortisporin otic solution 0.2 ml four times daily for 10 days. Eligible study population consisted of males and non-pregnant, non-lactating females, who met all inclusion/exclusion criteria.

Study visits were scheduled for Visit 1 (Pre-Therapy Visit), Visit 2 (During Therapy Visit), Visit 3 (Post Therapy Visit), and Visit 4 (Test of Cure Visit). Table 2.1 demonstrates study visit schedules which were specified by the protocol. Safety and efficacy evaluations were performed according to this schedule. Additionally, the investigator provided a final evaluation of clinical response. All compliance information reported was recorded on the CRF by the unblinded study nurse/coordinator. All concomitant medications were recorded on the appropriate CRF.

Subjects in the ofloxacin group were instructed to instill 0.5 ml (10 drops) into the affected ears(s) twice daily approximately 12 hours apart. Subjects in the cortisporin group were instructed to instill 0.2 ml (4 drops) into the affected ear(s) 4 times daily approximately 6 hours apart. No adjustments in dose were permitted. The unblinded study nurse/coordinator recorded all study drugs received, dispensed, and returned by subjects.

TABLE 2.1: STUDY PRT-002: VISIT TIMING AND PROCEDURES

Visit Number	Visit 1 Pre-Therapy	Visit 2 During Therapy	Visit 3 Post Therapy	Visit 4 Test of Cure
Allowable Study Window	Day 1	Day 3-5	Day 11-13	Day 17-20
Medical History	X			
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
External Canal Measurement	X	X	X	X
Signs, Symptoms, Severity	X	X	X	X
Culture	X	X	X	X
Urine β -hCG Pregnancy Test	X		X	
Dispense Medication	X	X		
Collect Medication		X	X	
Medication Application	X			
Adverse Event Assessment	X	X	X	X
Subject Diary	X			
Subject Satisfaction		X	X	

EFFICACY EVALUATION

Efficacy evaluations included evaluation of clinical signs and symptoms, clinical response rates, and microbiological efficacy rates. Efficacy analyses were performed on clinically evaluable and microbiologically evaluable subjects. The primary efficacy parameter was the overall clinical response for the clinical evaluable population. All other efficacy measures were considered secondary.

At each visit, clinical signs and symptoms of acute otitis externa were assessed. The clinical responses were evaluated at Visits 2, 3, and 4 based on the subject's clinical signs and symptoms scores. An overall clinical assessment was made by the Applicant based on the clinical responses at Visit 4. A microbiological response was assigned to each pathogen isolated at admission and to each subject at the Visits 3 and 4, respectively. At the Visit 4, an overall response was assigned, by subject and by pathogen(s), taking into consideration those individual microbiological responses assigned at Visit 3 and Visit 4.

Clinical response was classified as cure, improvement, failure, or indeterminate; subject and pathogen microbiological response was classified as documented eradication, presumed eradication, persistence, recurrence, or reinfection.

Reviewer's Note: *The Medical Officer also defined her clinically evaluable subjects, and assessed clinical and efficacy outcomes according to her clinical criteria. The Medical Officer consented with the Applicant's definition of microbiological evaluable criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. Safety evaluations included the incidence of adverse events, changes from baseline in physical examinations, including vital signs, and changes from baseline in bone and air conduction thresholds in subjects who participated in the audiometry arm.

At each visit after initiation of therapy, subjects were observed for adverse events. All adverse events, whether or not they were considered drug related, were recorded on the CRF along with the date of onset, date of resolution, duration, intermittency, and severity. The investigator's determination of relationship of each adverse event to the study drug administration, and the outcome for each event were also recorded. If serious adverse events were observed, the monitor and the Applicant were immediately notified. Complete physical examinations were performed at the Pre-Therapy and Post Therapy Visits. Focused physical examinations were performed at the During Therapy and Test of Cure Visits. Any abnormalities or changes from baseline were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between ofloxacin and cortisporin.

Efficacy analyses were based on the clinical and microbiological responses at Visits 2, 3, and 4. The treatment groups were compared with respect to the clinical cure rate, the subject microbiological eradication rate, and the pathogen microbiological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the overall clinical cure rate in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: All efficacy analyses were conducted for the Medical Officer clinically evaluable subjects, and the Applicant clinically and microbiologically evaluable subjects. All of the subjects in these three groups were assessed for their clinical or microbiological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. Confidence interval based on Cochran's method, after adjusting for center, was also used to assess the differences in the proportion of interest. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals. Homogeneity of treatment effect across centers was evaluated by Breslow-Day's test.

Subset analyses by gender, age, and race were performed for the Medical Officer's primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of severe adverse events, the rate of serious adverse events, and the rate of discontinuation due to adverse events. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the test of homogeneity.

I.B.2. RESULTS

Reviewer's Note: In the following analysis, both the Applicant's population and the Medical Officer's population excluded subjects in the centers of investigators A and B. Please find more details in Section V. (Appendix).

An actual total of 256 subjects were enrolled at 21 centers in the USA between July 19, 1994 and November 11, 1994. Of these enrolled subjects, 129 ofloxacin treated subjects and 127 cortisporin treated subjects were included in the intent-to-treat analyses. The Applicant clinically evaluable group comprised 100 ofloxacin subjects and 98 cortisporin subjects. There were 99 ofloxacin subjects and 98 cortisporin subjects in the Medical Officer clinically evaluable group.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 2.2. There were no notable treatment differences with respect to the percentage of subjects included in each analysis group. Demographic data are described for the Medical Officer clinically evaluable subjects in Table 2.3, and no statistically significant differences were detected in these pretreatment characteristics of the two treatment groups.

TABLE 2.2: STUDY PRT-002: SUBJECTS POPULATIONS		
Treatment Group for Clinical Response	Subjects Included	
	Ofloxacin (N=129)	Cortisporin (N=127)
Intent-to-Treat	129 (100%)	127 (100%)
Applicant Clinically Evaluable	100 (77.5%)	98 (77.2%)
MO Clinically Evaluable	99 (76.7%)	98 (77.2%)
Applicant Microbiologically Evaluable	45 (34.9%)	47 (37.0%)

**APPEARS THIS WAY
ON ORIGINAL**

Number of Subjects	Ofloxacin (N=99)	Cortisporin (N=98)	P-value
Age (yrs.)	37.5 ± 17.1	37.4 ± 18.1	*0.950
< 65 yrs.	91 (91.9%)	88 (89.8%)	0.630
≥ 65 yrs.	8 (8.1%)	10 (10.2%)	
Gender			
Male	57 (57.6%)	46 (46.9%)	0.155
Female	42 (42.4%)	52 (53.1%)	
Race			
White	87 (87.9%)	89 (90.8%)	0.841
Black	5 (5.1%)	5 (5.1%)	
Hispanic	4 (4.0%)	3 (3.1%)	
Other	3 (3.0%)	1 (1.0%)	
Infection			
Unilateral	83 (83.8%)	74 (75.5%)	0.160
Bilateral	16 (16.2%)	24 (24.5%)	
Reference Ear Status			
Exacerbating	90 (90.9%)	91 (92.9%)	0.795
Stable	9 (9.1%)	7 (7.1%)	
Duration of Episode	5.8 ± 5.0	5.4 ± 5.6	*0.560
Total Sign/Symptoms Score	8.0 ± 1.3	8.0 ± 1.3	*0.706
Number of Organism/Subject			
Polymicrobial	35 (35.4%)	39 (39.8%)	0.777
Monomicrobial	35 (35.4%)	34 (34.7%)	
None	29 (29.3%)	25 (25.5%)	

* P-value is obtained by t-test, otherwise, by Fisher's exact test

Reviewer's Note: The overall clinical responses as per the Applicant and the Medical Officer clinical evaluable populations are presented in Tables 2.4 and 2.5, respectively. Comparisons (95% confidence intervals) of the difference between the two treatment groups do not show that ofloxacin was therapeutically equivalent to cortisporin with respect to overall clinical outcomes.

Table 2.6 presents the evaluation of overall clinical responses, stratified by center, for the Medical Officer clinically evaluable subjects. Confidence interval results by center adjusted Cochran's method show that ofloxacin was therapeutically equivalent in efficacy to cortisporin with respect to the cure rates. Breslow-Day's test demonstrates that treatment effects were homogeneous (p -value=0.657) across the centers.

Subset analyses by gender, age, and race for the overall clinical cure rates in the Medical Officer clinically evaluable subjects are shown in Table 2.7. Results are consistent across all three demographic aspects.

Clinical Response	Ofloxacin (N=100)	Cortisporin (N=98)
Cure	77 (77.0%)	79 (80.2%)
Failure	23 (23.0%)	19 (19.4%)
Ofloxacin vs Cortisporin by Cure	-3.6%, 95% C.I.: -16.0%, 8.8%	

TABLE 2.5: STUDY PRT-002: OVERALL CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS		
Clinical Response	Ofloxacin (N=99)	Cortisporin (N=98)
Cure	76 (76.8%)	79 (80.6%)
Failure	23 (23.2%)	19 (19.4%)
Ofloxacin vs Cortisporin by Cure	-3.8%, 95% C.I.: -16.3%, 8.6%	

TABLE 2.6: STUDY PRT-002: EVALUATION OF OVERALL CLINICAL RESPONSE, STRATIFIED BY CENTER, FOR THE MO CLINICALLY EVALUABLE SUBJECTS		
Center	Ofloxacin (N=99)	Cortisporin (N=98)
03	12/16 (75.0%)	12/13 (92.3%)
04	7/15 (46.7%)	8/13 (61.5%)
06	10/11 (90.9%)	9/9 (100%)
08	9/10 (90.0%)	9/9 (100%)
19	5/5 (100%)	5/5 (100%)
20	6/9 (66.7%)	5/9 (55.6%)
21	6/8 (75.0%)	7/9 (77.8%)
*000	21/25 (84.0%)	24/31 (77.4%)
Total	76/99 (76.8%)	79/98 (80.6%)
95% C.I. by Center Adjusted Cochran's Method: -14.4%, 6.6%		
Breslow-Day's P-value: 0.657		
* Includes all those centers which had less than five subjects in at least one arm		

TABLE 2.7: STUDY PRT-002: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL CLINICAL CURE RATES OF THE MO CLINICALLY EVALUABLE SUBJECTS				
Subset	Ofloxacin (N=99)	Cortisporin (N=98)	95% C.I.	P-value Breslow-Day's
Male	39/57 (68.4%)	34/46 (73.9%)	(-25.0%, 14.0%)	0.593
Female	37/42 (88.1%)	45/52 (86.5%)	(-14.1%, 17.2%)	
< 65 yrs.	72/91 (79.1%)	72/88 (81.8%)	(-15.4%, 10.0%)	0.522
≥ 65 yrs.	4/8 (50.0%)	7/10 (70.0%)	NA	
White	65/87 (74.7%)	71/89 (79.8%)	(-18.6%, 8.4%)	0.416
Black	5/5 (100%)	4/5 (80.0%)	NA	
Hispanic	4/4 (100%)	3/3 (100%)	NA	
Other	2/3 (66.7%)	1/1 (100%)	NA	

The 95% confidence interval for the difference in cure rates of intent-to-treat population between ofloxacin and cortisporin groups indicates the therapeutic equivalence of the two treatment groups, which is presented in Table 2.8.

Tables 2.9 and 2.10 show clinical responses of the Applicant and the Medical Officer clinically evaluable subjects at Visit 4, respectively. Confidence interval results from both evaluable populations show that the

two treatment groups were therapeutically equivalent with respect to the cure rates at this time point.

The subject overall microbiological responses are shown for the Applicant microbiologically evaluable subjects in Table 2.11. Comparisons (95% confidence intervals) of the difference between the two treatment groups illustrate the equivalence of ofloxacin to cortisporin.

The subject eradication rates of the Applicant microbiologically evaluable subjects at Visits 3 and 4 are presented in Tables 2.12 and 2.13, respectively. Both confidence interval results show that ofloxacin was therapeutically equivalent to cortisporin with respect to the eradication rates.

The pathogen eradication rates for the most common isolated baseline pathogens are summarized for the Applicant microbiologically evaluable subjects in Table 2.14.

