

- Had valid pathogen(s) isolated at Visit 1;
- Returned for Visit 3 between 8 hours after the last dose and Day 20;
- Had a successful culture obtained at Visit 3 and Visit 4 (provided appropriate specimen was available), or if no appropriate source was present and culture was not done at Visit 3 and Visit 4;
- Had a culture obtained in cases of clinical failure.

Medical Officer's Comment: *The Medical Officer agreed with the above criteria.*

Endpoint Response Definitions

Clinical Response of Ofloxacin Group

The definitions for clinical response at each visit and Overall were the same as for the ofloxacin-treated subjects in Protocol 008, found on pages 90-91 of this review.

Clinical Response of Historical and Current Practice Groups

The definition for clinical response used for these groups was the same as outlined for Protocol 007 on page 133 of this review.

Microbiological Response of Ofloxacin Group

The microbiologic response definitions used for the ofloxacin-treated group in this study were the same as those in Protocol 008, found on pages 91-93 of this review.

Medical Officer's Comment: *The Medical Officer agreed with the clinical and microbiologic response definitions used in this study.*

Statistical Considerations

Sample Size

The Applicant expected that at least 70% of the subjects treated with ofloxacin would have an Overall Clinical Response of cure. The Applicant hypothesized that if a standard therapy was available for this condition with a similar profile of effectiveness, then the number of clinically evaluable subjects for each treatment required to establish equivalence would have been 120 for 2-tailed alpha = .05, power = 80%, and zone of indifference = 15%. The Applicant assumed that if 5% of the subjects dropped out from the study before the first post-therapy visit, a sample size of 126 subjects per treatment group would be required.

Analyses Planned and Populations

-Analysis of Clinical Response

The primary analysis of interest, per the protocol, was to be the comparison of the Overall Clinical Cure rate of the clinically evaluable subjects of the ofloxacin group to the "Dry Ear" rate in the Historical Practice Group subjects with a follow-up visit.

-Populations

- **Ofloxacin Group**
In the ofloxacin group, the Applicant defined three different populations that were to be considered for various analyses:

- **Intent-to-Treat Population:** Included all subjects who received at least one dose of study drug.
- **Clinically Evaluable Population:** As previously defined
- **Microbiologically Evaluable Population:** As previously defined

- **Historical and Current Practice Groups**

These groups were considered as having 2 populations: all subjects (i.e., the ITT Population), and those who had an actual follow-up visit (i.e., the "Clinically Evaluable" Population).

Statistical Methods

For clinical response, the primary efficacy analysis was to be the comparison of the Overall Clinical Cure rate of the clinically-evaluable ofloxacin-treated subjects to the "Dry Ear" rate in the Historical Practice Group subjects with a follow-up visit. In addition, between-treatment group differences in Clinical Response among the ofloxacin, Historical Practice Group, and Current Practice Group were to be examined: for all Historical and Current Practice subjects; for Historical and Current Practice subjects who did not return for a follow-up visit; and for ofloxacin subjects in each of the clinically evaluable, microbiologically evaluable and intent-to-treat populations.

Medical Officer's Comment: -The use of Historical and Current Practice Groups was intended to provide a context for the interpretation of the results of an open-label study conducted in the absence of an approved comparator agent. For further information regarding the statistical analyses and methods, please see the review by Biostatistician, Dr. Joel Jiang.

Study Results

Evaluability and Demographics

-Evaluability

The Medical Officer did not exclude any of the thirty-five centers in this study from clinical or microbiological efficacy assessments.

The number of subjects in each group, per center, is summarized in the table below:

<u>Investigator (Center)</u>	<u>Number of Subjects at Each Center</u>		<u>Historical Practice</u> <u>Met Inc/Exc</u>	<u>Current Practice</u> <u>Met Inc/Exc</u>
	<u>Ofloxacin 0.5 mL b.i.d</u> <u>Enrolled</u>	<u>Met Inc/Exc</u>		
U.S. Centers				
Agro (602)	42	41	15	17
Goldberg (604)	8	7	5	1
Golshan (605)	0	0	0	0
Haddad (606)	1	1	0	0
Hirsch (607)	1	1	1	0
Huff (608)	0	0	0	1
Jahn (609)	1	1	0	0
Levine (610)	4	0	0	0
Schall (612)	2	2	6	3
Telisch (613)	7	7	10	7
Vrabec (614)	5	4	14	11
Wayman (615)	9	9	12	1
Greenberg (616)	3	2	8	0
Rosenthal (617)	8	8	6	0
McClellan (618)	0	0	0	0
Albery (640)	6	6	1	0
Biel (641)	6	5	15	0
Bolz (642)	1	0	1	1
Drake (643)	2	0	0	0
Fritsch (644)	0	0	0	0
Gamer (645)	10	9	10	0
Goldblatt (646)	1	1	0	0
Nechtman (647)	3	3	0	0
Larsen (649)	0	0	0	0
Nielsen (650)	6	5	12	0
Smith (651)	1	1	1	0
Wright (652)	11	11	11	0
Ziering (653)	0	0	0	0
Yee (654)	2	2	14	2
Tran (655)	0	0	0	0
Schenkel (656)	9	9	9	0
Love (657)	0	0	0	0
Bertino (658)	1	1	18	0
Latin American Centers				
Caballeros de Escobar (680)	27	27	26	10
Villeda (681)	30	30	25	9
Total	207	193	220	63

All 207 subjects received study medication at Visit 1, thereby constituting the Intent-to-Treat Population. The following table gives the range of treatment days the subjects received.

Number of Days on Treatment for Ofloxacin-Treated Intent-to-Treat Population

<u>Number of Days</u>	<u>All Centers</u>	<u>U.S. Centers</u>	<u>Latin American Centers</u>
<3	5 (2%)	5 (3%)	0
3-8	11 (5%)	10 (7%)	1 (2%)
9-13	10 (5%)	9 (6%)	1 (2%)
14-17	176 (85%)	121 (81%)	55 (97%)
>17	1 (1%)	1 (1%)	0
Missing	4 (2%)	4 (3%)	0
Total	207	150	57

The majority of subjects (85%), from all centers, received at least 14 days (a full course) of treatment, and the bulk of the remaining subjects (10%) received between 3 to 13 days of treatment. When separating the domestic and foreign sites, one sees that a higher percentage of subjects received 14-17 days of treatment at the Latin American sites (97%) than did those at U.S. sites (81%).

Medical Officer's Comment:

As shown in the table above, the Applicant composed the table such that the information delineates the results from U.S. centers, Latin American centers, as well as, the collective results from all centers. This was true for most of the tables presented in the Study Report for this protocol. Because of the large contribution of subjects from Latin American sites, the Medical Officer considers this breakdown of information useful and will follow the Applicant's format where applicable.

The following table summarizes the accountability of the 207 subjects enrolled in the ofloxacin group.

Subject Accountability for the Ofloxacin-Treated Subjects

<u>Parameter</u>	<u>All Centers</u>		<u>U.S. Centers</u>		<u>Latin American Centers</u>	
Number of Subjects Enrolled	207		150		57	
Received Drug	207	(100%)	150	(100%)	57	(100%)
Fulfilled Inclusion/Exclusion Criteria	193	(93%)	136	(91%)	57	(100%)
Visit 2 Procedures Completed	196	(95%)	140	(93%)	56	(98%)
Visit 3 Procedures Completed *	198	(96%)	142	(95%)	56	(98%)
Visit 4 Procedures Completed **	173	(84%)	119	(79%)	54	(95%)
Intent-to-Treat Population	207	(100%)	150	(100%)	57	(100%)
Clinically Evaluable Population	162	(78%)	108	(72%)	54	(95%)
Microbiologically Evaluable Population	99	(48%)	55	(37%)	44	(77%)

* Includes 7 subjects that completed Visit 3 procedures on their 2nd visit.

** Includes 1 subject that completed Visit 4 procedures on their 3rd visit.

Fourteen subjects, all of whom were from U.S. centers, did not fulfill the inclusion/exclusion criteria. Eleven subjects (207-196=11) did not have Visit 2 procedures completed, nine subjects (207-198=9) did not have Visit 3 procedures completed, and 34 subjects (207-173=34) did not have Visit 4 procedures completed. As noted above, the "Visit 3 Procedures" performed for some of the subjects did not necessarily correlate with the actual visit number. This typically was in the case of an early withdrawal and the subject had the Visit 3 procedures performed for study exit. There was one subject who had Visit 4 procedures done at the third actual visit because of early withdrawal from the study, otherwise the completion of Visit 4 procedures signified study completion.

Compared to the U.S. sites, the Latin American sites had a greater percentage of subjects who had Visit 4 procedures completed (95% vs. 79%), a greater percentage of clinically evaluable subjects (95% vs. 72%), and a much greater percentage of microbiologically evaluable subjects (77% vs. 37%).