TABLE 2.8: STUDY PRT-002: OVERALL CLINICAL RESPONSE OF THE INTENT-TO-TREAT SUBJECTS		
Clinical Response	Ofloxacin (N=129)	Cortisporin (N=127)
Cure	81 (62.8%)	89 (70.1%)
Failure	48 (37.2%)	38 (29.9%)
Ofloxacin vs Cortisporin by Cure	-7.3%, 95% C.I.: -19.6%, 5.0%	

TABLE 2.9: STUDY PRT-002: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT VISIT 4		
Clinical Response	Ofloxacin (N=89)	Cortisporin (N=91)
Cure	77 (86.5%)	79 (86.8%)
Failure	12 (13.5%)	12 (13.2%)
Ofloxacin vs Cortisporin by Cure	-0.3%, 95% C.I.: -11.3%, 10.7%	

TABLE 2.10: STUDY PRT-002: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT VISIT 4		
Clinical Response	Ofloxacin (N=89)	Cortisporin (N=91)
Cure	77 (86.5%)	78 (85.7%)
Failure	12 (13.5%)	13 (14.3%)
Ofloxacin vs Cortisporin by Cure	0.8%, 95% C.I.: -10.4%, 12.0%	

TABLE 2.11: STUDY PRT-002: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS		
Subject Bacteriological Response	Ofloxacin (N=45)	Cortisporin (N=47)
Eradication	44 (97.8%)	46 (97.9%)
Persistent+Recurrence	1 (2.2%)	1 (2.1%)
Oflox vs Corti by Eradication	-0.1%, 95% C.I.: -8.2%, 8.0%	

TABLE 2.12: STUDY PRT-002: SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS AT VISIT 3		
Subject Bacteriological Response	Ofloxacin (N=45)	Cortisporin (N=47)
Eradication	45 (100%)	46 (97.9%)
Persistent	0 (0%)	1 (2.1%)
Oflox vs Corti by Eradication	2.1%, 95% C.I.: -4.2%, 8.4%	

TABLE 2.13: STUDY PRT-002: SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS AT VISIT 4		
Subject Bacteriological Response	Ofloxacin (N=41)	Cortisporin (N=42)
Eradication	40 (97.6%)	42 (100%)
Persistent	1 (2.4%)	0 (0%)
Oflox vs Corti by Eradication	-2.4%, 95% C.I.: -9.6%, 4.7%	

TABLE 2.14: STUDY PRT-002: OVERALL PATHOGEN ERADICATION RATE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)		
Pathogen	Ofloxacin	Cortisporin
<i>P. aeruginosa</i>	32/32 (100%)	38/39 (97.4%)
<i>S. aureus</i>	6/6 (100%)	6/6 (100%)
<i>E. faecalis</i>	5/5 (100%)	5/5 (100%)
<i>K. pneumoniae</i>	5/5 (100%)	1/1 (100%)
<i>P. mirabilis</i>	2/2 (100%)	6/6 (100%)
Oflox vs Corti for <i>P.aeruginosa</i>	2.6%, 95% C.I.: -5.2%, 10.4%	

Reviewer's Note: For all treated subjects, the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rate of discontinuations due to adverse events, the rates of severe adverse events, and the rates of serious adverse events, are presented in Table 2.15. No significant differences were detected regarding these safety parameters between the two treatment groups.

TABLE 2.15: STUDY PRT-002: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Ofloxacin (N=129)	Cortisporin (N=127)	Fisher's P-value
Subject with any AE	57 (44.2%)	47 (37.0%)	0.255
Subject with Treatment Related AEs	24 (18.6%)	17 (13.4%)	0.307
Subject with Severe or Life Threatening AEs	6 (4.7%)	3 (2.4%)	0.500
Subject with Serious AEs	3 (2.3%)	2 (1.6%)	1.000
Subject Discontinued due to AEs	4 (3.1%)	2 (1.6%)	0.684

No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication. Six ofloxacin treated subjects and 3 cortisporin

treated subjects were reported as having severe adverse events. Three ofloxacin treated subjects and 2 cortisporin treated subject experienced adverse events that were considered to be serious.

Reviewer's Summary and Conclusions: See Section IV.

I.C. STUDY PRT-003

I.C.1. METHODS

Approximately 300 subjects under 12 years of age (1 through 11) were collectively enrolled to ensure clinically evaluable data from a minimum of 224 subjects (112 subjects per treatment group). Subjects with a clinical diagnosis of acute otitis externa (current episode < 2 weeks) of presumed bacterial origin were eligible for enrollment, and were randomized to one of the two treatment groups in a 1:1 ratio to either ofloxacin otic solution 0.25 ml twice daily or cortisporin otic solution 0.15 ml four times daily for 10 days. Eligible study population consisted of females who had not reached menarche and males, who met all inclusion/exclusion criteria.

Study visits were scheduled for Visit 1 (Pre-Therapy Visit), Visit 2 (During Therapy Visit), Visit 3 (Post Therapy Visit), and Visit 4 (Test of Cure Visit). Table 3.1 demonstrates study visit schedules which were specified by the protocol. Safety and efficacy evaluations were performed according to this schedule. Additionally, the investigator provided a final evaluation of clinical response. All compliance information reported was recorded on the CRF by the unblinded study nurse/coordinator. All concomitant medications were recorded on the appropriate CRF.

Parents and guardian of subjects in the ofloxacin group were instructed to instill 0.25 ml (5 drops) into the affected ears(s) twice daily approximately 12 hours apart. Parents and guardian of subjects in the Cortisporin group were instructed to instill 0.15 ml (3 drops) into the affected ear(s) 4 times daily approximately 6 hours apart. No adjustments in dose were permitted. The unblinded study nurse/coordinator recorded all study drugs received, dispensed, and returned by subjects.

TABLE 3.1: STUDY PRT-003: VISIT TIMING AND PROCEDURES

Visit Number	Visit 1 Pre-Therapy	Visit 2 During-Therapy	Visit 3 Post-Therapy	Visit 4 Test of Cure
Allowable Study Window	Day 1	Day 3-5	Day 11-13	Day 17-20
Medical History	X			
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Externa Canal Measurement	X	X	X	X
Signs, Symptoms, Severity	X	X	X	X
Culture	X	X	X	X
Dispense Medication	X	X		
Collect Medication		X	X	
Medication Application	X		X	
Adverse Event Assessment	X	X	X	X
Subject Diary	X		X	
Subject/Guardian Satisfaction		X	X	

Efficacy evaluation, safety evaluation, and statistical method were similar to those described for Study PRT-002 in Section I.B.1.

I.C.2. RESULTS

Reviewer's Note: *In the following analysis, both the Applicant's population and the Medical Officer's population excluded subjects in the centers of investigators A, B, and C. Please find more details in Section V. (Appendix).*

An actual total of 202 subjects were enrolled at 20 centers in the USA between July 16, 1994 and June 9, 1995. Of these enrolled subjects, 100 ofloxacin treated subjects and 102 cortisporin treated subjects were included in the intent-to-treat analyses. The Applicant clinically evaluable group comprised 80 ofloxacin subjects and 78 cortisporin subjects. There were 81 ofloxacin subjects and 78 cortisporin subjects in the Medical Officer clinically evaluable group.

Reviewer's Note: *The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 3.2. There were no notable treatment differences with respect to the percentage of subjects included in each analysis group. Demographic data are described for the Medical Officer clinically evaluable subjects in Table 3.3. There appears to be a statistical imbalance in the age composition of the treatment population and more subjects in the cortisporin group were between the ages of 7 years and less than 12 years.*

Treatment Group for Clinical Response	Subjects Included	
	Ofloxacin (N=100)	Cortisporin (N=102)
Intent-to-Treat	100 (100%)	102 (100%)
Applicant Clinically Evaluable	80 (80.0%)	78 (76.5%)
MO Clinically Evaluable	81 (81.0%)	78 (76.5%)
Microbiologically Evaluable	33 (33.0%)	44 (43.1%)

TABLE 3.3: STUDY PRT-003: SUMMARY OF DEMOGRAPHIC DATA FOR THE MO CLINICALLY EVALUABLE SUBJECTS			
Number of Subjects	Ofloxacin (N=81)	Cortisporin (N=78)	P-value
Age (yrs.)	7.3 ± 2.5	8.5 ± 2.2	*0.003
2 yrs. ~ 7 yrs.	30 (37.0%)	14 (18.0%)	0.008
7 yrs. ~ 12 yrs.	51 (63.0%)	64 (82.0%)	
Gender			
Male	35 (43.2%)	30 (38.5%)	0.629
Female	46 (56.8%)	48 (61.5%)	
Race			
White	75 (92.6%)	73 (93.6%)	0.945
Black	3 (3.7%)	4 (5.1%)	
Hispanic	2 (2.5%)	1 (1.3%)	
Other	1 (1.2%)	0 (0%)	
Infection			
Unilateral	68 (84.0%)	72 (92.3%)	0.142
Bilateral	13 (16.0%)	6 (7.7%)	
Reference Ear Status			
Exacerbating	74 (91.4%)	68 (87.2%)	0.795
Stable	7 (8.6%)	10 (12.8%)	
Duration of Episode	2.7 ± 3.6	3.0 ± 2.2	*0.580
Total Sign/Symptoms Score	7.9 ± 1.3	7.8 ± 1.3	*0.597
Number of Organism/Subject			
Polymicrobial	13 (16.1%)	19 (24.4%)	0.287
Monomicrobial	35 (43.2%)	35 (44.9%)	
None	33 (40.7%)	24 (30.8%)	

* P-value is obtained by t-test, otherwise, by Fisher's exact test

Reviewer's Note: The overall clinical responses as per the Applicant and the Medical Officer clinical evaluable populations are presented in Tables 3.4 and 3.5, respectively. Comparisons (95% confidence intervals) of the difference between the two treatment groups show that ofloxacin and cortisporin were therapeutically equivalent with respect to overall clinical outcomes.

Table 3.6 presents the evaluation of overall clinical responses, stratified by center, for the Medical Officer clinically evaluable subjects. Confidence interval results by center adjusted Cochran's method show that ofloxacin was therapeutically equivalent in efficacy to cortisporin with respect to the cure rates. Breslow-Day's test demonstrated that treatment effects were homogeneous (p -value=0.274) across the centers.

Subset analyses by gender, age, and race for the overall clinical cure rates in the Medical Officer clinically evaluable subjects are shown in Table 3.7. Results were consistent across all three demographic aspects.

TABLE 3.4: STUDY PRT-003: OVERALL CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS		
Clinical Response	Ofloxacin (N=80)	Cortisporin (N=78)
Cure	78 (97.5%)	73 (93.6%)
Failure	2 (2.5%)	5 (6.4%)
Ofloxacin vs Cortisporin by Cure	3.9%, 95% C.I.: -3.8%, 11.6%	

TABLE 3.5: STUDY PRT-003: OVERALL CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS		
Clinical Response	Ofloxacin (N=81)	Cortisporin (N=78)
Cure	78 (96.3%)	72 (92.3%)
Failure	3 (3.7%)	6 (7.7%)
Ofloxacin vs Cortisporin by Cure	4.0%, 95% C.I.: -4.5%, 12.4%	

TABLE 3.6: STUDY PRT-003: EVALUATION OF OVERALL CLINICAL RESPONSE, STRATIFIED BY CENTER, FOR THE MO CLINICALLY EVALUABLE SUBJECTS		
Center	Ofloxacin (N=81)	Cortisporin (N=78)
53	7/8 (87.5%)	5/6 (83.3%)
54	6/7 (85.7%)	5/7 (71.4%)
57	5/5 (100%)	6/6 (100%)
58	25/26 (96.2%)	26/26 (100%)
61	10/10 (100%)	8/8 (100%)
*000	25/25 (100%)	22/25 (88.0%)
Total	78/81 (96.3%)	72/78 (92.3%)
95% C.I. Center Adjusted Cochran's Method: -2.4%, 9.3%		
Breslow-Day's P-value: 0.274		
* Includes all those centers which had less than five subjects in at least one arm		

TABLE 3.7: STUDY PRT-003: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL CLINICAL CURE RATES OF THE MO CLINICALLY EVALUABLE SUBJECTS				
Subset	Ofloxacin (N=81)	Cortisporin (N=78)	95% C.I.	P-value Breslow-Day's
Male	45/46 (97.8%)	45/48 (93.8%)	(-6.1%, 14.2%)	0.743
Female	33/35 (94.3%)	27/30 (90.0%)	(-12.0%, 20.6%)	
2 yrs. ~ 7 yrs.	28/30 (93.3%)	13/14 (92.9%)	(-20.9%, 21.9%)	0.404
7 yrs ~ 12 yrs.	50/51 (98.0%)	59/64 (92.2%)	(-3.5%, 15.2%)	
White	72/75 (96.0%)	68/73 (93.2%)	(-5.8%, 11.5%)	0.480
Black	3/3 (100%)	3/4 (75.0%)	NA	
Hispanic	2/2 (100%)	1/1 (100%)	NA	
Other	1/1 (100%)	0/0	NA	

The 95% confidence interval for the difference in overall cure rates of intent-to-treat population between ofloxacin and cortisporin groups indicates the therapeutic equivalence of the two treatment groups, which is presented in Table 3.8.

Table 3.9 show clinical responses of the Applicant and the Medical Officer clinically evaluable subjects at Visit 4. Confidence interval results show that the two treatment groups were therapeutically equivalent with respect to the cure rates at this time points.

The subject overall microbiological responses are shown for the Applicant microbiologically evaluable subjects in Table 3.10. Comparisons (95% confidence intervals) of the difference between the two treatment groups illustrate the equivalence of ofloxacin to cortisporin with respect to the eradication rates.

The subject eradication rates of the Applicant microbiologically evaluable subjects at Visits 3 and 4 are presented in Tables 3.11 and 3.12, respectively. Both confidence interval results show that ofloxacin was therapeutically equivalent to cortisporin.

The pathogen eradication rates for the most common isolated baseline pathogens are summarized for the Applicant microbiologically evaluable subjects in Table 3.13.

TABLE 3.8: STUDY PRT-003: OVERALL CLINICAL RESPONSE OF THE INTENT-TO-TREAT SUBJECTS		
Clinical Response	Ofloxacin (N=100)	Cortisporin (N=102)
Cure	80 (80.0%)	80 (78.4%)
Failure	20 (20.0%)	22 (21.6%)
Ofloxacin vs Cortisporin by Cure	1.6%, 95% C.I.: -10.6%, 13.7%	

TABLE 3.9: STUDY PRT-003: CLINICAL RESPONSE OF THE APPLICANT AND MO CLINICALLY EVALUABLE SUBJECTS AT VISIT 4		
Clinical Response	Ofloxacin (N=80)	Cortisporin (N=76)
Cure	78 (97.5%)	73 (96.1%)
Failure	2 (2.5%)	3 (4.0%)
Ofloxacin vs Cortisporin by Cure	1.4%, 95% C.I.: -5.4%, 8.3%	

TABLE 3.10: STUDY PRT-003: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS		
Subject Bacteriological Response	Ofloxacin (N=33)	Cortisporin (N=44)
Eradication	33 (100%)	44 (100%)
Persistent+Recurrence	0 (0%)	0 (0%)
Oflox vs Corti by Eradication	0%, 95% C.I.: -2.7%, 2.7%	

TABLE 3.11: STUDY PRT-003: SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS AT VISIT 3		
Subject Bacteriological Response	Ofloxacin (N=33)	Cortisporin (N=44)
Eradication	33 (100%)	44 (100%)
Persistent	0 (0%)	0 (0%)
Oflox vs Corti by Eradication	-0%, 95% C.I.: -2.7%, 2.7%	

TABLE 3.12: STUDY PRT-003: SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS AT VISIT 4		
Subject Bacteriological Response	Ofloxacin (N=33)	Cortisporin (N=44)
Eradication	33 (100%)	44 (100%)
Persistent	0 (0%)	0 (0%)
Oflax vs Corti by Eradication	0%, 95% C.I.: -2.7%, 2.7%	

TABLE P3.13: STUDY PRT-003: OVERALL PATHOGEN ERADICATION RATE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)		
Pathogen	Ofloxacin	Cortisporin
<i>P. aeruginosa</i>	28/28 (100%)	35/35 (100%)
<i>P. mirabilis</i>	0/0	1/1 (100%)
<i>S. aureus</i>	1/1 (100%)	4/4 (100%)
<i>E. cloacae</i>	3/3 (100%)	0/0
<i>K. pneumoniae</i>	0/0	1/1 (100%)
Oflax vs Corti for <i>P.aeruginosa</i>	0%, 95% C.I.: -3.2%, 3.2%	

Reviewer's Note: For all treated subjects, the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to adverse events, the rates of severe adverse events, and the rates of serious adverse events, are presented in Table 3.14. No significant difference was detected regarding these safety parameters between the treatment groups.

TABLE 3.14: STUDY PRT-003: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Ofloxacin (N=100)	Cortisporin (N=102)	Fisher's P-value
Subject with any AE	41 (41.0%)	32 (31.4%)	0.188
Subject with Treatment Related Aes	3 (3.0%)	4 (3.9%)	1.000
Subject with Severe or Life Threatening AEs	0 (0%)	0 (0%)	NA
Subject with Serious Aes	2 (2.0%)	0 (0%)	0.244
Subject Discontinued due to Aes	2 (2.0%)	5 (4.9%)	0.445

No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication. Neither ofloxacin treated subjects nor cortisporin treated subjects were reported as having severe adverse events. Two ofloxacin treated subjects experienced adverse events that were considered to be serious.

Reviewer's Summary and Conclusions: See Section IV.

II. CHRONIC SUPPURATIVE OTITIS MEDIA IN ADOLESCENTS AND ADULTS WITH PERFORATED TYMPANIC MEMBRANE

II.A. INTRODUCTION

The Applicant submitted one study, Study PRT-006, as evidence to support Ofloxacin Otic Solution regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general designs of this study are as follows:

Study PRT-006 was a multicenter, prospective with historical and current practice control, open-label trial which examined the safety and efficacy of 0.3% ofloxacin otic solution for the treatment of acute purulent otorrhea (draining ear) in adolescent and adult subjects (12 years of age or older) with chronic perforation of tympanic membranes. It was initiated on December 23, 1994 and completed on February 23, 1996.

II.B. STUDY PRT-006

II.B.1. METHODS

For the ofloxacin (prospective) group, approximately 150 subjects were enrolled to ensure data from a minimum of 126 clinically evaluable subjects at approximately 15 investigative centers. Of the 15 centers, no more than five came from Latin America. A maximum of 50 subjects were enrolled at Latin American centers, in order to provide a maximum of 42 clinically evaluable subjects. Subjects with perforation of TMs for at least 21 days were eligible for enrollment and received ofloxacin otic solution 0.5 ml b.i.d. (12 hours apart) for 14 days. The records of historical practice at the same institutions for up to four years prior to study initiation served as the source of the historical practice group. The subjects who fulfilled the inclusion/exclusion criteria, but did not participate in the prospective study arm (ofloxacin group) were reviewed as the source of the current practice group. All eligible subjects were at the ages of 12 years or older. Subjects who were included in the historical practice group were allowed to be included in either the ofloxacin group or the current practice group. However, subjects were not to be allowed to be included in both the ofloxacin group and the current practice group.

Study visits were scheduled for Visit 1 (Pre-Therapy Visit), Visit 2 (During Therapy Visit), Visit 3 (Post Therapy Visit), and Visit 4 (Test of Cure Visit). Table 6.1 demonstrates study visit schedules which were specified by the protocol. Safety and efficacy evaluations were performed according to this schedule. Additionally, the investigator provided a final evaluation of clinical response. All compliance information reported was recorded on the CRF by the unblinded study nurse/coordinator. All concomitant medications were recorded on the appropriate CRF and in the source document.

The subject (or the parent or guardian of the subject) was instructed to instill 0.5 ml (10 drops) of the otic solution into the affected ear(s) twice daily approximately 12 hours apart. Subjects with bilateral infection at baseline were administered 0.5 ml (10 drops) of the otic solution in each ear twice daily approximately 12 hours apart. The study drug was administered for 14 consecutive days (28 doses of ofloxacin otic solution). No adjustments in dose were permitted. To assure that the subject (or the parent or guardian of the subject) understood the drug administration procedures, the first administration was made in the

physician's office. Administration of the otic solution took place with the subject recumbent and with the head placed in a lateral decubitus position.

TABLE 6.1: STUDY PRT-006: VISIT TIMING AND PROCEDURES

Visit Number	Visit 1 Pre-Therapy	Visit 2 During Therapy	Visit 3 Post Therapy	Visit 4 Test of Cure
Allowable Study Window	Day 1	Day 4-6	Day 15-17	Day 21-24
Informed Consent	X			
Medical History	X			
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Signs/Symptoms	X	X	X	X
Culture	X	X	X	X
Dispense Medication	X	X		
Collect Medication		X	X	
Medication Application	X		X	
Bitter Taste Assessment	X			
Adverse Event Assessment	X	X	X	X
Subject Diary	X		X	
Parent/Guardian Satisfaction		X	X	
Urine β -HGG Pregnancy Test	X			

EFFICACY EVALUATION

Efficacy evaluations included evaluation of clinical characteristics of otorrhea and the presence or absence of odor, clinical response rates, and microbiological efficacy rates. Efficacy analyses were performed on clinically evaluable and microbiologically evaluable subjects in the ofloxacin group, and subjects with a follow-up visit in the historical and current practice groups. The primary efficacy parameter was the overall clinical response for the clinical evaluable population in the ofloxacin group and subjects who returned for a follow-up visit in the historical practice group. All other efficacy measures were considered secondary.

At each visit, the clinical characteristics of otorrhea and the presence or absence of odor in both ears were assessed. For ofloxacin subjects, the clinical responses were evaluated at Visits 2, 3, and 4, in reference to baseline evaluations. Clinical response was classified as cure, improvement, failure, or indeterminate. The medical records of each subject in the historical and current practice groups were reviewed to determine the clinical response at the follow-up visit. The response was recorded as either "dry ear" (cure) or "not dry ear" (failure). Those who did not remember the clinical outcome were considered "dry ear" (cure), and those who could not be reached by telephone were considered "not dry ear" (failure).

Microbiological assessments were made only on ofloxacin subjects in the microbiologically evaluable population based on pathogen(s) isolated at baseline. The microbiological response of the subject was evaluated at Visits 3 and 4. An overall microbiological response by subjects and by pathogen, respectively, was determined using the responses observed at Visits 3 and 4. Subject and pathogen microbiological response was classified as documented eradication, presumed eradication, persistence, recurrence, or reinfection.

Reviewer's Note: The Medical Officer also defined her clinically evaluable subjects, and assessed clinical and efficacy outcomes according to her clinical criteria. The Medical Officer consented with the Applicant's definition of microbiological evaluable criteria.

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects in the ofloxacin group who received at least one dose of study medication were evaluable for safety. Safety evaluations included the incidence of adverse events, changes from baseline in physical examinations, including vital signs.

At each visit after initiation of therapy, subjects were observed for adverse events. All adverse events, whether or not they were considered drug related, were recorded on the CRF along with the date of onset, date of resolution, duration, intermittency, and severity. The investigator's determination of relationship of each adverse event to the study drug administration, and the outcome for each event were also recorded. If serious adverse events were observed, the monitor and the Sponsor were immediately notified. Complete physical examinations were performed at the Pre-Therapy and Post Therapy Visits. Focused physical examinations were performed at the During Therapy and Test of Cure Visits. Any abnormalities or changes from baseline were recorded on the CRF.

No safety data were collected on historical or current practice group subjects.

STATISTICAL METHODS

The comparisons of interest in the study were conducted among the ofloxacin, historical practice group, and current practice group.

The treatment groups were compared or described with respect to the clinical cure rate, the subject microbiological eradication rate, and the pathogen microbiological eradication rate. Between treatment group differences in clinical response among the ofloxacin, historical practice group, and current practice group were examined for clinically evaluable ofloxacin subjects and historical and current practice subjects with a follow-up visit. The primary efficacy analysis was the comparison of the overall clinical cure rate of the clinically evaluable ofloxacin treated subjects to the dry ear (cure) rate in the historical practice group subjects with a follow-up visit.

For the ofloxacin group, the frequency counts of the microbiological responses by subject at Visits 3 and 4 and overall microbiologically were summarized for the microbiologically evaluable population. For each valid baseline pathogen, the frequency counts of the overall microbiological responses were also summarized for the microbiologically evaluable population.

Description of safety data was based on review of adverse events for ofloxacin subjects who received at least one dose of study drug.

Reviewer's Note: All efficacy analyses were conducted for ofloxacin subjects in each of the Medical Officer clinically evaluable subjects, the Applicant clinically and microbiologically evaluable subjects, for the historical and current practice subjects with a follow-up visit. All of the subjects in these groups were assessed for their clinical or microbiological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals. Homogeneity of treatment effect across centers was evaluated by Breslow-Day's

test.

Subset analyses by gender and age were performed for the Medical Officer's primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer summarized safety information in terms of measures of the incidence rates of the following variables: at least one adverse event, at least one treatment related adverse event, severe adverse events, serious adverse events, and discontinuation due to adverse events.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to demographics. Quantitative variables were assessed using one-way ANOVA. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the test of homogeneity.

II.B.2. RESULTS

An actual total of 207 subjects were enrolled into the ofloxacin group across centers in the USA (33) (but eight centers did not enroll any subjects indeed) and Latin America (2) between December 23, 1994 and February 23, 1996, among whom there were 162 clinically evaluable subjects and 99 microbiologically evaluable subjects. A total of 220 and 63 subjects met the inclusion/exclusion criteria and were included in the historical and current practice groups, respectively, among whom there were 185 and 54 subjects with a follow-up visit in the two groups, respectively.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group for all centers, U.S. centers, and Latin American centers, evaluated by either the Applicant or the Medical Officer, are presented in Tables 6.2A, 6.2B, and 6.2C. There were no notable treatment differences with respect to the percentage of subjects included in each analysis group. Demographic data are described for the Medical Officer clinically evaluable subjects in Table 6.3, and no statistically significant differences were detected in these demographic characteristics of the three treatment groups. The background information of some pretreatment characteristics including baseline disease and target ear characteristics for the historical and current practice groups were not available.

The protocol remarked that subjects who were included in the historical practice group were allowed to be included in either the ofloxacin group or the current practice group, however, subjects were not allowed to be included in both the ofloxacin group and the current practice group. The Medical Officer outlined populations to be the subjects included only in the treatment group to which they were first assigned.