The primary reasons for exclusion from the clinical and microbiologically evaluable populations are shown in the following table.

Primary Reasons for Exclusion from Ofloxacin-Treated Analyzed Populations

	All Centers	U.S. Centers	Latin American Centers
Total Number of Subjects Enrolled	207	150	57
Excluded from Intent-to-Treat	0	0	0
Total Intent-to-Treat Population	207 (100%)	150 (100%)	57 (100%)
Excluded from Clinically Evaluable:	45 (22%)	42 (28%)	3 (5%)
Did Not Meet Inclusion/Exclusion Criteria	14 (7%)	14 (9%)	0
Fungus Found	10 (5%)	10 (7%)	0
Protocol Non-Compliance	6 (3%)	6 (4%)	0
Took Prohibited Medication	3 (1%)	3 (2%)	0
No Post Baseline Response	2 (1%)	1 (1%)	1 (2%)
Discontinued for Other Reason	2 (1%)	1 (1%)	1 (2%)
Group A Streptococci Found	2 (1%)	2 (1%)	0
Not Assessed at Visit 4	2 (1%)	1 (1%)	1 (2%)
Lost to Follow-up	1 (1%)	1 (1%)	0
Bilateral Infection After Visit 1	1 (1%)	1 (1%)	0
Pre-existing Violation	1 (1%)	1 (1%)	0
Out of Visit 4 Window*	1 (1%)	1 (1%)	0
Total Clinically Evaluable Population	162 (78%)	108 (72%)	54 (95%)
Excluded from Microbiologically Evaluable:	63 (30%)	53 (35%)	10 (18%)
No Valid Baseline Pathogen	55 (27%)	45 (30%)	10 (18%)
Out of Visit 3 Window*	5 (2%)	5 (3%)	0
Source Present but Culture Not Done	3 (1%)	3 (2%)	0
Total Microbiologically Evaluable Population	99 (48%)	55 (37%)	44 (77%)

* Visit 3 window is from 8 hours after last dose to Day 20, Visit 4 window is Day 21-28

The two most common reasons for excluding subjects from the clinical evaluability were: did not meet inclusion/exclusion criteria (14 subjects), and fungus (with no identifiable bacterial pathogen) found (10 subjects). A much higher percentage of subjects from U.S. sites (28%) were excluded from the clinically evaluable population than from Latin American sites (18%). The most common primary reason for this exclusion from microbiological evaluability was the lack of a valid pathogen being isolated from the target ear at Baseline.

There were 220 subjects who met the inclusion/exclusion criteria for the Historical Practice Group and 63 subjects who met the inclusion/exclusion criteria for the Current Practice Group. The follow-up of these subjects is outlined in the following table.

Summary of Follow-Up Experience for the Historical and Current Practice Arms of Protocol 006-CSOM		
	Historical Practice Group	Current Practice Group
Fulfilled Inclusion/Exclusion Criteria	220	63
Had Follow-up Visit	185/220 (84%)	54/63 (86%)
Had Attempted Phone Contact	35/220 (16%)	9/63 (14%)
-Successful Phone Contact	19/35 (54%) (9% of 220)	7/9 (78%) (11% of 63)
Remembered Outcome	19/19	7/7
Did Not Remember Outcome	0/19	0/7
-Could Not Be Reached	16/35 (46%) (7% of 220)	2/9 (22%) (3% of 63)
Could Not Be Reached therefore Outcome of a "Wet Ear" (Failure) Assigned per Protocol without actual documentation/recollection of such	16/220 (7% of 220)	2/63 (3% of 63)
Had Follow-up Visit so Considered Clinically Evaluable Population	185	54

Of the 220 subjects in the Historical Practice Group, 185 (84%) had a recorded follow-up visit, and 54 of 63 subjects (86%) in the Current Practice Group did. Attempts were made to contact all other subjects by telephone (35 in HP Group and 9 in the CP Group). Successful telephone contact was made with 19/35 in the HP Group and 7/9 in the CP Group. All 19 of the subjects in the HP Group and all 7 subjects in the CP Group who were reached by telephone recalled the outcome of the episode treated. The other 16/35 in the HP Group and the other 2/9 in the CP Group could not be reached by telephone. Therefore, the subjects who could not be reached by telephone were the only subjects who had an outcome that was assigned per protocol without the actual recollection or documentation of such. For these subjects the outcome was considered to be "wet ear" (failure). Thus, only 16/220 (7%) of the Historical Practice Group, and only 2/63 (3%) of the Current Practice Group subjects were assigned the outcome of "failure" without actual documentation of such. No subjects in either group were given an assigned outcome of "dry ear" (cure) without actual recollection or documentation of such.

However, the primary efficacy variable in this study was to be the comparison clinical outcome of the clinically evaluable subjects in the ofloxacin arm versus the outcome of the subjects in the Historical Practice Group who had an actual follow-up visit (clinically evaluated). By only considering subjects with a follow-up visit, all subjects in the comparator groups (HP & CP) would have a documented clinical outcome, not an assigned outcome.

The Medical Officer changed the evaluability status of only one subject in the ofloxacin group. This was Subject (from a U.S. site), whom the Applicant excluded from clinical and microbiological efficacy analyses because of the development of "Bilateral Infection After Visit 1." In this case, the Medical Officer considered the subject to be clinically evaluable because the target ear had persistent otorrhea throughout the study, and the Investigator had considered the subject a clinical failure. The subject was not microbiologically evaluable because there was no pathogen isolated from the target ear at Baseline. Therefore, the Medical Officer's Clinically Evaluable Population of ofloxacin-treated subjects differs from that of the Applicant by one additional evaluable clinical failure, but the Medical Officer's Microbiologically Evaluable Population is the same as that of the Applicant. The Medical Officer did not change the status of

any subject in the Historical or Current Practice Groups.

Because the Medical Officer's Clinically Evaluable Population only differs from that of the Applicant by one subject and the Microbiologically Evaluable Population and the HP and CP Groups are the same, the Medical Officer will essentially accept the Applicant's data as presented for everything but the Overall Clinical Assessment.

In total, there are 163 ofloxacin-treated subjects in the Medical Officer's Clinically Evaluable Population, 99 in the Microbiologically Evaluable Population, and 185 Historical Practice and 54 Current Practice Group subjects with a follow-up visit.

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ON ORIGINAL**

The following table summarizes the Medical Officer's Evaluability per center.

PRT-006 Medical Officer's Evaluable Subjects per Center				
<u>Investigator (Center)</u>	<u>Ofloxacin Group</u>		<u>Historical Practice Group</u>	<u>Current Practice Group</u>
	<u>Clinically Eval.</u>	<u>Microbiologically Eval.</u>	<u>Subjects with a Follow-up Visit</u>	<u>Subjects with a Follow-up Visit</u>
U.S. Centers				
Agro (602)	34	23	13	15
Goldberg (604)	6	2	3	1
Gotshan (605)	0	0	0	0
Haddad (606)	0	0	0	0
Hirsch (607)	1	1	1	0
Huff (608)	0	0	0	1
Jahn (609)	0	0	0	0
Levine (610)	0	0	0	0
Schall (612)	1	1	4	2
Telischi (613)	5	2	9	4
Vrabec (614)	4	3	14	8
Wayman (615)	8	4	12	1
Greenberg (616)	2	2	6	0
Rosenthal (617)	5	3	6	0
McClellan (618)	0	0	0	0
Albery (640)	5	1	0	0
Biel (641)	3	2	10	0
Bolz (642)	0	0	1	1
Drake (643)	0	0	0	0
Fritsch (644)	0	0	0	0
Gamer (645)	8	2	5	0
Goldblatt (646)	1	1	0	0
Nechtman (647)	3	3	0	0
Larsen (649)	0	0	0	0
Nielsen (650)	3	2	7	0
Smith (651)	1	1	1	0
Wright (652)	10	1	8	0
Ziering (653)	0	0	0	0
Yee (654)	2	1	12	2
Tran (655)	0	0	0	0
Schenkel (656)	7	0	9	0
Love (657)	0	0	0	0
Bertino (658)	0	0	14	0
Latin American Centers				
Caballeros de Escobar (680)	25	24	26	10
Villeda (681)	22	20	24	9
Total	163	99	185	54

-Demographics

The demographic characteristics of the ofloxacin group were compared to those of the other two treatment groups for the Intent-to-Treat and Clinically Evaluable Populations for all centers, the U.S. centers, and for the Latin American centers. The demographics of the Microbiologically Evaluable Population of the ofloxacin-treated subjects were presented for all centers, the U.S. centers, and the Latin American centers. No microbiological data were collected for the HP and CP groups.

The following table summarizes the demographic data for the Intent-to-Treat Population of the ofloxacin group compared to the Historical Practice and Current Practice Groups for all centers.

**Summary of Demographic Data for the Ofloxacin (Intent-to-Treat Population),
 Historical Practice, and Current Practice Groups (All Centers)**

	Ofloxacin	Historical	Current	P-value ¹	P-value ²	P-value ³
Number of Subjects	207	220	63			
Age (yrs.)						
Mean ± S.D.	44.4 ± 21.1	45.9 ± 21.5	49.4 ± 21.1	0.680	0.069	0.121
Age Group (# subjects)						
2-12	7 (3%)	8 (4%)	0	0.946	0.229	0.430
13-16	14 (7%)	15 (7%)	3 (5%)			
17-45	94 (45%)	89 (41%)	24 (38%)			
46-65	47 (23%)	56 (26%)	20 (32%)			
>65	45 (22%)	52 (24%)	16 (25%)			
Gender (# subjects)						
Male	113 (55%)	108 (49%)	26 (41%)	0.285	0.064	0.251
Female	94 (45%)	112 (51%)	37 (59%)			
Race (# subjects)						
Caucasian	119 (58%)					
Hispanic	71 (34%)					
Asian	9 (4%)					
Native American/Alaskan	4 (2%)					
African American	2 (1%)					
Other	2 (1%)					

Chi-square test was used to compare age group and gender. Age was compared using 1-way ANOVA test.
 1 Ofloxacin v. Historical, 2 Ofloxacin v. Current, 3 Historical v. Current

The ofloxacin-treated subjects in the Intent-to-Treat Population were not statistically different from the Historical Practice and Current Practice Groups with respect to demographic characteristics for all centers. The mean age of the ofloxacin-treated subjects was 44.4 years, 45.9 years for the subjects in the HP Group, and 49.4 years for subjects in the CP Group. In all groups, the majority of the subjects were adults age 17 years and older. Race was presented only for the ofloxacin group; thus, no between-group comparison was made.

Medical Officer's Comment: *The Applicant also examined the demographic characteristics of the Intent-to-Treat Population of ofloxacin-treated subjects, HP Group, and CP Group subjects enrolled at investigational centers in the United States compared to those enrolled at Latin American sites. While the three treatment groups were balanced within each geographic region, the mean age of the Latin American subjects was younger (range years) than for the respective groups in the U.S. The mean ages of the U.S. subject groups more closely resembled those of the entire Intent-to-Treat Population. The mean ages of the Latin American groups ranged from years younger than those of the entire ITT Population. Also, the race distributions differed between geographic regions because all subjects from Latin American sites were Hispanic.*

The Applicant made similar comparisons of the demographics of just the clinically evaluable subjects.

Medical Officer's Comment: *The Applicant compared the clinically evaluable ofloxacin-treated subjects to all of the subjects, not just those with a follow-up visit, in the Historical and Current Practice Groups. The Medical Officer considered the comparison of clinically evaluable ofloxacin-treated subjects to the Historical and Current Practice Group subjects who had a follow-up visit more appropriate. However, the Medical Officer only compared the information for all centers, not for centers divided by geographic region.*

For all centers in the Medical Officer's Clinically Evaluable Populations, there were no statistically significant differences between the three treatment groups for the demographic features of age, age distribution above and below 65 years, and gender. The mean ages of subjects in the respective treatment arms of the MO's Clinically Evaluable Populations resemble those of the ITT Population. Race information was collected only for subjects in the ofloxacin group, so no between-group comparison can be made.)

Microbiological data ~~was~~ collected only for subjects in the ofloxacin group. The Medical Officer's Microbiologically Evaluable Population is the same as the Applicant's Microbiologically Evaluable Population. As expected, considering the microbiologically evaluable subjects are a subset of the clinically evaluable subjects, the mean age of the microbiologically evaluable ofloxacin-treated subjects from the U.S. centers (51.6 years) was older than the mean age of the Latin American subjects (33.6 years). But, the mean age of all microbiologically evaluable subjects (43.6 years) was similar to the mean age of ofloxacin-treated subjects in the ITT Population (44.4 years).

As noted previously, the Latin American centers had a higher percentage of subjects who were microbiologically evaluable than did the U.S. centers. Because of this, when looking at all centers, the overall percentage of Hispanic subjects in this particular population (49%) is higher than that of both the Intent-to-Treat Population (34%) and the Clinically Evaluable Population (39%).

Other baseline and target ear characteristics were recorded for subjects in the ofloxacin treatment group, but not for subjects in the Historical Practice or Current Practice Groups. Recorded were: the target ear, laterality of infection, duration of perforation, duration of drainage, number of baseline organisms, and the number of valid pathogens.

Medical Officer's Comment: *Ideally this information should have been collected for subjects in the Historical and Current Practice groups as well to ensure the comparison of similar conditions of disease accross treatment groups. In this open-label study, the use of the Historical and Current Practice Groups was to provide a context for evaluating the response of subjects in the ofloxacin treatment group.*

**APPEARS THIS WAY
ON ORIGINAL**

The following table summarizes the Baseline and Target Ear characteristics for the Intent-to-Treat Population of ofloxacin- treated subjects at all centers.

Summary of Baseline and Target Ear Characteristics for the Ofloxacin-Treated Intent-to-Treat Population (All Centers)

<u>Characteristic</u>	<u>Characteristic</u>	<u>Characteristic</u>
Number of Subjects 207	<u>Drainage (Days)</u>	<u>Valid pathogens</u>
<u>Target ear</u>	Mean ± S.D. 96.5 ± 194.8	None 80 (39%)
Right 110 (53%)	Median 28.0	One 85 (41%)
Left 97 (47%)	<u>Organisms</u>	Two 26 (13%)
<u>Infection</u>	None 18 (9%)	Three or more 15 (7%)
Unilateral 202 (98%)	One 75 (36%)	
Bilateral 5 (2%)	Two 61 (30%)	
<u>Perforation (Days)</u>	Three 29 (14%)	
Mean ± S.D. 1425 ± 2281.0	Four or more 23 (11%)	
Median 776		

Medical Officer's Comment: The Medical Officer did not reproduce the tables for these characteristics delineated by U.S. and Latin American Centers. For the Intent-to-Treat Population, the mean and median duration of drainage was significantly longer in Latin American subjects (227.5 days and 114.0 days) than U.S. subjects (53.8 days and 13.0 days), respectively. Also, the percentage of U.S. subjects with no valid pathogen (46%) was significantly higher than for Latin American subjects (21%). Overall, in the Intent-to-Treat Population the vast majority of subjects, 97% at U.S. sites and 100% at the Latin American sites, had a unilateral infection at Baseline.

For both the Clinically Evaluable and Microbiologically Evaluable Populations, the Applicant examined the Baseline and Target Ear characteristics for all centers, U.S. only sites, and Latin American sites. The Medical Officer did not reproduce these tables in this review, but the salient points are described in the MO Comment below.

Medical Officer's Comment:

• **Clinically Evaluable Population**

- The Clinically Evaluable Population mirrors the Intent-to-Treat Population inasmuch as, at the Latin American centers the subjects had a longer mean and median duration of drainage (214.3 and 100.0 days, respectively) than the U.S. subjects (50.5 and 10.0 days, respectively).
- More Latin American subjects had at least one valid Baseline pathogen (82%) than did the U.S. subjects (58%).
- In the clinically evaluable subjects at both the U.S. and Latin American sites, the infections were unilateral in the overwhelming majority of the subjects.

• **Microbiologically Evaluable Population**

- In the Microbiologically Evaluable Population, Latin American subjects had significantly longer mean and median durations of drainage (224.9 and 100 days, respectively) than did the U.S. subjects (59.4 and 13 days, respectively).
- A significantly higher percentage (23%) of Latin American subjects had three or more valid pathogens than did U.S. subjects (4%).

Efficacy Results

Clinical Efficacy

As in Protocol 007, the primary efficacy variable was the Overall Clinical Response for the clinically evaluable ofloxacin-treated subjects versus the clinical outcome of Historical Practice Group subjects who had a follow-up visit. All other efficacy measures were to be considered secondary.

The Applicant presented outlines of the clinical responses for each post-baseline visit for the Intent-to-Treat, and Clinically Evaluable Populations for all centers. The Medical Officer did not reproduce these in this review, but the MO agreed with the assessments. The subjects who had indeterminant outcomes or were clinical failures were carried forward appropriately.

For the purpose of comparing the ofloxacin group to the Historical Practice and Current Practice Groups, each ofloxacin-treated subject was assessed as having "Dry Ear" when the Overall Clinical Response of the subject was cure. Otherwise, the ofloxacin-treated subject was assessed as having "Not Dry Ear."