TABLE 6.2A: STUDY PRT-006: SUBJECTS POPULATIONS

Treatment Group for Response	Subjects Included		
	Ofloxacin (N=207)	Historical (N=220)	Current (N=63)
Intent-to-Treat	207 (100%)	220 (100%)	63 (100%)
Applicant Clinically Evaluable	162 (78.3%)	*185 (84.1%)	*54 (85.7%)
MO Clinically Evaluable	163 (78.7%)	*185 (84.1%)	*54 (85.7%)
Applicant Microbiologically Evaluable	99 (47.8%)	NA	NA

* The number of subjects with a follow-up visit

TABLE 6.2B: STUDY PRT-006: SUBJECTS POPULATIONS IN US CENTERS

Treatment Group for Response	Subjects Included		
	Ofloxacin (N=150)	Historical (N=169)	Current (N=44)
Intent-to-Treat	150 (100%)	169 (100%)	44 (100%)
Applicant Clinically Evaluable	108 (72.0%)	*135 (79.9%)	*35 (79.5%)
MO Clinically Evaluable	109 (72.7%)	*135 (79.9%)	*35 (79.5%)
Applicant Microbiologically Evaluable	55 (36.7%)	NA	NA

* The number of subjects with a follow-up visit

TABLE 6.2C: STUDY PRT-006: SUBJECTS POPULATIONS IN LATIN AMERICAN CENTERS

Treatment Group for Response	Subjects Included		
	Ofloxacin (N=57)	Historical (N=51)	Current (N=19)
Intent-to-Treat	57 (100%)	51 (100%)	19 (100%)
Applicant Clinically Evaluable	54 (94.7%)	*50 (98.0%)	*19 (100%)
MO Clinically Evaluable	54 (94.7%)	*50 (98.0%)	*19 (100%)
Applicant Microbiologically Evaluable	44 (77.2%)	NA	NA

* The number of subjects with a follow-up visit

TABLE 6.3: STUDY PRT-006: SUMMARY OF DEMOGRAPHIC DATA FOR THE MO CLINICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP OR THE SUBJECTS WITH A FOLLOW-UP VISIT IN HISTORICAL OR IN CURRENT GROUP (ALL CENTERS)

Number of Subjects	Ofloxacin (N=163)	Historical (N=185)	Current (N=54)	P-value
Age (yrs.)	45.2 ± 20.9	45.7 ± 21.3	51.9 ± 21.1	0.111*
< 65 yrs.	124 (76.1%)	143 (77.3%)	38 (70.4%)	0.566
≥ 65 yrs.	39 (23.9%)	42 (22.7%)	16 (29.6%)	
Gender				0.082
Male	89 (54.6%)	93 (50.3%)	20 (37.0%)	
Female	74 (45.4%)	92 (49.7%)	34 (63.0%)	
Race				NA
White	91 (55.8%)	NA	NA	
Black	0 (0%)			
Hispanic	6 (3.7%)			
Other	66 (40.5%)			

* P-value is obtained by one-way ANOVA, otherwise, by Fisher's exact test

Reviewer's Note: The overall clinical responses for clinically evaluable population in the ofloxacin group, and subjects with a follow-up visit in the historical practice group and the current practice group are presented in Tables 6.4 and 6.5, as per the Applicant and Medical Officer, respectively. Comparisons (95% confidence intervals) of the difference between ofloxacin and the two practice treatments show that ofloxacin therapy was therapeutically superior in efficacy to historical therapy and current therapy with respect to overall clinical outcomes, and historical therapy showed therapeutic equivalence with current therapy.

Table 6.6 presents the evaluation of overall clinical responses, stratified by center, for the Medical Officer clinically evaluable subjects. Breslow-Day's test demonstrated that significant heterogeneity (p-value=0.012) of treatment effects existed across the centers.

Subset analyses by gender and age for the overall clinical cure rates in clinically evaluable subjects in the ofloxacin group and subjects with a follow-up visit in the historical group are shown in Table 6.7. Results were consistent across the gender and age subgroups.

TABLE 6.4: STUDY PRT-006: OVERALL CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS OR THE SUBJECTS WITH A FOLLOW-UP VISIT (ALL CENTERS)

Clinical Response	Ofloxacin (N=162)	Historical (N=185)	Current (N=54)
Cure (Dry Ear)	148 (91.4%)	124 (67.0%)	38 (70.4%)
Failure (Not Dry-Ear)	14 (8.6%)	61 (33.0%)	16 (29.6%)
Ofloxacin vs Historical	24.3%, 95% C.I.: 15.7%, 32.9%		
Ofloxacin vs Current	21.0%, 95% C.I.: 6.8%, 35.1%		
Historical vs Current	-3.3%, 95% C.I.: -18.5%, 11.8%		

TABLE 6.5: STUDY PRT-006: OVERALL CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS OR THE SUBJECTS WITH A FOLLOW-UP VISIT (ALL CENTERS)

Clinical Response	Ofloxacin (N=163)	Historical (N=185)	Current (N=54)
Cure (Dry Ear)	148 (90.8%)	124 (67.0%)	38 (70.4%)
Failure (Not Dry Ear)	15 (9.2%)	61 (33.0%)	16 (29.6%)
Ofloxacin vs Historical	23.8%, 95% C.I.: 15.1%, 32.4%		
Ofloxacin vs Current	20.4%, 95% C.I.: 6.2%, 34.6%		
Historical vs Current	-3.3%, 95% C.I.: -18.5%, 11.8%		

TABLE 6.6: STUDY PRT-006: SUBSET ANALYSES BY CENTERS OF THE OVERALL CLINICAL CURE RATES OF THE MO CLINICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP AND THE SUBJECTS WITH A FOLLOW-UP VISIT IN HISTORICAL GROUP (ALL CENTERS)

Center	Ofloxacin (N=163)	Historical (N=185)
602	33/34 (97.1%)	10/13 (76.9%)
613	2/5 (40.0%)	8/9 (88.9%)
615	7/8 (87.5%)	9/12 (75.0%)
617	3/5 (60.0%)	1/6 (16.7%)
645	7/8 (87.5%)	3/5 (60.0%)
656	7/7 (100%)	4/9 (44.4%)
680	25/25 (100%)	16/26 (61.5%)
681	29/29 (100%)	23/24 (95.8%)
*000	35/42 (83.3%)	50/81 (61.7%)

Breslow-Day's P-value: 0.012

* Includes all those centers which had less than five subjects in at least one arm

TABLE 6.7: STUDY PRT-006: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL CLINICAL CURE RATES OF THE MO CLINICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP AND THE SUBJECTS WITH A FOLLOW-UP VISIT IN HISTORICAL GROUP (ALL CENTERS)

Subset	Ofloxacin (N=163)	Historical (N=185)	95% C.I.	P-value Breslow-Day's
Male	80/89 (89.9%)	80/124 (64.5%)	(13.9%, 36.8%)	0.660
Female	68/74 (91.9%)	60/94 (63.8%)	(15.3%, 40.8%)	
< 65 yrs.	115/124 (92.7%)	51/76 (67.1%)	(13.1%, 38.2%)	0.435
≥ 65 yrs.	33/39 (84.6%)	17/28 (60.7%)	(-0.5%, 48.3%)	
White	79/91 (86.2%)	NA	NA	NA
Hispanic	6/6 (83.3%)			
Other	0/1 (0%)			

The 95% confidence interval for the difference in cure rates of intent-to-treat population between ofloxacin and two control groups indicates the therapeutic superiority of ofloxacin group over historical practice group, which is presented in Table 6.8. Ofloxacin and historical practice showed therapeutic equivalence with current practice, respectively.

Reviewer's Note: The overall clinical responses in the USA centers are shown in Table 6.9 for the Medical Officer clinically evaluable population in the ofloxacin group, and subjects with a follow-up visit in the historical practice group and the current practice group. Confidence interval results show that the ofloxacin group was therapeutically superior to the historical practice group and equivalent to the current practice group with respect to the cure rates, however, the historical practice group failed to show therapeutically equivalence with the current practice group. Table 6.10 presents the overall clinical responses in Latin American centers, which demonstrates the ofloxacin group was therapeutically superior to the historical practice group and the current practice group, and the historical practice group showed therapeutically equivalence with the current practice group.

The subject eradication rates of the microbiologically evaluable subjects in the ofloxacin group at Visits 3 and 4, and overall response are presented in Tables 6.11A, 6.11B, and 6.11C as per all centers, USA centers, and Latin American centers, respectively. The pathogen eradication rates for the most common isolated baseline pathogens are summarized in Tables 6.12 for the microbiologically evaluable subjects in the ofloxacin group.

TABLE 6.8: STUDY PRT-006: OVERALL CLINICAL RESPONSE OF THE INTENT-TO-TREAT (ALL CENTERS)

Clinical Response	Ofloxacin (N=207)	Historical (N=220)	Current (N=63)
Cure (Dry Ear)	157 (75.8%)	140 (63.6%)	42 (66.7%)
Failure (Not Dry Ear)	50 (24.2%)	80 (36.4%)	21 (33.3%)
Ofloxacin vs Historical	12.2%, 95% C.I.: 3.1%, 21.3%		
Ofloxacin vs Current	9.2%, 95% C.I.: -4.9%, 23.2%		
Historical vs Current	-3.0%, 95% C.I.: -17.3%, 11.3%		

TABLE 6.9: STUDY PRT-006: OVERALL CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS OR THE SUBJECTS WITH A FOLLOW-UP VISIT (US CENTERS)

Clinical Response	Ofloxacin (N=109)	Historical (N=135)	Current (N=35)
Cure (Dry Ear)	94 (86.2%)	85 (63.0%)	26 (74.3%)
Failure (Not Dry Ear)	15 (13.8%)	50 (37.0%)	9 (25.7%)
Ofloxacin vs Historical	23.3%, 95% C.I.: 12.0%, 34.5%		
Ofloxacin vs Current	12.0%, 95% C.I.: -5.8%, 29.7%		
Historical vs Current	-11.3%, 95% C.I.: -29.7%, 7.1%		

TABLE 6.10: STUDY PRT-006: OVERALL CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS OR THE SUBJECTS WITH A FOLLOW-UP VISIT (LATIN AMERICAN CENTERS)

Clinical Response	Ofloxacin (N=54)	Historical (N=50)	Current (N=19)
Cure (Dry Ear)	54 (100%)	39 (78.0%)	12 (63.2%)
Failure (Not Dry Ear)	0 (0%)	11 (22.0%)	7 (36.8%)
Ofloxacin vs Historical	22.0%, 95% C.I.: 8.6%, 35.4%		
Ofloxacin vs Current	36.8%, 95% C.I.: 11.6%, 62.1%		
Historical vs Current	14.8%, 95% C.I.: -13.3%, 43.0%		

TABLE 6.11A: STUDY PRT-006: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF MICROBIOLOGICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP (ALL CENTERS)

Subject Bacteriological Response	Visit 3 (N=99)	Visit 4 (N=96)	Overall (N=99)
Eradication	94 (94.9%)	93 (96.9%)	93 (93.9%)
Persistent	5 (5.1%)	3 (3.1%)	6 (6.1%)

TABLE 6.11B: STUDY PRT-006: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF MICROBIOLOGICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP (US CENTERS)

Subject Bacteriological Response	Visit 3 (N=55)	Visit 4 (N=52)	Overall (N=55)
Eradication	50 (90.9%)	49 (94.2%)	49 (89.1%)
Persistent	5 (9.1%)	3 (5.8%)	6 (10.9%)

TABLE 6.11C: STUDY PRT-006: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF MICROBIOLOGICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP (LATIN AMERICAN CENTERS)

Subject Bacteriological Response	Visit 3 (N=44)	Visit 4 (N=44)	Overall (N=44)
Eradication	44 (100%)	44 (100%)	44 (100%)
Persistent	0 (0%)	0 (0%)	0 (0%)

TABLE 6.12: STUDY PRT-006: OVERALL PATHOGEN ERADICATION RATE OF MICROBIOLOGICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) (ALL CENTERS)			
Outcome	Ofloxacin		
	All Center	US	Latin America
<i>S. aureus</i>	40/40 (100%)	29/29 (100%)	11/11 (100%)
<i>P. aeruginosa</i>	39/39 (100%)	16/16 (100%)	23/23 (100%)
<i>P. mirabilis</i>	15/15 (100%)	3/3 (100%)	12/12 (100%)
<i>E. faecalis</i>	7/7 (100%)	5/5 (100%)	2/2 (100%)

For all ofloxacin treated subjects, the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to adverse events, the rates of severe adverse events, and the rates of serious adverse events, are presented in Table 6.13.

No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication, and no adverse events occurred that were considered to be serious.

TABLE 6.13: STUDY PRT-006: CLINICAL ADVERSE EVENT RATES			
Outcome	Ofloxacin		
	All Center (N=207)	US (N=150)	Latin America (N=57)
Subject with any AE	81 (39.1%)	73 (48.7%)	8 (14.0%)
Subject with Treatment Related AEs	47 (22.7%)	40 (18.0%)	7 (12.3%)
Subject with Severe AEs	4 (1.9%)	4 (2.7%)	0
Subject with Serious AEs	0	0	0
Subject Discontinued due to AEs	5 (2.4%)	5 (3.3%)	0

Reviewer's Summary and Conclusions: See Section IV.

**APPEARS THIS WAY
ON ORIGINAL**

III. ACUTE OTITIS MEDIA IN CHILDREN WITH TYMPANOSTOMY TUBES

III.A. INTRODUCTION

The Applicant submitted two studies, PRT-007 and PRT-008, as evidence to support Ofloxacin Otic Solution regarding this indication, and statistical review focuses on the controlled clinical trial PRT-008 which forms the basis of this application. The general designs of the two studies are as follows:

Study PRT-007 was a multicenter, prospective with historical and current practice control, open-label trial which examined the safety and efficacy of 0.3% ofloxacin otic solution for the treatment of acute purulent otorrhea (draining ear) in pediatric subjects with tympanostomy tubes. The qualified subjects in three treatment groups were between the ages of 1 year and less than 12 years with a clinical diagnosis of acute purulent or mucopurulent otorrhea of presumed bacterial origin and tympanostomy tube placement. It was initiated on December 27, 1994 and completed on September 13, 1995.

Study PRT-008 was a multicenter, randomized, parallel group, evaluator-blind, comparative trial which compared the safety and efficacy of 0.3% ofloxacin otic solution versus augmentin oral suspension for the treatment of acute purulent otorrhea (draining ear) in pediatric subjects with tympanostomy tubes. A subgroup of approximately fifty qualified subjects 4 years of age and older had pre and post-therapy audiometric studies performed. It was initiated on January 20, 1995 and completed on June 18, 1996.