The following table summarizes the Overall Clinical Response for the Intent-to-Treat Population and the Clinically Evaluable subjects (those with follow-up visit in the HP and CP groups) for each treatment arm.

Protocol 006-CSOM			
Comparison of Clinical Response for the Medical Officer's Ofloxacin, Historical Practice, and Current Practice Groups			
	Ofloxacin-Treated	Historical Practice	Current Practice
All Subjects	207	220	63
(Intent-to-Treat)			
Dry Ear	157 (76%)	140 (64%)	42 (67%)
Not Dry Ear	50 (24%)	80 (36%)	21 (33%)
Total	207	220	63
<u>Subjects w/ F/U Visit</u>	163	185	54
(Clinically Evaluable)			
Dry Ear	148 (91%)	124 (67%)	38 (70%)
Not Dry Ear	15 (9%)	61 (33%)	16 (30%)
Total	163	185	54

In both the Intent-to-Treat Population and the Clinically Evaluable Population (Subjects with Follow-up Visit), the ofloxacin-treated subjects had higher cure rates than for the Historical and Current Practice Groups.

The following table outlines success rates and the 95% confidence intervals for the comparisons of the difference in success ("dry ear") rates for the various populations and treatment groups. The primary efficacy parameter of the response of clinically evaluable ofloxacin-treated subjects vs. historical practice group subjects with a follow-up visit (i.e., clinically evaluable) is shown in bold print.

Protocol 006- Chronic Suppurative Otitis Media Clinical Response Rates for the Medical Officer's Intent-to-Treat and Clinically Evaluable Populations		
	<u>Intent to Treat Population</u>	<u>Clinically Evaluable Population</u>
Ofloxacin Success Rate ("Dry Ear")	157/207 (76%)	148/163 (91%)
Historical Practice Success Rate ("Dry Ear")	140/220 (64%)	124/185 (67%)
Current Practice Success Rate ("Dry Ear")	42/63 (67%)	38/54 (70%)
Ofloxacin vs. Historical Practice by "Dry Ear" for the Intent to Treat Population	12%, 95% C.I. (3.1%, 21.3%)	
Ofloxacin vs. Current Practice by "Dry Ear" for the Intent to Treat Population	9%, 95% C.I. (-4.9%, 23.2%)	
Historical vs. Current Practice by "Dry Ear" for the Intent-to-Treat Population	-3%, 95% C.I. (-17.3%, 11.3%)	
Ofloxacin vs. Historical Practice by "Dry Ear" for the Clinically Evaluable Population	24%, 95% C.I. (15.1%, 32.4%)	
Ofloxacin vs. Current Practice by "Dry Ear" for the Clinically Evaluable Population	21%, 95% C.I. (6.2%, 34.6%)	
Historical vs. Current Practice by "Dry Ear" for the Clinically Evaluable Population	-3%, 95% C.I. (-18.5%, 11.8%)	

In the Intent-to-Treat Population, the 95% confidence interval (3.1%, 21.3%) for the difference in cure rates between the ofloxacin group and the historical practice group showed superiority of ofloxacin. Based on the 95% confidence intervals, the ofloxacin group showed equivalence to the Current Practice group, and the Historical Practice group showed equivalence to the Current Practice group with respect to the difference in clinical cure rates between these groups.

In the Clinically Evaluable Population, the 95% confidence interval (15.1%, 32.4%) showed ofloxacin to be therapeutically superior to the treatments employed in the Historical Practice Group. The 95% confidence interval (6.2%, 34.6%) showed ofloxacin to be therapeutically superior to the treatments employed in the Current Practice Group. The 95% confidence interval (-18.5%, 11.8%) for the difference in cure rates between the Historical Practice Group and Current Practice Group showed therapeutic equivalence between the two.

Microbiological Efficacy

The microbiological results were reported by subject and by pathogen, as well as an Overall Clinical/Microbiological Assessment for microbiologically evaluable subjects in the ofloxacin treatment group. No microbiological data were collected for subjects in the Historical or Current Practice Groups. The Medical Officer's Microbiologically Evaluable Population is the same as the Applicant's.

Microbiological Response by Subject

The Overall microbiological response by subject was derived from the microbiological response of the subjects at Visits 3 and 4. Ninety-nine subjects (55 from U.S. sites and 44 from Latin American sites) were microbiologically evaluable. The following table summarizes the per subject microbiological and clinical responses at Visit 3, Visit 4, and Overall.

Microbiological and Clinical Response by Subject per Visits 3 and 4 and Overall for the Ofloxacin-Treated Microbiologically Evaluable Population (All Centers)			
	<u>Visit 3</u>	<u>Visit 4</u>	<u>Overall</u>
Number Evaluated	n=99	n=96	n=99
<u>Response</u>			
Eradication	99 (100%)	96 (100%)	99 (100%)
Clinical Cure with Eradication	N/A*	93/96 (96.9%)	93/99 (93.9%)
Clinical Failure with Eradication	3/99 (3.0%)	3/96 (3.1%)	6/99 (6.1%)

*An valid assessment of "clinical cure" can not be made until the Test-of-Cure Visit (Visit 4).

At Visit 3, "Eradication" was the per subject response for the pathogens in 100% (99/99) of the subjects. However, three of these subjects (Subjects _____) were clinical failures, despite the documented eradication of the baseline pathogens, and did not return for Visit 4. Eradication of baseline pathogens was seen in all of the 96 remaining subjects who presented for Visit 4. However, at Visit 4 three of the 96 subjects (Subjects _____) were clinical failures despite eradication of the baseline pathogens. Thus there were six subjects in the Microbiologically Evaluable Population who were clinical failures despite the documented eradication of the baseline pathogens.

There were no were microbiologically evaluable clinical failures who had documented persistence of the pathogens.

The six subjects who were clinical failures but had documented eradication of the baseline pathogens are listed below by subject number and baseline pathogen(s).

<u>Subject Number</u>	<u>Baseline Pathogen</u>
	Beta-lactamase negative <i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i>
	<i>Staphylococcus aureus</i> <i>Enterococcus faecalis</i> <i>Staphylococcus aureus</i>

Pseudomonas aeruginosa
Staphylococcus aureus

Medical Officer's Comment:

There was a total of 15 clinical failures (all from U.S. sites) in the Medical Officer's Clinically Evaluable Population. Six of these 15 were in the Microbiologically Evaluable Population, and they are the same six subjects presented above. Of the nine other subjects who were clinical failures, eight subjects were not microbiologically evaluable because they did not have a pathogen isolated at Baseline. One subject (Subject who failed had a baseline pathogen (*S. aureus*)-isolated, but was not microbiologically evaluable because a repeat culture was not done at Visit 4.

Microbiological Response by Pathogen

In the Microbiologically Evaluable Population of ofloxacin-treated subjects, there were a total of 145 isolates of 26 valid baseline pathogens isolated from the target ears of the 99 subjects. The Overall Microbiological Response and the Overall Clinical Response by pathogen in the table below:

Overall Microbiological Response and Overall Clinical Response by Pathogen for the Ofloxacin-Treated Microbiologically Evaluable Population (All Centers)

Pathogen	Overall Microbiological Response		Overall Clinical Response		
	Eradication	Total	Cure	Failure	Total
<i>Staphylococcus aureus</i>	40 (100%)	40	36 (90%)	4 (10%)	40
<i>Pseudomonas aeruginosa</i>	39 (100%)	39	38 (97%)	1 (3%)	39
<i>Proteus mirabilis</i>	15 (100%)	15	15 (100%)	0	15
<i>Enterococcus faecalis</i>	7 (100%)	7	6 (86%)	1 (14%)	7
<i>Enterobacter cloacae</i>	4 (100%)	4	4 (100%)	0	4
<i>Klebsiella oxytoca</i>	4 (100%)	4	4 (100%)	0	4
<i>Serratia marcescens</i>	4 (100%)	4	4 (100%)	0	4
<i>Alcaligenes faecalis</i>	3 (100%)	3	3 (100%)	0	3
<i>Citrobacter freundii</i>	3 (100%)	3	3 (100%)	0	3
<i>Morganella morganii</i>	3 (100%)	3	3 (100%)	0	3
<i>Citrobacter diversus</i>	2 (100%)	2	2 (100%)	0	2
<i>Haemophilus influenzae</i>	2 (100%)	2	1 (50%)	1 (50%)	2
<i>Klebsiella ozaenae</i>	2 (100%)	2	2 (100%)	0	2
<i>Klebsiella pneumoniae</i>	2 (100%)	2	2 (100%)	0	2
<i>Proteus vulgaris</i>	2 (100%)	2	2 (100%)	0	2
<i>Providencia rettgeri</i>	2 (100%)	2	2 (100%)	0	2
<i>Streptococcus pneumoniae</i>	2 (100%)	2	2 (100%)	0	2
<i>A. calcoaceticus</i> <i>V. anitratus</i>	1 (100%)	1	1 (100%)	0	1
<i>Acinetobacter junii</i>	1 (100%)	1	1 (100%)	0	1
<i>Alcaligenes species</i>	1 (100%)	1	1 (100%)	0	1
<i>Alcaligenes xylosoxidans</i>	1 (100%)	1	1 (100%)	0	1
<i>Enterobacter aerogenes</i>	1 (100%)	1	1 (100%)	0	1
<i>Escherichia coli</i>	1 (100%)	1	1 (100%)	0	1
<i>Proteus penneri</i>	1 (100%)	1	1 (100%)	0	1
<i>Pseudomonas fluorescens</i>	1 (100%)	1	1 (100%)	0	1
<i>Vibrio alginolyticus</i>	1 (100%)	1	1 (100%)	0	1
Total	145	145	138	7	145