III.B. STUDY PRT-007

III.B.1. METHODS

For the ofloxacin (prospective) group, approximately 180 subjects were enrolled to ensure data from a minimum of 150 clinically evaluable subjects at approximately 15 investigative centers. Of the 15 centers, no more than five came from Latin America. A maximum of 60 subjects were enrolled at Latin American centers, in order to provide a maximum of 50 clinically evaluable subjects. Subjects with tympanostomy tube(s) in place and acute purulent otorrhea, defined as a purulent or mucopurulent secretion of less than 3 weeks duration through a tympanostomy tube were eligible for enrollment and received ofloxacin otic solution 0.25ml b.i.d. (12 hours apart) for 10 days. The records of historical practice at the same institutions for up to four years prior to study initiation served as the source of the historical practice group.

The subjects who fulfilled the inclusion/exclusion criteria, but did not participate in the prospective study arm (ofloxacin group) were reviewed as the source of the current practice group. All eligible subjects were at the ages between 1 year and less than 12 years. Subjects who were included in the historical practice group were allowed to be included in either the ofloxacin group or the current practice group. However, subjects were not to be allowed to be included in both the ofloxacin group and the current practice group.

Study visits were scheduled for Visit 1 (Pre-Therapy Visit), Visit 2 (During Therapy Visit), Visit 3 (Post Therapy Visit), and Visit 4 (Test of Cure Visit). Table 7.1 demonstrates study visit schedules which were specified by the protocol. Safety and efficacy evaluations were performed according to this schedule. Additionally, the investigator provided a final evaluation of clinical response. All compliance information

reported was recorded on the CRF by the unblinded study nurse/coordinator. All concomitant medications were recorded on the appropriate CRF and in the source document.

The parent or guardian of the subject was instructed to instill 0.25 ml (5 drops) of the otic solution into the affected ear(s) twice daily approximately 12 hours apart. Subjects with bilateral infection at baseline were administered 0.25 ml (5 drops) of the otic solution in each ear twice daily approximately 12 hours apart. The study drug was administered for 10 consecutive days (20 doses of ofloxacin otic solution). No adjustments in dose were permitted. To assure that the parent or guardian understood the drug administration procedures, the first administration was made in the physician's office. Administration of the otic solution took place with the subject recumbent and with the head placed in a lateral decubitus position.

Visit Number	Visit 1 Pre-Therapy	Visit 2 During Therapy	Visit 3 Post Therapy	Visit 4 Test of Cure
Allowable Study Window	Day 1	Day 4-6	Day 11-13	Day 17-20
Informed Consent	X			
Medical History	X			
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Signs/Symptoms	X	X	X	X
Culture	X	X	X	X
Dispense Medication	X	X		
Collect Medication		X	X	
Medication Application	X		X	
Adverse Event Assessment	X	X	X	X
Subject Diary	X		X	
Parent/Guardian Satisfaction		X	X	

EFFICACY EVALUATION

Efficacy evaluations included evaluation of clinical characteristics of otorrhea and the presence or absence of odor, clinical response rates, and microbiological efficacy rates. Efficacy analyses were performed on clinically evaluable and microbiologically evaluable subjects in the ofloxacin group, and subjects with a follow-up visit in the historical and current practice groups. The primary efficacy parameter was the overall clinical response for the clinical evaluable population in the ofloxacin group and subjects with a follow-up visit in the historical practice group. All other efficacy measures were considered secondary.

At each visit, the clinical characteristics of otorrhea and the presence or absence of odor in both ears were assessed. For ofloxacin subjects, the clinical responses were evaluated at Visits 2, 3, and 4, in reference to baseline evaluations. Clinical response was classified as cure, improvement, failure, or indeterminate. The medical records of each subject in the historical and current practice groups were reviewed to determine the clinical response at the follow-up visit. The response was recorded as either "dry ear" (cure) or "not dry ear" (failure). Those who did not remember the clinical outcome were considered "dry ear" (cure), and those who could not be reached by telephone were considered "not dry ear" (failure).

Microbiological assessments were made only on ofloxacin subjects in the microbiologically evaluable population based on pathogen(s) isolated at baseline. The microbiological response of the subject was evaluated at Visits 3 and 4. An overall microbiological response by subjects and by pathogen,

respectively, was determined using the responses observed at Visits 3 and 4. Subject and pathogen microbiological response was classified as documented eradication, presumed eradication, persistence, recurrence, or reinfection.

Reviewer's Note: *The Medical Officer agreed with both clinical and bacteriological evaluability criteria chosen by the Applicant, and assessed clinical and bacteriological efficacy outcomes according to the Applicant clinical and bacteriological criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's efficacy outcome definitions and Medical Officer's comments.

SAFETY EVALUATION

All subjects in the ofloxacin group who received at least one dose of study medication were evaluable for safety. Safety evaluations included the incidence of adverse events, changes from baseline in physical examinations, including vital signs.

At each visit after initiation of therapy, subjects were observed for adverse events. All adverse events, whether or not they were considered drug related, were recorded on the CRF along with the date of onset, date of resolution, duration, intermittency, and severity. The investigator's determination of relationship of each adverse event to the study drug administration, and the outcome for each event were also recorded. If serious adverse events were observed, the monitor and the Sponsor were immediately notified. Complete physical examinations were performed at the Pre-Therapy and Post Therapy Visits. Focused physical examinations were performed at the During Therapy and Test of Cure Visits. Any abnormalities or changes from baseline were recorded on the CRF.

No safety data were collected on historical or current practice group subjects.

STATISTICAL METHODS

The comparisons of interest in the study were conducted among the ofloxacin, historical practice group, and current practice group.

The treatment groups were compared or described with respect to the clinical cure rate, the subject microbiological eradication rate, and the pathogen microbiological eradication rate. Between-treatment group differences in clinical response among the ofloxacin, historical practice group, and current practice group were examined for clinically evaluable ofloxacin subjects and historical and current practice subjects with a follow-up visit. The primary efficacy analysis was the comparison of the overall clinical cure rate of the clinically evaluable ofloxacin treated subjects to the dry ear (cure) rate in the historical practice group subjects with a follow-up visit.

For the ofloxacin group, the frequency counts of the microbiological responses by subject at Visits 3 and 4 and overall microbiologically were summarized for the microbiologically evaluable population. For each valid baseline pathogen, the frequency counts of the overall microbiological responses were also summarized for the microbiologically evaluable population.

Description of safety data was based on review of adverse events for ofloxacin subjects who received at least one dose of study drug.

Reviewer's Note: *All efficacy analyses were conducted for ofloxacin subjects in each of the Applicant clinically evaluable, microbiologically evaluable populations, for all historical and current practice subjects*

with a follow-up visit. All of the subjects in these groups were assessed for their clinical or microbiological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals. Homogeneity of treatment effect across centers was evaluated by Breslow-Day's test.

Subset analyses by gender and age were performed for the primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer summarized safety information in terms of measures of the incidence rates of the following variables: at least one adverse event, at least one treatment related adverse event, severe adverse events, serious adverse events, and discontinuation due to adverse events.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to demographics. Quantitative variables were assessed using one-way ANOVA. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the test of homogeneity.

III.B.2. RESULTS

An actual total of 226 subjects were enrolled into the ofloxacin group at 27 centers in the USA (but three centers did not enroll any subjects indeed) between December 27, 1994 and September 13, 1995, among whom there were 141 clinically evaluable subjects and 107 microbiologically evaluable subjects. A total of 309 and 68 subjects met the inclusion/exclusion criteria and were included in the historical and current practice groups, respectively, among whom there were 218 and 47 subjects with a follow-up visit in the historical and current practice groups, respectively.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 7.2. There were no notable treatment differences with respect to the percentage of subjects included in each analysis group. Demographic data are described for the Medical Officer clinically evaluable subjects in Table 7.3, and no statistically significant differences were detected in these demographic characteristics of the three treatment groups. The background information of some pretreatment characteristics including baseline disease and target ear characteristics for the historical and current practice groups were not available.

The protocol remarked that subjects who were included in the historical practice group were allowed to be included in either the ofloxacin group or the current practice group, however, subjects were not allowed to be included in both the ofloxacin group and the current practice group. The Medical Officer outlined populations to be the subjects included only in the treatment group to which they were first assigned.

TABLE 7.2: STUDY PRT-007: SUBJECTS POPULATIONS

Treatment Group for Response	Subjects Included		
	Ofloxacin (N=226)	Historical (N=309)	Current (N=68)
Intent-to-Treat	224 (99.1%)	309 (100%)	67 (98.5%)
Applicant Clinically Evaluable	141 (62.4%)	*218 (70.6%)	*47 (69.1%)
Applicant Microbiologically Evaluable	107 (47.3%)	NA	NA

* The number of subjects with a follow-up visit

TABLE 7.3: STUDY PRT-007: SUMMARY OF DEMOGRAPHIC DATA FOR THE CLINICALLY EVALUABLE SUBJECTS OR THE SUBJECTS WITH A FOLLOW-UP VISIT

Number of Subjects	Ofloxacin (N=141)	Historical (N=218)	Current (N=47)	P-value
Age (yrs.)	3.7 ± 2.7	3.6 ± 2.4	3.8 ± 2.4	0.833*
1 yr. ~ 2 yrs.	50 (35.5%)	76 (34.9%)	17 (36.2%)	0.923
2 yrs. ~ 7 yrs.	73 (51.8%)	114 (52.3%)	22 (46.8%)	
7 yrs. ~ 12 yrs.	18 (12.8%)	28 (12.8%)	8 (17.0%)	
Gender				0.660
Male	87 (61.7%)	124 (56.9%)	28 (59.6%)	
Female	54 (38.3%)	94 (43.1%)	19 (40.4%)	
Race				NA
White	116 (82.3%)	NA	NA	
Black	12 (8.5%)			
Hispanic	1 (0.7%)			
Other	12 (8.5%)			

* P-value is obtained by one-way ANOVA, otherwise, by Fisher's exact test

The overall clinical responses for clinically evaluable population in the ofloxacin group, and subjects with a follow-up visit in the historical practice group and the current practice group are presented in Table 7.4. Comparisons (95% confidence intervals) of the difference overall cure rate in between ofloxacin and the two control treatments show that ofloxacin therapy was therapeutically superior in efficacy to historical therapy, and was therapeutically equivalent to current therapy. The historical practice group failed to show therapeutic equivalence with the current practice group.

Reviewer's Note: Table 7.5 presents the evaluation of overall clinical responses, stratified by center, for the clinically evaluable subjects. Breslow-Day's test demonstrated that treatment effects were homogeneous (p -value=0.352) across the centers.

Subset analyses by gender and age for the overall clinical cure rates in clinically evaluable subjects in the ofloxacin group and subjects with a follow-up visit in the historical group are shown in Table 7.6. Significant heterogeneity of treatment effects was detected between the gender subgroups, and the treatment effects more favored ofloxacin in male subjects. Significant heterogeneity of treatment effects also existed among the age subgroup, and the treatment effect favored ofloxacin in older subjects.

TABLE 7.4: STUDY PRT-007: OVERALL CLINICAL RESPONSE OF THE CLINICALLY EVALUABLE SUBJECTS OR THE SUBJECTS WITH A FOLLOW-UP VISIT			
Clinical Response	Ofloxacin (N=141)	Historical (N=218)	Current (N=47)
Cure (Dry Ear)	119 (84.4%)	140 (64.2%)	33 (70.2%)
Failure (Not Dry ear)	22 (15.6%)	78 (35.8%)	14 (29.8%)
Ofloxacin vs Historical	20.2%, 95% C.I.: 10.9%, 29.5%		
Ofloxacin vs Current	14.2%, 95% C.I.: -1.6%, 30.0%		
Historical vs Current	-6.0%, 95% C.I.: -21.8%, 9.8%		

TABLE 7.5: STUDY PRT-007: SUBSET ANALYSES BY CENTERS OF THE OVERALL CLINICAL CURE RATES OF THE CLINICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP AND THE SUBJECTS WITH A FOLLOW-UP VISIT IN HISTORICAL GROUP		
Center	Ofloxacin (N=141)	Historical (N=218)
702	16/17 (94.1%)	4/11 (36.4%)
708	6/7 (85.7%)	9/12 (75.0%)
710	9/9 (100%)	9/12 (75.0%)
712	5/8 (62.5%)	3/5 (60.0%)
713	6/6 (100%)	13/15 (86.7%)
741	8/10 (80.0%)	8/11 (72.7%)
745	16/19 (84.2%)	8/10 (80.0%)
746	8/9 (88.9%)	6/14 (42.9%)
750	14/16 (87.5%)	6/14 (42.9%)
751	5/8 (62.5%)	4/7 (57.1%)
*000	26/32 (81.3%)	70/107 (65.4%)
Breslow-Day's P-value: 0.352		
* Includes all those centers which had less than five subjects in at least one arm		

TABLE 7.6: STUDY PRT-007: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL CLINICAL CURE RATES OF THE CLINICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP AND THE SUBJECTS WITH A FOLLOW-UP VISIT IN HISTORICAL GROUP				
Subset	Ofloxacin (N=141)	Historical (N=218)	95% C.I.	P-value Breslow-Day's
Male	78/87 (89.7%)	80/124 (64.5%)	(13.6%, 36.7%)	0.074
Female	41/54 (75.9%)	60/94 (63.8%)	(-4.3%, 28.5%)	
1 yr. ~ 2 yrs.	39/50 (78.0%)	51/76 (67.1%)	(-6.4%, 28.2%)	0.068
2 yrs. ~ 7 yrs.	62/73 (84.9%)	72/114 (63.2%)	(8.6%, 35.0%)	
7 yrs. ~ 12 yrs.	18/18 (100%)	17/28 (60.7%)	(16.6%, 61.9%)	
White	100/116 (86.2%)	NA	NA	NA
Black	9/12 (75.0%)			
Hispanic	10/12 (83.3%)			
Other	0/1 (0%)			

The 95% confidence interval for the difference in cure rates of intent-to-treat population between ofloxacin and two control groups indicates that the therapeutic equivalence was only shown between the ofloxacin group and historical practice group, which is presented in Table 7.7.