Medical Officer's Comment: There were 7 isolates of baseline pathogens from the six microbiologically evaluable subjects who failed clinically. As reviewed above, these 7 isolates were actually documented to be eradicated, but in the table above the overall clinical outcome is correlated to the identity, not the outcome per se, of the pathogen isolated at baseline. These six clinical failures were all from U.S. sites.

Overall Clinical/Microbiological Response

The Overall Clinical/Microbiological Response was a success if the subject had an Overall Microbiological Response of eradication and an Overall Clinical Response of cure. All other subjects were to be given the Overall Clinical/Microbiological Response of failure. The following table summarizes the clinical and microbiological responses for subjects at all centers, U.S. Centers, and Latin American Centers:

Clinical Response by Microbiological Response for the Ofloxacin-Treated Microbiologically Evaluable Population

Visit	Clinical Response	Microbiological Response		
		All Centers	U.S. Centers	Latin American Centers
3	Clinical Improvement	95 (96%)	51 (93%)	44 (100%)
	No Clinical Change	1 (1%)	1 (2%)	0
	Clinical Failure	3 (3%)	3 (6%)	0
4	Clinical Cure	93 (97%)	49 (94%)	44 (100%)
	Clinical Failure	3 (3%)	3 (6%)	0
Overall	Cure	93 (94%)	49 (89%)	44 (100%)
	Failure	6 (6%)	6 (11%)	0

In this study, the Microbiologically Evaluable Population had only six subjects who did not have a clinical response of cure, but all subjects had a microbiological response of eradication. Therefore, only 6/99 (6%) subjects in the Microbiologically Evaluable Population had an Overall Clinical/Microbiological Response of failure. The Overall Clinical/Microbiological success rate was 93/99 (94%).

Response Based on Ofloxacin Susceptibility of Pathogen

NCCLS guidelines were used to determine the susceptibility of each pathogen; however, the relevance of these guidelines to topical applications is unknown. For subjects in the ofloxacin-treated group, a pathogen was considered resistant if the MIC value of ofloxacin was greater than 4 µg/mL, intermediate if the MIC value was equal to 4 µg/mL, and sensitive if the MIC value was less than 4 µg/mL. All other pathogens were to be considered sensitive.

The following table outlines the correlation of the Overall Clinical Response by pathogen sensitivity to ofloxacin for the 145 valid Baseline pathogens isolated from the 99 subjects in the Microbiologically Evaluable Population.

Overall Clinical Response by Pathogen Sensitivity for the Ofloxacin-Treated Microbiologically Evaluable Population

Valid Baseline Pathogen	Overall Clinical Response		
	Cure	Failure	Total
Sensitive	124 (95%)	7 (5%)	131
Intermediate	7 (100%)	0	7
Resistant	6 (100%)	0	6
Acquired Resistance	1 (100%)	0	1

Note: Counts by pathogen

Of the 145 valid pathogens isolated at Baseline, 131 (90.3%) were considered to be sensitive to ofloxacin. Approximately 95% (124/131) of sensitive pathogens isolated at Baseline came from subjects with an Overall Clinical Response of cure, and approximately 5% (7/131) of the sensitive

pathogens isolated at Baseline were found in subjects who were clinical failures. There was a total of 14 pathogens that had intermediate, resistant, or acquired resistance sensitivity patterns to ofloxacin.

Of the seven sensitive pathogens that were isolated at Baseline from six subjects who were clinical failures, all 7 isolates were eradicated. These subjects were listed in the "Microbiological Response by Subject" section above, but are summarized by pathogen in the following table:

**Sensitive Pathogens Isolated at Baseline from
 Ofloxacin-Treated Subjects who were Clinical Failures**

Pathogen	Count	Subjects	Eradicated
<i>Staphylococcus aureus</i>	4		4
<i>Pseudomonas aeruginosa</i>	2		2
<i>Haemophilus influenzae</i>	1		1
<i>Enterococcus faecalis</i>	1		1
Total	7		7

While all Baseline pathogens were eradicated, all of these subjects did have some growth on their final culture. But, none of the organisms on the final culture were considered valid pathogens. It is worth noting that five of the six subjects had 1+ to 2+ growth of fungi on their final culture. Subject who was the only clinical failure to have had two Baseline pathogens (*S. aureus* and *H. influenzae*), had 2+ growth of *Candida albicans* on the final culture. Subject had 2+ *C. albicans*. Subject had 1+ *Aspergillus niger*. Subject had 1+ *C. parapsilosis*, and Subject had 2+ *C. parapsilosis*. Subject was the only clinical failure who did not have a fungus isolated on the final culture. This subject had 1+ growth of *E. coli* and 1+ growth of coagulase negative staphylococcus species isolated at Visit 4.

The following table outlines the fourteen pathogens, of the 145 total pathogens isolated at Baseline, that were found to have intermediate ofloxacin sensitivity, to be resistant, or to have acquired resistance during the study.

**Intermediate Sensitive and Resistant Pathogens Isolated at Baseline and
 Pathogens that Acquired Resistance During the Study**

	Count	Subject (MIC)	Clin Resp	Eradicated
Pathogens with Intermediate Sensitivity				
<i>Pseudomonas aeruginosa</i>	5	(4 µg/mL)	Cure	Yes
		(4 µg/mL)	Cure	Yes
		(4 µg/mL)	Cure	Yes
		(4 µg/mL)	Cure	Yes
		(4 µg/mL)	Cure	Yes
<i>Enterococcus faecalis</i>	1	(4 µg/mL)	Cure	Yes
<i>Streptococcus pneumoniae</i>	1	(4 µg/mL)	Cure	Yes
Resistant Pathogens				
<i>Pseudomonas aeruginosa</i>	2	(16 µg/mL)	Cure	Yes
		(16 µg/mL)	Cure	Yes
<i>Enterococcus faecalis</i>	2	(>32 µg/mL)	Cure	Yes
		(8 µg/mL)	Cure	Yes
<i>Staphylococcus aureus</i>	1	(32 µg/mL)	Cure	Yes
<i>Alcaligenes xylosoxidans</i>	1	(16 µg/mL)	Cure	Yes
Pathogens that Acquired Resistance				
<i>Pseudomonas aeruginosa</i>	1	(4 µg/mL at Baseline) (8 µg/mL at Visit 2)	Cure	Yes

*A one dilution change is within the error of the method.

Seven subjects had pathogens with intermediate sensitivity at Baseline, and six subjects had Baseline pathogens that were resistant to ofloxacin. All of these pathogens were eradicated and the subjects were cured.

One subject, Subject [redacted] had a *Pseudomonas aeruginosa* isolate that had intermediate resistance at Baseline, but at Visit 2 had an MIC of 8 µg/mL which was considered resistant. However, it should be noted that at Visit 2 the growth index was only 1+ and this was not considered a valid pathogen at the time it was isolated. This subject was a clinical cure.

Beta-lactamase Testing of *H. influenzae* isolates

There were only two isolates of *H. influenzae* from subjects in the microbiologically evaluable population. Beta-lactamase testing by the chromogenic cephalosporin method was performed for these isolates. Both were Beta lactamase negative. The results of the test along with the Overall Clinical Response of subjects is presented in the table below.

Overall Clinical Response by Beta-Lactamase Result of <i>Haemophilus influenzae</i> isolated from the Target Ear for the Ofloxacin-Treated Microbiologically Evaluable Population							
Centers	Pathogen	Negative Result			Positive Result		
		Cure	Failure	Total	Cure	Failure	Total
All Centers	<i>H. influenzae</i>	1 (50%)	1 (50%)	2	0	0	0
U.S.	<i>H. influenzae</i>	0	1 (100%)	1	0	0	0
Latin American	<i>H. influenzae</i>	1 (100%)	0	1	0	0	0

One isolate was from a 24 year old U.S. subject [redacted] and one was from a 12 year old Latin American subject [redacted]. As previously noted, the U.S. subject, Subject [redacted] was a clinical failure, but the *Haemophilus influenzae* isolate was eradicated. The Latin American subject was a clinical cure.

Further Susceptibility Testing of *Streptococcus pneumoniae* isolates

There were only two Baseline isolates of *S. pneumoniae* from two subjects in the microbiologically evaluable population. One was from a U.S. subject, Subject [redacted] age 13 and one was from a Latin American subject, Subject [redacted] age 12. These isolates were also tested for susceptibility to penicillin and trimethoprim/sulfamethoxazole (TMP/SMZ). Both isolates were sensitive to penicillin. The isolate from the Latin American subject was sensitive to TMP/SMZ, but the one from the U.S. subject was resistant to TMP/SMZ. Both subjects were clinical cures.

Medical Officer's Comment:

In this study there were numerous isolates of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*, but very few *Haemophilus influenzae* and *Streptococcus pneumoniae*. The fact that there were very few isolates of *Haemophilus influenzae* and *Streptococcus pneumoniae* in this study is consistent with the spectrum of microorganisms associated with Chronic Suppurative Otitis Media in adolescents and adults, as opposed to that associated Acute Otitis Media in children with or without tympanostomy tubes.

In both CSOM in with adults with a perforated tympanic membrane and Acute Otitis Media in children with tympanostomy tubes, infections can arise as a result of pathogens gaining entry to the middle ear from either the pharynx via the eustachian tube or from the external auditory canal through the perforation or the tube. However, irrespective of the presence of a tympanostomy tube, young children are more prone to infections due to the respiratory (pharyngeal) pathogens because the eustachian tube is virtually horizontal which favors reflux of secretions from the pharynx. With growth and development, the eustachian tube becomes more vertical and reflux is considerably less common. The pathogens in children over the age of six years who have tympanostomy tubes closely resemble those found in adults and adolescents with perforated tympanic membranes, with *S. aureus* and *P. aeruginosa* the most typically isolated pathogens.

SUMMARY OF CLINICAL AND MICROBIOLOGICAL EFFICACY-PRT006

Summary of Clinical Efficacy

Protocol 006- Chronic Suppurative Otitis Media Clinical Response Rates for the Medical Officer's Intent-to-Treat and Clinically Evaluable Populations		
	Intent to Treat Population	Clinically Evaluable Population
Ofloxacin Success Rate ("Dry Ear")	157/207 (76%)	148/163 (91%)
Historical Practice Success Rate ("Dry Ear")	140/220 (64%)	124/185 (67%)
Current Practice Success Rate ("Dry Ear")	42/63 (67%)	38/54 (70%)
Ofloxacin vs. Historical Practice by "Dry Ear" for the Clinically Evaluable Population	24%, 95% C.I. (15.1%, 32.4%)	

Summary of Microbiological Efficacy

The Medical Officer did not make any changes to the Microbiological data as presented by the Applicant. Microbiological data were only collected for the ofloxacin group. The Microbiologically Evaluable Population consisted of 99 subjects from whose target ears were collected 145 isolates of 26 valid baseline pathogens.

• Per Subject Response

On a per subject basis, eradication occurred in all 99 subjects (100%). (But there were six subjects who were clinical failures despite the documented eradication of all baseline pathogens from these six subjects.)

• Per Pathogen Response (selected baseline pathogens)

Overall Clinical/Microbiological Response per Selected Baseline Pathogens in the Microbiologically Evaluable Population of Ofloxacin-treated Subjects-PRT006	
<i>Staphylococcus aureus</i>	36/40 (90%)
<i>Pseudomonas aeruginosa</i>	38/39 (97%)
<i>Proteus mirabilis</i>	15/15 (100%)
<i>Enterococcus faecalis</i>	6/7 (86%)
<i>Enterobacter cloacae</i>	4/4 (100%)
<i>Klebsiella pneumoniae</i>	2/2 (100%)

• Overall Clinical/Microbiological Response (all baseline pathogens)

The Overall Clinical/Microbiological Success rate for ofloxacin was 94% (93/99.)

Safety Analyses-PRT006

The safety data were collected, and analyses performed, for only the ofloxacin-treated subjects. Analyses were performed for the 207 subjects in the Intent-to-Treat Population.

ADVERSE EVENTS

All Adverse Events

The following table outlines the number (%) of ofloxacin-treated subjects, at U.S. centers, Latin American centers, and at all centers combined, who experienced adverse events during the study.

Clinical Adverse Event Rates in the Ofloxacin-Treated Subjects-PRT006			
Parameter	U.S. Centers (N=150)	Latin American (N=57)	All Centers (n=207)
Subject with any Adverse Event (AE)	73 (48.7%)	8 (14.0%)	81 (39.1%)
Subject with Treatment-Related AE	40 (18.0%)	7 (12.3%)	47(22.7%)
Subject with Severe Adverse Event(s)	4 (2.7%)	0	4 (1.9%)
Subject with Serious Adverse Event(s)	0	0	0
Subject Discontinued due to AE(s)	5 (3.3%)	0	5 (2.4%)

Across all centers, adverse events occurred in 39% (81/207) of the ofloxacin-treated subjects. Most adverse events were mild or moderate in severity, but adverse events that were considered by the respective investigators to be severe occurred in 4 subjects.

Deaths and Other Serious Adverse Events

There were no life-threatening adverse events seen for any ofloxacin-treated subject in this study.

There were no deaths during this study or within 30 days of the last dose of study medication.

There were no serious adverse events reported in this study.

Severe Adverse Events

- Subject Earache (not treatment-related)
Vertigo (probably treatment-related)
- Subject Migraine headache (not treatment-related)
- Subject Fever (not treatment-related)
- Subject Taste perversion (probably treatment-related)

Subjects Discontinued due to Adverse Events

- There were five subjects who experienced adverse events that caused them to discontinue study medication. These subjects and the adverse events are listed below:

Subject This subject experienced urticaria that was felt by the Investigator to be of moderate severity and probably related to study medication.

Subject This subject experienced a mild burning sensation (paraesthesia) in the treated ear immediately after dosing. The Investigator and Applicant were each of the opinion that this event was probably related to the study medication. It should be noted that although this subject discontinued study medication as a result of the adverse event, the subject had taken an adequate course of therapy, >75% compliance, to be considered clinically evaluable. This subject was an evaluable cure.

Subject This subject was a 74-year old female with a medical history that included mitral valve prolapse and hypertension. Study medication was discontinued after 2 doses on Day 1 because the subject complained of tachycardia. In the opinion of the Investigator, the tachycardia was of moderate severity and possibly related to the study medication.

Subject This subject experienced intermittent dizziness and nausea from Day 1 to Day 4 that began immediately after dosing. The study medication was discontinued on Day 4. In the opinion of the Investigator, the nausea and dizziness were considered moderate in severity and probably related to the study medication.

Subject This subject discontinued study medication on Day 6 due to intermittent vertigo that the Investigator deemed severe in nature and probably related to the study medication. This subject also experienced a mild continuous bitter taste (taste perversion) which was ameliorated by chewing gum and did not cause discontinuation of the study medication, but was also considered to be treatment-related.

- There were three subjects who experienced adverse events that caused them to withdraw from the study during the follow-up period after the completion of the study medication dosing period. These three subjects and the adverse events are listed below.

Subject This subject experienced a sore throat, headache, and earaches in the right ear in the cold. The subject was discontinued from the study at Visit 3 because remedial therapy for an upper respiratory tract infection was initiated. In the opinion of the Investigator, the URI, headache, and sore throat were not related to the study medication, but the earache was considered to be remotely related to the study medication.

Subject This subject experienced granular myringitis in the non-target ear and was discontinued at Visit 3 of remedial otological therapy of this. The granular myringitis was considered by the Investigator to be mild and not related to study medication.

Subject This subject experienced intermittent headaches considered by the Investigator to be of moderate severity and remotely related to the study medication, and moderate intermittent tinnitus possibly related to study medication.

Medical Officer's Comment: Both the Applicant and the Medical Officer concur with the respective Investigator's assessments of study drug attribution for the adverse events reported in the eight subjects listed above.

Most Common Adverse Events

The adverse events that were seen in 5 or more subjects. These adverse events and the distribution of the intensity (mild or moderate, or severe) of the events are shown in the following table.