The subject eradication rates of the microbiologically evaluable subjects in the ofloxacin group at Visits 3 and 4, and overall response are presented in Table 7.8. The pathogen eradication rates for the most common isolated baseline pathogens are summarized in Tables 7.9 for the microbiologically evaluable subjects in the ofloxacin group.

TABLE 7.7: STUDY PRT-007: OVERALL CLINICAL RESPONSE OF THE INTENT-TO-TREAT SUBJECTS			
Clinical Response	Ofloxacin (N=224)	Historical (N=309)	Current (N=67)
Cure (Dry Ear)	135 (60.3%)	187 (60.5%)	47 (70.1%)
Failure (Not Dry ear)	89 (39.7%)	122 (39.5%)	20 (29.9%)
Ofloxacin vs Historical	-0.2%, 95% C.I.: -9.0%, 8.5%		
Ofloxacin vs Current	-9.9%, 95% C.I.: -23.5%, 3.8%		
Historical vs Current	-9.6%, 95% C.I.: -22.8%, 3.5%		

TABLE 7.8: STUDY PRT-007: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF MICROBIOLOGICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP			
Subject Bacteriological Response	Visit 3 (N=106)	Visit 4 (N=99)	Overall (N=107)
Eradication	102 (96.2%)	99 (100%)	103 (96.3%)
Persistent	4 (3.8%)	0 (0%)	4 (3.7%)

TABLE 7.9: STUDY PRT-007: OVERALL PATHOGEN ERADICATION RATE OF MICROBIOLOGICALLY EVALUABLE SUBJECTS IN OFLOXACIN GROUP (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)	
Outcome	Ofloxacin
<i>S. pneumoniae</i>	31/33 (93.9%)
<i>H. influenzae</i>	30/30 (100%)
<i>S. aureus</i>	28/29 (96.6%)
<i>M. catarrhalis</i>	26/26 (100%)
<i>P. aeruginosa</i>	15/15 (100%)

For all ofloxacin treated subjects, the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to adverse events, the rates of severe adverse events, and the rates of serious adverse events, are presented in Table 7.10.

No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication.

Outcome	Ofloxacin (N=226)
Subject with any AE	120 (53.1%)
Subject with Treatment Related AEs	29 (12.8%)
Subject with Severe AEs	7 (3.1%)
Subject with Serious AEs	3 (1.3%)
Subject Discontinued due to AEs	6 (2.7%)

Reviewer's Summary and Conclusions: See Section IV.

III.C. STUDY PRT-008

III.C.1. METHODS

Approximately 320 subjects between the ages of 1 year and less than 12 years were collectively enrolled at approximately 20 investigative centers to ensure data from a minimum of 276—clinically evaluable subjects. Of the 20 centers, no more than six were located in Latin America. A maximum of 106 subjects were enrolled at Latin American centers, in order to provide a maximum of 92 clinically evaluable subjects. Each investigator enrolled at least 20 evaluable subjects (10 per treatment group). Subjects with acute purulent otorrhea were eligible for enrollment, and were randomized to one of the two treatment groups in a 1:1 ratio to received either ofloxacin otic solution 0.25 ml b.i.d. (12 hours apart) or augmentin 40 mg/kg/day (administered in three divided doses 8 hours apart) for 10 days. Eligible study population consisted of females who had not reached menarche and males, who met all inclusion/exclusion criteria.

Study visits were scheduled for Visit 1 (Pre-Therapy Visit), Visit 2 (During Therapy Visit), Visit 3 (Post Therapy Visit), and Visit 4 (Test of Cure Visit). Table 8.1 demonstrates study visit schedules which were specified by the protocol. Safety and efficacy evaluations were performed according to this schedule. Additionally, the investigator provided a final evaluation of clinical response. All compliance information reported was recorded on the CRF by the unblinded study nurse/coordinator. All concomitant medications were recorded on the appropriate CRF.

The first administration was made in the physician's office by the unblinded study coordinator in order to assure that the parent or guardian understood the drug administration procedure. The parents or guardians of the subjects randomized to ofloxacin otic solution treatment were instructed to instill 0.25 ml (5 drops) of the otic solution into the affected ear(s) twice daily approximately 12 hours apart. No adjustment in the dose of ofloxacin otic solution was permitted. The parents or guardians of the subjects randomized to augmentin oral suspension treatment were instructed to administer augmentin oral suspension (50 mg/ml) so that the subject received 13.3 mg/kg three times daily (40 mg/kg/day) approximately 8 hours apart. In the event a subject under 2 years of age developed diarrhea, the dose of augmentin could be reduced to 25 mg/kg/day without unblinding the investigator. The adjustment in dose was recorded on the augmentin Medication Accountability Ledger by the unblinded study coordinator.

TABLE 8.1: STUDY PRT-008: VISIT TIMING AND PROCEDURES

Visit Number	Visit 1 Pre-Therapy	Visit 2 During Therapy	Visit 3 Post Therapy	Visit 4 Test of Cure
Allowable Study Window	Day 1	Day 4-6	Day 11-13	Day 17-20
Informed Consent	X			
Medical History	X			
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Signs/Symptoms	X	X	X	X
Culture	X	X	X	X
Dispense Medication	X	X		
Collect Medication		X	X	
Medication Application	X		X	
Adverse Event Assessment	X	X	X	X
Subject Diary	X		X	
Parent/Guardian Satisfaction		X	X	
Audiometry	X			X

EFFICACY EVALUATION

Efficacy evaluations included evaluation of clinical characteristics of otorrhea and the presence or absence of odor, clinical response rates, and microbiological efficacy rates. Efficacy analyses were performed on clinically evaluable and microbiologically evaluable subjects. The primary efficacy parameter was the overall clinical response for the clinical evaluable population. All other efficacy measures were considered secondary.

At each visit, the clinical characteristics of otorrhea and the presence or absence of odor in both ears were assessed. The clinical responses were evaluated at Visits 2, 3, and 4, in reference to baseline evaluations. Microbiological assessments were made on subjects in the microbiologically evaluable population based on pathogen(s) isolated at baseline. The microbiological response of the subject was evaluated at Visits 3 and 4. An overall microbiological response by subjects and by pathogen, respectively, was determined using the responses observed at Visits 3 and 4.

Clinical response was classified as cure, improvement, failure, or indeterminate; subject and pathogen microbiological response was classified as documented eradication, presumed eradication, persistence, recurrence, or reinfection.

Reviewer's Note: *The Medical Officer also defined her clinically and microbiologically evaluable subjects, and assessed clinical and microbiological efficacy outcomes according to her clinical and microbiological criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. Safety evaluations included the incidence of adverse events, changes from baseline in physical examinations, including vital signs, and changes from baseline in bone and air conduction thresholds in subjects who participated in the audiometry arm.

At each visit after initiation of therapy, subjects were observed for adverse events. All adverse events, whether or not they were considered drug related, were recorded on the CRF along with the date of onset, date of resolution, duration, intermittency, and severity. The investigator's determination of relationship of each adverse event to the study drug administration, and the outcome for each event were also recorded. If serious adverse events were observed, the monitor and the Sponsor were immediately notified. Complete physical examinations were performed at the Pre-Therapy and Post Therapy Visits. Focused physical examinations were performed at the During Therapy and Test of Cure Visits. Any abnormalities or changes from baseline were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between ofloxacin and augmentin.

Efficacy analyses were based on the clinical and microbiological responses at Visits 2, 3, and 4. The treatment groups were compared with respect to the clinical cure rate, the subject microbiological eradication rate, and the pathogen microbiological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the overall clinical cure rate in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: All efficacy analyses were conducted for the Medical Officer clinically and microbiologically evaluable subjects, and the Applicant clinically and microbiologically evaluable subjects. All of the subjects in these four groups were assessed for their clinical or microbiological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. Confidence interval based on Cochran's method, after adjusting for center, was also used to assess the differences in the proportion of interest. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points-to-Consider" document pertaining to results of confidence intervals. Homogeneity of treatment effect across centers was evaluated by Breslow-Day's test.

Subset analyses by gender, age, and race were performed for the Medical Officer's primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of severe adverse events, the rate of serious adverse events, and the rate of discontinuation due to adverse events. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the test of homogeneity.

III.C.2. RESULTS

Reviewer's Note: In the following analysis, both the Applicant's population and the Medical Officer's population excluded subjects in the centers of investigator C. Please find more details in Section V. (Appendix).

An actual total of 462 subjects were enrolled across centers in the USA (36) and Latin America (2) between January 20, 1995 and June 18, 1996. Of these enrolled subjects, 223 ofloxacin treated subjects and 239 augmentin treated subjects were included in the intent-to-treat analyses. The Applicant clinically evaluable group comprised 137 ofloxacin subjects and 143 augmentin subjects. There were 135 ofloxacin subjects and 145 augmentin subjects in the Medical Officer clinically evaluable group.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 8.2. There were no notable treatment differences with respect to the percentage of subjects included in each analysis group. Demographic data are described for the Medical Officer clinically evaluable subjects in Table 8.3, and no statistically significant differences were detected in these pretreatment characteristics of the two treatment groups.

TABLE 8.2: STUDY PRT-008: SUBJECTS POPULATIONS		
Treatment Group for Clinical Response	Subjects Included	
	Ofloxacin (N=223)	Augmentin (N=239)
Intent-to-Treat	223 (100%)	239 (100%)
Applicant Clinically Evaluable	137 (61.4%)	143 (59.8%)
MO Clinically Evaluable	135 (60.5%)	145 (60.7%)
Applicant Microbiologically Evaluable	83 (37.2%)	93 (38.9%)
MO Microbiologically Evaluable	85 (38.1%)	96 (40.2%)

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TABLE 8.3: STUDY PRT-008: SUMMARY OF DEMOGRAPHIC DATA FOR THE MO CLINICALLY EVALUABLE SUBJECTS			
Number of Subjects	Ofloxacin (N=135)	Augmentin (N=145)	P-value
Age (yrs.)	3.7 ± 2.5	3.5 ± 2.6	*0.408
1 yr. ~ 2 yrs.	45 (33.3%)	64 (44.1%)	0.152
2 yrs. ~ 7 yrs.	72 (53.3%)	62 (42.8%)	
7 yrs. ~ 12 yrs.	18 (13.3%)	19 (13.1%)	
Gender			
Male	73 (54.1%)	89 (61.4%)	0.228
Female	62 (45.9%)	56 (38.6%)	
Race			
White	112 (83.0%)	118 (81.4%)	0.696
Black	7 (5.2%)	12 (8.3%)	
Hispanic	2 (1.5%)	1 (0.7%)	
Other	14 (10.4%)	14 (9.7%)	
Target Ear			
Right	65 (48.2%)	80 (55.2%)	0.282
Left	70 (51.9%)	65 (44.8%)	
Infection			
Unilateral	107 (79.3%)	121 (83.5%)	0.442
Bilateral	28 (20.7%)	24 (16.6%)	
Tube Placement (Days)	331.7 ± 377.5	319.2 ± 389.6	*0.785
Drainage (Days)	2.9 ± 3.4	3.2 ± 3.9	*0.513
Granulation Tissue			
Absent	119 (88.2%)	125 (86.2%)	0.746
Mild	14 (10.4%)	15 (10.3%)	
Moderate	2 (1.5%)	2 (1.4%)	
Severe	0 (0%)	2 (1.4%)	

* P-value is obtained by t-test, otherwise, by Fisher's exact test

Reviewer's Note: The overall clinical responses as per the Applicant and the Medical Officer clinical evaluable populations are presented in Tables 8.4 and 8.5, respectively. Comparisons (95% confidence intervals) of the difference between the two treatment groups show that ofloxacin was therapeutically equivalent to augmentin with respect to overall clinical outcomes.

Table 8.6 presents the evaluation of overall clinical responses, stratified by center, for the Medical Officer clinically evaluable subjects. Confidence interval results by center adjusted Cochran's method show that ofloxacin was therapeutically equivalent in efficacy to augmentin with respect to the cure rates. Breslow-Day's test demonstrated that significant heterogeneity (p -value=0.031) of treatment effects existed across the centers.

Subset analyses by gender, age, and race for the overall clinical cure rates in the Medical Officer clinically evaluable subjects are shown in Table 8.7. Results were consistent across all three demographic aspects.