<u>Adverse Events by Body System</u>	<u>Mild or Moderate</u>		<u>Severe</u>		<u>Total</u>
	<u>Subjects(%)</u>	<u>Events²</u>	<u>Subjects(%)</u>	<u>Events²</u>	
<u>Special Senses Other Disorders</u>					
Taste perversion	34 (16%)	37	1 (1%)	1	35 (17%)
<u>Hearing and Vestibular Disorders</u>					
Earache	11 (5%)	16	1 (1%)	1	12 (6%)
Tinnitus	5 (2%)	5	0	0	5 (2%)
<u>Centr & Periph Nerv Sys Disorders</u>					
Headache	10 (5%)	11	0	0	10 (5%)
Dizziness	6 (3%)	7	0	0	6 (3%)
<u>Skin and Appendages Disorders</u>					
Pruritus	7 (3%)	8	0	0	7 (3%)
<u>Respiratory System Disorders</u>					
Upper respiratory tract infection	5 (2%)	5	0	0	5 (2%)

¹The number 5 was chosen to separate the more common AEs from the less frequent AEs in the study.

²Subjects may experience more than one event during the study.

Medical Officer's Comment: Bitter taste, a known circumstance with ofloxacin, was captured in the subject's diary and reported in the table above as "taste perversion."

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Treatment-related Adverse Events

Across all centers, 47 subjects experienced adverse events that were considered to be possibly or probably related to the study medication. These are outlined in the table below:

All Treatment-Related Adverse Events Seen in The Ofloxacin-Treated Subjects in the Medical Officer's Intent-to-Treat Population CSOM Protocol PRT-006		
Body System Specific Adverse Event	Ofloxacin Subjects PRT-006 (N=207) (% of 207)	Total Number of Episodes of the Specific Event*
<u>Special Senses</u>		
Taste Perversion	35 (16.9%)	38
<u>Skin and Appendages Disorders</u>		
Pruritus	5 (2.4%)	6
Urticaria	1 (0.5%)	1
Rash, NOS	1 (0.5%)	1
<u>Central and Peripheral Nervous System</u>		
Dizziness	5 (2.4%)	6
Headache	1 (0.5%)	1
Paraesthesia	2 (1.0%)	2
Vertigo	3 (1.4%)	3
<u>Hearing and Vestibular System Disorders</u>		
Earache	2 (1.0%)	3
Tinnitus	1 (0.5%)	1
<u>Gastrointestinal System Disorders</u>		
Dry Mouth	3 (1.4%)	3
Nausea	1 (0.5%)	1
<u>Heart Rate and Rhythm Disorders</u>		
Tachycardia	1 (0.5%)	1

*Subjects may have experienced more than one episode of same adverse event.

The treatment-related adverse events that were seen in $\geq 1\%$ of the subjects in this study were: taste perversion, pruritus, dizziness, paraesthesia, vertigo, earache, and dry mouth.

Subgroup Analyses for Adverse Events

The Applicant presented a summary of the number of subjects with adverse events according to the severity of the event for the subgroups of age, race, and gender for the Intent-to-Treat Population. This was also done for the same subgroups based on the relationship of the adverse event to the study medication. Overall, neither age, race, gender, nor geographic region (U.S. or Latin America) appeared to be associated with the severity of adverse events.

SUMMARY OF SAFETY-PRT006

- Treatment-related adverse events occurred in 23% (47/207) of the ofloxacin-treated subjects.
- The treatment-related adverse events that were seen in $\geq 1\%$ of the Intent-to-Treat Population in this study were: taste perversion, pruritus, dizziness, paraesthesia, vertigo, earache, and dry mouth.

Medical Officer's Summary Comments and Conclusion of Protocol 006

This was the only study planned and performed for this indication because 1.) there is a relative dearth of subjects in the U.S. with this condition, and 2.) this indication was felt to be closely related, clinically and microbiologically, to acute otitis media in children with tympanostomy tubes.

The primary efficacy variable was to be the Overall Clinical Response of the clinically evaluable ofloxacin-treated subjects versus the clinical outcome of Historical Practice Group subjects who had a follow-up visit (i.e., clinically evaluable). All other efficacy measures were to be considered secondary.

Protocol 006- Chronic Suppurative Otitis Media Clinical Response Rates for the Medical Officer's Intent-to-Treat and Clinically Evaluable Populations		
	Intent to Treat Population	Clinically Evaluable Population
Ofloxacin Success Rate ("Dry Ear")	157/207 (76%)	148/163 (91%)
Historical Practice Success Rate ("Dry Ear")	140/220 (64%)	124/185 (67%)
Current Practice Success Rate ("Dry Ear")	42/63 (67%)	38/54 (70%)

Medical Officer's Comment: *The limitation of this study is the lack of information (disease conditions and specific treatments) collected for the HP and CP groups. Essentially, the MO viewed this as an uncontrolled trial.*

Microbiological data were only collected for the ofloxacin group. The Microbiologically Evaluable Population consisted of 99 subjects.

The Overall Clinical/Microbiological Success rate for ofloxacin was 94% (93/99).

The following table summarizes the eradication rate and combined clinical cure/pathogen eradication rates for the six pathogens the Applicant requested in the labeling:

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Six Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects (N=99) PRT-006 CSOM		
Baseline Pathogen Requested	Pathogens Eradicated	Clinical Cure + Pathogen Eradication
<i>Enterococcus faecalis</i>	7/7	6/7 (86%)
<i>Staphylococcus aureus</i>	40/40	36/40 (90%)
<i>Enterobacter cloacae</i>	4/4	4/4 (100%)
<i>Klebsiella pneumoniae</i>	2/2	2/2 (100%)
<i>Proteus mirabilis</i>	15/15	15/15 (100%)
<i>Pseudomonas aeruginosa</i>	39/39	38/39 (97%)

The safety analyses showed ofloxacin to be generally well-tolerated. Most adverse events were of mild to moderate severity. The treatment-related adverse events that were seen in greater than or equal to 1% of the population were: taste perversion, pruritus, dizziness, paraesthesia, vertigo, earache, and dry mouth.

Indication Summary-Chronic Suppurative Otitis Media

Summary of Clinical and Microbiological Efficacy in CSOM

For this indication, the Applicant conducted one clinical trial, Protocol 006. But, the studies of CSOM and acute otitis media in children with tympanostomy tubes were viewed as supportive of each other due to the similarities of pathophysiology and microbiology of the infections. In both cases, patients have infection in the middle ear with non-intact tympanic membranes, and the infection can occur as a result of the pathogens having gained access to the middle ear either from the pharynx via the eustachian tube or from the external auditory canal.

• Clinical Efficacy

The primary efficacy analysis was the comparison of the clinically evaluable ofloxacin group vs. the Historical Practice subjects who had a follow-up visit.

- The percentage of clinically evaluable ofloxacin-treated subjects (91%) (148/163) with "Dry Ear" was significantly higher than for subjects in the Historical Practice Group (67%) (124/185). The 95% confidence interval (15.1%, 32.4%) for the difference in success rates of these subjects suggests superiority of ofloxacin vs. the treatments employed in the Historical Practice Group.

• Microbiological Efficacy

- On a per subject basis, eradication occurred in all 99 subjects (100%)
- The Overall Clinical/Microbiological Success rate for ofloxacin was 94% (93/99.)
- The following table summarizes the eradication rate and combined clinical cure/pathogen eradication rates for the six pathogens the Applicant requested in the labeling:

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Six Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects (N=99) PRT-006 CSOM		
Baseline Pathogen Requested	Pathogens Eradicated	Clinical Cure + Pathogen Eradication
<i>Enterococcus faecalis</i>	7/7	6/7 (86%)
<i>Staphylococcus aureus</i>	40/40	36/40 (90%)
<i>Enterobacter cloacae</i>	4/4	4/4 (100%)
<i>Klebsiella pneumoniae</i>	2/2	2/2 (100%)
<i>Proteus mirabilis</i>	15/15	15/15 (100%)
<i>Pseudomonas aeruginosa</i>	39/39	38/39 (97%)

The per pathogen eradication rates were 100% for all six of these pathogens. The combined clinical and microbiological success rates were very good for all six of these pathogens, but there were very few isolates of *Enterococcus faecalis*, *Enterobacter cloacae*, and *Klebsiella pneumoniae*. *Staphylococcus aureus*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* were seen in sufficient number and had success rates high enough to warrant consideration for labeling.

Summary of Safety in CSOM

The safety analyses showed ofloxacin to be generally well-tolerated. Most adverse events were of mild to moderate severity. There were no life-threatening adverse events, and there were no deaths during the study or within 30 days of the last dose of study medication.

Treatment-related adverse events were seen in 23% (47/207) of the ofloxacin-treated subjects. The following table lists all treatment-related adverse events seen in this study.