TABLE 8.4: STUDY PRT-008: OVERALL CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS

Clinical Response	Ofloxacin (N=137)	Augmentin (N=143)
Cure	105 (76.6%)	98 (68.5%)
Failure	32 (23.4%)	45 (31.5%)
Ofloxacin vs Augmentin by Cure	8.1%, 95% C.I.: -3.0%, 19.2%	

TABLE 8.5: STUDY PRT-008: OVERALL CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS

Clinical Response	Ofloxacin (N=135)	Augmentin (N=145)
Cure	103 (76.3%)	99 (68.3%)
Failure	32 (23.7%)	46 (31.7%)
Ofloxacin vs Augmentin by Cure	8.0%, 95% C.I.: -3.1%, 19.2%	

TABLE 8.6: STUDY PRT-008: EVALUATION OF OVERALL CLINICAL RESPONSE, STRATIFIED BY CENTER, FOR THE MO CLINICALLY EVALUABLE SUBJECTS

Center	Ofloxacin (N=135)	Augmentin (N=145)
802	12/12 (100%)	8/9 (88.9%)
804	5/7 (71.4%)	8/10 (80.0%)
806	4/7 (57.1%)	3/6 (50.0%)
808	4/7 (57.1%)	2/5 (40.0%)
810	6/6 (100%)	6/9 (66.7%)
815	3/5 (60.0%)	3/5 (60.0%)
817	4/8 (50.0%)	4/5 (80.0%)
841	7/7 (100%)	6/7 (85.7%)
852	1/8 (12.5%)	7/9 (77.8%)
855	11/13 (84.6%)	8/12 (66.7%)
857	2/5 (40.0%)	6/10 (60.0%)
880	7/7 (100%)	7/7 (100%)
*000	37/43 (86.1%)	31/51 (60.8%)
Total	103/135 (76.3%)	99/145 (68.3%)
95% C.I. by Center Adjusted Cochran's Method: -1.7%, 17.1%		
Breslow-Day's P-value: 0.031		
* Includes all those centers which had less than five subjects in at least one arm		

Subset	Ofloxacin (N=135)	Augmentin (N=145)	95% C.I.	P-value Breslow-Day's
Male	57/73 (78.1%)	58/89 (65.2%)	(-2.0%, 27.9%)	0.282
Female	46/62 (74.2%)	41/56 (73.2%)	(-16.6%, 18.6%)	
1 yr. ~ 2 yrs.	28/45 (62.2%)	42/64 (65.6%)	(-23.6%, 16.8%)	0.245
2 yrs. ~ 7 yrs.	62/72 (86.1%)	45/62 (72.6%)	(-1.6%, 28.7%)	
7 yrs. ~ 12 yrs.	13/18 (72.2%)	12/19 (63.2%)	(-26.3%, 44.5%)	
White	86/112 (76.8%)	82/118 (69.5%)	(-5.0%, 19.6%)	0.996
Black	4/7 (57.1%)	6/12 (50.0%)	NA	
Hispanic	11/14 (78.6%)	10/14 (71.4%)	NA	
Other	2/2 (100%)	1/1 (100%)	NA	

The 95% confidence interval for the difference in cure rates of intent-to-treat population between ofloxacin and augmentin groups indicates the therapeutic equivalence of the two treatment groups, which is presented in Table 8.8.

Tables 8.9, 8.10, and 8.11 show clinical responses of the Applicant and the Medical Officer clinically evaluable subjects at Visits 2, 3, and 4, respectively. Confidence interval results demonstrate that the two treatment groups were therapeutically equivalent with respect to the cure rates at the three time points.

The subject overall microbiological responses are shown for the Applicant and the Medical Officer microbiologically evaluable subjects in Tables 8.12 and 8.13, respectively. Both confidence interval results from analyses show that ofloxacin was therapeutically superior to augmentin with respect to the eradication rates.

The subject eradication rates of the Applicant and the Medical Officer microbiologically evaluable subjects at Visit 3 are presented in Table 8.14. Comparisons (95% confidence intervals) of the difference between the two treatment groups illustrate ofloxacin superiority over augmentin. Analyses of the eradication rates of the Applicant and the Medical Officer microbiologically evaluable subjects at Visit 4 are displayed in Tables 8.15 and 8.16, respectively, both of which show the therapeutic equivalence of ofloxacin to augmentin.

The pathogen eradication rates for the most common isolated baseline pathogens are summarized for the Applicant and the Medical Officer microbiologically evaluable subjects in Tables 8.17 and 8.18, respectively.

Clinical Response	Ofloxacin (N=223)	Augmentin (N=239)
Cure	105 (47.1%)	98 (41.0%)
Failure	118 (52.9%)	141 (59.0%)
Ofloxacin vs Augmentin by Cure	6.1%, 95% C.I.: -3.4%, 15.6%	

TABLE 8.9: STUDY PRT-008: CLINICAL RESPONSE OF THE APPLICANT AND MO CLINICALLY EVALUABLE SUBJECTS AT VISIT 2

Clinical Response	Ofloxacin (N=137)	Augmentin (N=143)
Cure	105 (76.6%)	98 (68.5%)
Failure	32 (23.4%)	45 (31.5%)
Ofloxacin vs Augmentin by Cure	8.1%, 95% C.I.: -3.0%, 19.2%	

TABLE 8.10: STUDY PRT-008: CLINICAL RESPONSE OF THE APPLICANT AND MO CLINICALLY EVALUABLE SUBJECTS AT VISIT 3

Clinical Response	Ofloxacin (N=134)	Augmentin (N=143)
Cure	113 (84.3%)	110 (76.9%)
Failure	21 (15.7%)	33 (23.1%)
Ofloxacin vs Augmentin by Cure	7.4%, 95% C.I.: -2.6%, 17.4%	

TABLE 8.11: STUDY PRT-008: CLINICAL RESPONSE OF THE APPLICANT AND MO CLINICALLY EVALUABLE SUBJECTS AT VISIT 4

Clinical Response	Ofloxacin (N=116)	Augmentin (N=111)
Cure	103 (88.8%)	99 (89.2%)
Failure	13 (11.2%)	12 (10.8%)
Ofloxacin vs Augmentin by Cure	-0.4%, 95% C.I.: -9.4%, 8.6%	

TABLE 8.12: STUDY PRT-008: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS

Subject Bacteriological Response	Ofloxacin (N=83)	Augmentin (N=93)
Eradication	80 (96.4%)	62 (66.7%)
Persistent+Recurrence	3 (3.6%)	31 (33.3%)
Oflox vs Corti by Eradication	29.7%, 95% C.I.: 18.2%, 41.2%	

TABLE 8.13: STUDY PRT-008: OVERALL SUBJECT MICROBIOLOGICAL RESPONSE OF THE MO MICROBIOLOGICALLY EVALUABLE SUBJECTS

Subject Bacteriological Response	Ofloxacin (N=85)	Augmentin (N=96)
Eradication	82 (96.5%)	64 (66.7%)
Persistent+Recurrence	3 (3.5%)	32 (33.3%)
Oflox vs Corti by Eradication	29.8%, 95% C.I.: 18.5%, 41.1%	

TABLE 8.14: STUDY PRT-008: SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT AND MO MICROBIOLOGICALLY EVALUABLE SUBJECTS AT VISIT 3

Subject Bacteriological Response	Ofloxacin (N=83)	Augmentin (N=93)
Eradication	82 (98.8%)	67 (72.0%)
Persistent	1 (1.2%)	26 (28.0%)
Oflox vs Corti by Eradication	26.8%, 95% C.I.: 16.2%, 37.3%	

TABLE 8.15: STUDY PRT-008: SUBJECT MICROBIOLOGICAL RESPONSE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS AT VISIT 4

Subject Bacteriological Response	Ofloxacin (N=71)	Augmentin (N=69)
Eradication	69 (97.2%)	63 (91.3%)
Persistent	2 (2.8%)	6 (8.7%)
Oflox vs Corti by Eradication	5.9%, 95% C.I.: -3.2%, 15.0%	

TABLE 8.16: STUDY PRT-008: SUBJECT MICROBIOLOGICAL RESPONSE OF THE MO MICROBIOLOGICALLY EVALUABLE SUBJECTS AT VISIT 4

Subject Bacteriological Response	Ofloxacin (N=73)	Augmentin (N=71)
Eradication	71 (97.3%)	65 (91.5%)
Persistent	2 (2.7%)	6 (8.5%)
Oflox vs Corti by Eradication	5.7%, 95% C.I.: -3.2%, 14.6%	

TABLE 8.17: STUDY PRT-008: OVERALL PATHOGEN ERADICATION RATE OF THE APPLICANT MICROBIOLOGICALLY EVALUABLE SUBJECTS (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

Pathogen	Ofloxacin	Augmentin
<i>S. pneumoniae</i>	36/36 (100.0%)	33/38 (86.8%)
<i>H. influenzae</i>	26/28 (92.9%)	30/39 (76.9%)
<i>S. aureus</i>	29/30 (96.7%)	13/26 (50.0%)
<i>M. catarrhalis</i>	13/14 (92.9%)	9/10 (90.0%)
<i>P. aeruginosa</i>	9/9 (100%)	3/7 (42.9%)
Oflox vs Augm for <i>S. pneumoniae</i>	13.2%, 95% C.I.: -0.3%, 26.6%	

TABLE 8.18: STUDY PRT-008: OVERALL PATHOGEN ERADICATION RATE OF THE MO MICROBIOLOGICALLY EVALUABLE SUBJECTS (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

Pathogen	Ofloxacin	Augmentin
<i>S. pneumoniae</i>	36/36 (100.0%)	33/39 (84.6%)
<i>H. influenzae</i>	28/30 (93.3%)	30/39 (76.9%)
<i>S. aureus</i>	29/30 (96.7%)	15/29 (51.7%)
<i>M. catarrhalis</i>	13/14 (92.9%)	9/10 (90.0%)
<i>P. aeruginosa</i>	9/9 (100.0%)	3/7 (42.9%)
Oflox vs Augm for <i>S. pneumoniae</i>	15.4%, 95% C.I.: 1.4%, 29.4%	

Reviewer's Note: For all treated subjects, the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to adverse events, the rates of severe adverse events, and the rates of serious adverse events, are presented in Table 8.19. Adverse events occurred in a significantly lower percentage of ofloxacin treated subjects than augmentin treated subjects. A significantly lower percentage of ofloxacin-treated subjects than augmentin-treated subjects experienced treatment related adverse events. No significant difference was detected in the number of subjects who discontinued due to adverse events between the treatment groups.

TABLE 8.19: STUDY PRT-008: CLINICAL ADVERSE EVENT RATES			
Outcome	Ofloxacin (N=223)	Augmentin (N=239)	Fisher's P-value
Subject with any AE	95 (42.6%)	125 (52.3%)	0.041
Subject with Treatment Related AEs	13 (5.8%)	77 (32.2%)	< 0.001
Subject with Severe AEs	7 (3.1%)	13 (5.4%)	0.259
Subject with Serious AEs	0 (0%)	2 (0.8%)	0.500
Subject Discontinued due to AEs	9 (4.0%)	18 (8.0%)	0.083

No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication. Seven ofloxacin treated subjects and 13 augmentin treated subjects were reported as having severe adverse events. Two augmentin treated subject experienced adverse events that were considered to be serious.

Reviewer's Summary and Conclusions: See Section IV.

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IV. SUMMARY AND CONCLUSIONS

(Which May be Conveyed to the Sponsor)

OTITIS EXTERNA IN ADULTS AND CHILDREN

This indication was supported by two controlled studies to demonstrate the efficacy and safety of ofloxacin: The target population of Study PRT-002 was the subjects 12 years of age and older with acute otitis externa, and the target population of Study PRT-003 was for the subjects under 12 years of age (1 through 12) with acute otitis externa.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of difference of overall clinical cure rates between the treatment groups in the Medical Officer clinically evaluable subjects.

Statistical evaluation of safety was based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

The following statements pertain to Study PRT-002 (subjects in the centers of investigators A and C were excluded):

1. The 95% confidence interval of the difference in overall clinical cure rates of the Medical Officer clinically evaluable subjects was $_{99, 98}$ (-16.3%, 8.6%) $_{78.8\%, 80.6\%}$ which failed to demonstrate that ofloxacin was therapeutically equivalent in efficacy to cortisporin in the treatment of otitis externa in adults, however, the results was marginal.
2. No significant differences between the ofloxacin and cortisporin treatment groups were detected with respect to the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, the rates of severe adverse events, and the rates of serious adverse events.

The following statements pertain to Study PRT-003 (subjects in the centers of investigators A, B, and C were excluded):

1. The 95% confidence interval of the difference in overall clinical cure rates of the Medical Officer clinically evaluable subjects was $_{81, 78}$ (-4.5%, 12.4%) $_{98.3\%, 92.3\%}$ which demonstrated that ofloxacin was therapeutically equivalent in efficacy to cortisporin in the treatment of otitis externa in pediatric subjects.
2. No significant differences between the ofloxacin and cortisporin treatment groups were detected with respect to the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, the rates of severe adverse events, and the rates of serious adverse events.

REVIEWER CONCLUSIONS: For the pivotal study PRT-002, the efficacy analyses of the clinically evaluable subjects failed to demonstrate that ofloxacin 0.3% otic solution was therapeutically equivalent in efficacy to cortisporin otic solution in the treatment of otitis externa in subjects 12 years of age or older, however, the result is statistically marginal. For the pivotal study PRT-003, the efficacy analyses of the clinically evaluable subjects demonstrated that ofloxacin 0.3% otic solution was therapeutically equivalent

in efficacy to cortisporin otic solution in the treatment of otitis externa in subjects under 12 years of age. Both Studies PRT-002 and PRT-003 provided the evidence that ofloxacin featured a similar safety profile to cortisporin.

RECOMMENDED REGULATORY ACTION: Based on the above analyses, from a statistical standpoint, an approvable regulatory decision toward ofloxacin 0.3% otic solution instilled twice daily is recommended for the treatment of otitis externa for pediatrics subjects. The Medical Officer will have to determine whether the observed overall cure rates are clinically acceptable toward ofloxacin regarding this indication for adolescent and adult subjects.

CHRONIC SUPPURATIVE OTITIS MEDIA IN ADOLESCENTS AND ADULTS WITH PERFORATED TYMPANIC MEMBRANE

This indication was supported by one open label study PRT-006 to demonstrate the efficacy and safety of ofloxacin.

The following statements pertain to Study PRT-006:

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of difference of overall clinical cure rates between the Medical Officer clinically evaluable ofloxacin subjects and the historical practice subjects with a follow-up visit.

Statistical evaluation of safety was based on summarizing adverse event within the ofloxacin treatment groups in all subjects receiving at least one dose of study medication.

1. The 95% confidence interval of the difference in overall clinical cure rates of the clinically evaluable subjects or subjects with a follow-up visit was $_{163, 165} (15.1\%, 32.4\%)$ $_{90.8\%, 67.0\%}$ which demonstrated that ofloxacin was therapeutically superior in efficacy to historical therapy in the treatment of chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane. Confidence interval results $_{163, 54} (6.2\%, 34.6\%)$ $_{90.8\%, 70.4\%}$ also illustrated that ofloxacin was therapeutically superior in efficacy to current therapy.
2. For the ofloxacin treated subjects, the rate of at least one adverse event was 39.1%, the rate of at least one treatment related adverse event was 22.7%, the rate of discontinuations due to adverse events was 2.4%, the rates of severe adverse events was 1.9%, and no adverse events occurred which were considered to be serious.

REVIEWER CONCLUSIONS: For the study PRT-006, the efficacy analyses of the clinically evaluable ofloxacin subjects and historical treated subjects with a follow-up visit demonstrated that ofloxacin 0.3% otic solution was therapeutically superior in efficacy to historical therapy in the treatment of chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane. Study PRT-006 also provided the evidence that ofloxacin was at least as safe as historical therapy.

RECOMMENDED REGULATORY ACTION: Upon considering the weakness of the trial toward ofloxacin 0.3% otic solution instilled twice daily for the treatment of chronic suppurative otitis media in subjects at age of 12 years or older with perforated tympanic membrane, only one open label study and unavailability of some post-treatment information, an approvable recommendation is pending but an endorsement to the application does not preclude. The regulatory action will be adopted after soliciting for medical standpoint.

ACUTE OTITIS MEDIA IN CHILDREN WITH TYMPANOSTOMY TUBES

This indication was supported by two studies to demonstrate the efficacy and safety of ofloxacin. PRT-007 was an open label study and PRT-008 was a controlled study.

The following statements pertain to Study PRT-007:

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of difference of overall clinical cure rates between the Applicant clinically evaluable ofloxacin subjects and the historical practice subjects with a follow-up visit.

Statistical evaluation of safety was based on summarizing adverse event within the ofloxacin treatment groups in all subjects receiving at least one dose of study medication.

1. The 95% confidence interval of the overall clinical cure rate of the clinically evaluable subjects or subjects with a follow-up visit was $_{141, 218}$ (10.9%, 29.5%) $_{84.4\%, 84.2\%}$ which demonstrated that ofloxacin was therapeutically superior in efficacy to historical therapy in the treatment of acute otitis media in children with tympanostomy tubes. Confidence interval results $_{141, 47}$ (-1.6%, 30.0%) $_{84.4\%, 70.2\%}$ illustrated that ofloxacin was therapeutically equivalent in efficacy to current therapy.
2. For the ofloxacin treated subjects, the rate of at least one adverse event was 53.1%, the rate of at least one treatment related adverse event was 12.8%, the rate of discontinuations due to adverse events was 2.7%, the rates of severe adverse events was 3.1%, and the rates of serious adverse events was 1.3%.

The following statements pertain to Study PRT-008 (subjects in the centers of investigator C were excluded):

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of difference of overall clinical cure rates between the treatment groups in the Medical Officer clinically evaluable subjects.

Statistical evaluation of safety was based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval of the overall clinical cure rate of the Medical Officer clinically evaluable subjects was $_{135, 145}$ (-3.1%, 19.2%) $_{78.3\%, 88.3\%}$ which demonstrated that ofloxacin was therapeutically equivalent in efficacy to augmentin in the treatment of acute otitis media in children with tympanostomy tubes.
2. The rate of at least one adverse event was significantly lower in the ofloxacin group (42.6%, 95/223) than the augmentin group (52.3%, 125/239) (Fisher's exact p-value=0.041); the rate of at least one treatment related adverse event was significantly lower in the ofloxacin group (5.8%, 13/223) than the augmentin group (32.2%, 77/239) (Fisher's exact p-value<0.001). There were no significant difference in severe adverse events, serious adverse event, or discontinuing due to adverse events.

REVIEWER CONCLUSIONS: For the study PRT-008, the efficacy analyses of the clinically evaluable

subjects demonstrated that ofloxacin 0.3% otic solution was therapeutically equivalent in efficacy to augmentin oral suspension in the treatment of acute otitis media in children with tympanostomy tubes. Study PRT-007 demonstrated that ofloxacin 0.3% otic solution was therapeutically superior in efficacy to historical therapy in this indication. Either study PRT-008 or study PRT-007 also provided the evidence that ofloxacin was at least as safe as augmentin or historical therapy.

RECOMMENDED REGULATORY ACTION: Based on the above analyses, from a statistical standpoint, an approvable regulatory decision toward ofloxacin 0.3% otic solution instilled twice daily is recommended for the treatment of acute otitis media in subjects between ≥ 1 and < 12 years of age with tympanostomy tubes.

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V. APPENDIX

The integrity of the data obtained from three investigators is questionable, which is considered to be not reliable in drug evaluation. Three studies in this NDA, PRT-002, PRT-003, and PRT-008, were impacted. According to the recommendation by the Division of Scientific Investigation, this review has proceeded by excluding those centers.

TABLE A.1: SUBJECTS IN INCLUDED AND EXCLUDED CENTERS									
	Study PRT-002			Study PRT-003			Study PRT-008		
	Oflox	Cortis	Total	Oflox	Cortis	Total	Oflox	Augme	Total
INTENT-TO-TEART POPULATION									
All Centers	158 (100%)	156 (100%)	314 (100%)	143 (100%)	144 (100%)	287 (100%)	228 (100%)	246 (100%)	474 (100%)
Included Centers	129 (81.6%)	127 (81.4%)	256 (81.5%)	100 (69.9%)	102 (70.8%)	202 (70.4%)	223 (97.8%)	239 (97.2%)	462 (97.5%)
Excluded Centers	29 (18.4%)	29 (18.6%)	58 (18.5%)	43 (30.1%)	42 (29.2%)	85 (29.6%)	5 (2.2%)	7 (2.8%)	12 (2.5%)
Investigator A	20	20	40	20	20	40	-	-	-
Investigator B	9	9	18	8	7	15	-	-	-
Investigator C	-	-	-	15	15	30	5	7	12
APPLICANT CLINICAL EVALUABLE POPULATION									
All Centers	126 (100%)	121 (100%)	247 (100%)	116 (100%)	111 (100%)	227 (100%)	140 (100%)	146 (100%)	286 (100%)
Included Centers	100 (79.4%)	98 (81.0%)	198 (80.2%)	80 (69.0%)	78 (70.3%)	158 (69.6%)	137 (97.9%)	143 (97.9%)	280 (97.9%)
Excluded Centers	26 (20.6%)	23 (19.0%)	49 (19.8%)	36 (31.0%)	33 (29.7%)	69 (30.4%)	3 (2.1%)	3 (2.1%)	6 (2.1%)
Investigator A	17	18	35	19	20	39	-	-	-
Investigator B	9	5	14	8	6	14	-	-	-
Investigator C	-	-	-	9	7	16	3	3	6

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Tables A.2, A.3, and A.4 present the clinical responses for the subject subsets in the impacted Studies 002, 003, and 008, respectively, and feature the clinical responses as including or excluding those questionable centers.

TABLE A.2: STUDY PRT-002: OVERALL CLINICAL RESPONSES			
Clinical Response	Ofloxacin	Cortisporin	95% C.I.
All Centers			
Intent-to-Treat	108/158 (68.4%)	111/156 (71.2%)	-13.6%, 8.0%
Applicant Clinically Evaluable	103/126 (81.7%)	101/121 (83.5%)	-12.0%, 8.5%
Included Centers			
Intent-to-Treat	81/129 (62.8%)	89/127 (70.1%)	-19.6%, 5.0%
Applicant Clinically Evaluable	77/100 (77.0%)	79/98 (80.6%)	-16.0%, 8.8%
MO Clinically Evaluable	76/99 (76.8%)	79/98 (80.6%)	-16.3%, 8.6%
Excluded Centers			
Intent-to-Treat	27/29 (93.1%)	22/29 (75.9%)	
Applicant Clinically Evaluable	26/26 (100%)	22/23 (95.7%)	

TABLE A.3: STUDY PRT-003: OVERALL CLINICAL RESPONSES			
Clinical Response	Ofloxacin	Cortisporin	95% C.I.
All Centers			
Intent-to-Treat	117/143 (81.8%)	116/144 (80.6%)	-8.5%, 11.0%
Applicant Clinically Evaluable	112/116 (96.6%)	105/111 (94.6%)	-4.3%, 8.2%
Included Centers			
Intent-to-Treat	80/100 (80.0%)	80/102 (78.4%)	-10.6%, 13.7%
Applicant Clinically Evaluable	78/80 (97.5%)	73/78 (93.6%)	-3.8%, 11.6%
MO Clinically Evaluable	78/81 (96.3%)	72/78 (92.3%)	-4.5%, 12.4%
Excluded Centers			
Intent-to-Treat	37/43 (86.0%)	36/42 (85.7%)	
Applicant Clinically Evaluable	34/36 (94.4%)	32/33 (97.0%)	

TABLE A.4: STUDY PRT-008: OVERALL CLINICAL RESPONSES			
Clinical Response	Ofloxacin	Augmentin	95% C.I.
All Centers			
Intent-to-Treat	107/228 (46.9%)	101/246 (41.1%)	-3.5%, 15.2%
Applicant Clinically Evaluable	107/140 (76.4%)	101/146 (69.2%)	-3.7%, 18.2%
Included Centers			
Intent-to-Treat	105/223 (47.1%)	98/239 (41.0%)	-3.4%, 15.6%
Applicant Clinically Evaluable	105/137 (76.6%)	98/143 (68.5%)	-3.0%, 19.2%
MO Clinically Evaluable	103/135 (76.3%)	99/145 (68.3%)	-3.1%, 19.2%
Excluded Centers			
Intent-to-Treat	2/5 (40.0%)	3/7 (42.9%)	
Applicant Clinically Evaluable	2/3 (66.7%)	3/3 (100%)	

Tables A.5 and A.6 present the clinical responses for the subject subsets in Studies 006 and 007, respectively.

TABLE A.5: STUDY PRT-006: OVERALL CLINICAL RESPONSES			
Clinical Response	Ofloxacin	Historical	Current
Intent-to-Treat	157/207 (75.8%)	140/220 (63.6%)	42/63 (66.7%)
Ofloxacin vs Historical	12.2%, 95% C.I.: 3.1%, 21.3%		
Ofloxacin vs Current	9.2%, 95% C.I.: -4.9%, 23.2%		
Historical vs Current	-3.0%, 95% C.I.: -17.3%, 11.3%		
Applicant Clinically Evaluable	148/162 (91.4%)	124/185 (67.0%)	38/54 (70.4%)
Ofloxacin vs Historical	24.3%, 95% C.I.: 15.7%, 32.9%		
Ofloxacin vs Current	21.0%, 95% C.I.: 6.8%, 35.1%		
Historical vs Current	-3.3%, 95% C.I.: -18.5%, 11.8%		
MO Clinically Evaluable	148/163 (90.8%)	124/185 (67.0%)	38/54 (70.4%)
Ofloxacin vs Historical	23.8%, 95% C.I.: 15.1%, 32.4%		
Ofloxacin vs Current	20.4%, 95% C.I.: 6.2%, 34.6%		
Historical vs Current	-3.3%, 95% C.I.: -18.5%, 11.8%		

TABLE A.6: STUDY PRT-007: OVERALL CLINICAL RESPONSES			
Clinical Response	Ofloxacin	Historical	Current
Intent-to-Treat	137/226 (60.6%)	187/309 (60.5%)	48/68 (70.6%)
Ofloxacin vs Historical	0.1%, 95% C.I.: -8.7%, 8.9%		
Ofloxacin vs Current	-10.0%, 95% C.I.: -23.5%, 3.6%		
Historical vs Current	-10.1%, 95% C.I.: -23.1%, 3.0%		
* Intent-to-Treat	135/224 (60.3%)	187/309 (60.5%)	47/67 (70.1%)
Ofloxacin vs Historical	-0.2%, 95% C.I.: -9.0%, 8.5%		
Ofloxacin vs Current	-9.9%, 95% C.I.: -23.5%, 3.8%		
Historical vs Current	-9.6%, 95% C.I.: -22.8%, 3.5%		
Clinically Evaluable	121/143 (84.6%)	140/218 (64.2%)	34/48 (70.8%)
Ofloxacin vs Historical	20.4%, 95% C.I.: 11.1%, 29.7%		
Ofloxacin vs Current	13.8%, 95% C.I.: -1.8%, 29.3%		
Historical vs Current	-6.6%, 95% C.I.: -22.2%, 9.0%		
* Clinically Evaluable	119/141 (84.4%)	140/218 (64.2%)	33/47 (70.2%)
Ofloxacin vs Historical	20.2%, 95% C.I.: 10.9%, 29.5%		
Ofloxacin vs Current	14.2%, 95% C.I.: -1.6%, 30.0%		
Historical vs Current	-6.0%, 95% C.I.: -21.8%, 9.8%		
* The subjects included only in the treatment group to which they were first assigned			

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