All Treatment-Related Adverse Events Seen in The Ofloxacin-Treated Subjects in the Medical Officer's Intent-to-Treat Population		
CSOM Protocol PRT-006		
<u>Body System</u> Specific Adverse Event	Ofloxacin Subjects PRT-006 (N=207) (% of 207)	Total Number of Episodes of the Specific Event*
<u>Special Senses</u>		
Taste Perversion	35 (16.9%)	38
<u>Skin and Appendages Disorders</u>		
Pruritus	5 (2.4%)	6
Urticaria	1 (0.5%)	1
Rash, NOS	1 (0.5%)	1
<u>Central and Peripheral Nervous System</u>		
Dizziness	5 (2.4%)	6
Headache	1 (0.5%)	1
Paraesthesia	2 (1.0%)	2
Vertigo	3 (1.4%)	3
<u>Hearing and Vestibular System Disorders</u>		
Earache	2 (1.0%)	3
Tinnitus	1 (0.5%)	1
<u>Gastrointestinal System Disorders</u>		
Dry Mouth	3 (1.4%)	3
Nausea	1 (0.5%)	1
<u>Heart Rate and Rhythm Disorders</u>		
Tachycardia	1 (0.5%)	1

*Subjects may have experienced more than one episode of same adverse event.

The treatment-related adverse events that were seen in greater than or equal to 1% of the population were: taste perversion, pruritus, dizziness, paraesthesia, vertigo, earache, and dry mouth.

Medical Officer's Recommendation-Indication of CSOM

In the opinion of the Medical Officer, adequate safety and efficacy data have been demonstrated to support approval for ofloxacin otic 0.3% solution in the treatment of chronic suppurative otitis media, due to *Staphylococcus aureus*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*, in adolescents and adults with chronic perforation of the tympanic membrane.

Overview of Efficacy-All Phase III NDA Protocols

CLINICAL EFFICACY (By Indication and Cumulative Total of Ofloxacin-Treated Subjects)

Otitis Externa

The following table outlines the clinical efficacy rates for Medical Officer's clinically evaluable ofloxacin and Cortisporin®-treated subjects with otitis externa in Protocols 002 and 003.

Clinical Cure Rates for the Medical Officer's Clinically Evaluable Subjects with Otitis Externa Protocols 002 and 003		
Protocol	Ofloxacin	Cortisporin®
PRT-002 Adults	76/99 (77%)	79/98 (81%)
PRT-003 Pediatrics	78/81 (96%)	72/78 (93%)
Combined PRT-002 and PRT-003	154/180 (86%)	151/176 (86%)
MO's Clinically Evaluable Population PRT-002 Ofloxacin vs. Cortisporin® by Cure	Weighted Mantel-Haenszel Method for the 95% C.I. 3.8% 95%C.I. (-14.4%, 6.6%)	
MO's Clinically Evaluable Population PRT-003 Ofloxacin vs. Cortisporin® by Cure	Weighted Mantel-Haenszel Method for the 95% C.I. 4.0% 95%C.I. (-2.4%, 9.3%)	
Ofloxacin vs. Cortisporin® by Cure for the Combined Populations from PRT-002 & PRT-003	95% C.I. by Normal Approximation for the Combined Populations 0% 95%C.I.(-8.0%, 7.6%)	

As shown above, the cure rates in adults with otitis externa were lower than for children for both study drugs. But, therapeutic equivalence between the two treatments was demonstrated in each otitis externa study. Additionally, when looking at all subjects treated for otitis externa, the 95% confidence interval (-8.0%, 7.6%) demonstrated therapeutic equivalence between ofloxacin and Cortisporin®.

Acute Otitis Media in Pediatric Subjects with Tympanostomy Tubes

The following table outlines the clinical efficacy rates for Medical Officer's clinically evaluable ofloxacin and Augmentin®-treated subjects who had acute otitis media with tympanostomy tubes in place in Protocol 008.

Protocol 008- Acute Otitis Media Populations and Response Rates After Exclusion of One Center		
	Ofloxacin	Augmentin®
Medical Officer's Clinically Evaluable Pop.	135	145
Medical Officer's Cure Rate	103/135 (76%)	99/145 (68%)
MO's Clinically Evaluable Population Ofloxacin vs. Cortisporin® by Cure	8.0%, 95% C.I. (-3.1%, 19.2%)	

In Protocol 008, therapeutic equivalence was demonstrated for ofloxacin and Augmentin® in the treatment of acute otitis media in pediatric subjects with tympanostomy tubes.

The following table outlines the clinical efficacy rates for Medical Officer's Intent-to-Treat Population and the clinically evaluable ofloxacin-treated subjects and subjects in Historical and Current Practice Groups who had acute otitis media with tympanostomy tubes in place in Protocol 007.

Protocol 007- Acute Otitis Media Clinical Response Rates Intent-to-Treat and Clinically Evaluable Populations		
	Intent to Treat Population	Clinically Evaluable Population
Ofloxacin Success Rate ("Dry Ear")	135/224 (60%)	119/141 (84%)
Historical Practice Success Rate ("Dry Ear")	187/309 (60%)	140/218 (64%)
Current Practice Success Rate ("Dry Ear")	47/67 (70%)	33/47 (70%)
Ofloxacin vs. Historical Practice by "Dry Ear" for the Intent to Treat Population	0%, 95% C.I. (-9.0%, 8.5%)	
Ofloxacin vs. Current Practice by "Dry Ear" for the Intent to Treat Population	-10%, 95% C.I. (-23.5%, 3.8%)	
Historical vs. Current Practice by "Dry Ear" for the Intent-to-Treat Population	-10%, 95% C.I. (-22.8%, 3.5%)	
Ofloxacin vs. Historical Practice by "Dry Ear" for the Clinically Evaluable Population	20%, 95% C.I. (10.9%, 29.5%)	
Ofloxacin vs. Current Practice by "Dry Ear" for the Clinically Evaluable Population	14%, 95% C.I. (-1.6%, 30.0%)	
Historical vs. Current Practice by "Dry Ear" for the Clinically Evaluable Population	-6%, 95% C.I. (-21.8%, 9.8%)	

In the Intent-to-Treat Population, only the difference in cure rates between the ofloxacin group and the historical practice group showed a 95% confidence interval (-9.0%, 8.5%) that meets the DAIDP criteria for establishing therapeutic equivalence.

In the Clinically Evaluable Population, the 95% confidence interval (10.9%, 29.5%) showed ofloxacin to be therapeutically superior to the treatments employed in the Historical Practice Group. The 95% confidence interval (-1.6%, 30.0%) showed ofloxacin to be therapeutically equivalent to the treatments employed in the Current Practice Group. By DAIDP criteria, therapeutic equivalence was not demonstrated for the treatments in the Historical Practice Group and Current Practice Groups.

A combined success rate for the ofloxacin-treated subjects in Protocols 008 and 007 can be examined, but the comparator arms were different so they can not be combined to use as a reference. The following table shows the success rates of ofloxacin in the treatment of acute otitis media in pediatric subjects with tympanostomy tubes in place in Protocol 008, Protocol 007, and combined.

Clinical Success Rates of Ofloxacin in the Treatment of Acute Otitis Media in Pediatric Subjects with Tympanostomy Tubes PRT-008 and 007	
MO Clin. Eval Ofloxacin-treated Subjects Protocol 008	103/135 (76.3%)
MO Clin. Eval Ofloxacin-treated Subjects Protocol 007	119/141 (84%)
Combined Ofloxacin-treated Subjects PRT-008 and 007	222/276 (80%)

The success rate for ofloxacin in Protocols 008 was 76%, and 84% in Protocol 007. These rates were higher than those of the agent in the respective comparator arms. The combined rate of success for ofloxacin in the treatment of acute otitis media in pediatric subjects with tympanostomy tubes was 80%.

Chronic Suppurative Otitis Media

The following table outlines success rates and the 95% confidence intervals for the comparisons of the difference in success ("dry ear") rates for the various populations and treatment groups. The primary efficacy parameter of the response of clinically evaluable ofloxacin-treated subjects vs. historical practice group subjects with a follow-up visit (i.e., clinically evaluable) is shown in bold print.

Protocol 006- Chronic Suppurative Otitis Media Clinical Response Rates for the Medical Officer's Intent-to-Treat and Clinically Evaluable Populations		
	Intent to Treat Population	Clinically Evaluable Population
Ofloxacin Success Rate ("Dry Ear")	157/207 (76%)	148/163 (91%)
Historical Practice Success Rate ("Dry Ear")	140/220 (64%)	124/185 (67%)
Current Practice Success Rate ("Dry Ear")	42/63 (67%)	38/54 (70%)
Ofloxacin vs. Historical Practice by "Dry Ear" for the Intent to Treat Population	12%, 95% C.I. (3.1%, 21.3%)	
Ofloxacin vs. Current Practice by "Dry Ear" for the Intent to Treat Population	9%, 95% C.I. (-4.9%, 23.2%)	
Historical vs. Current Practice by "Dry Ear" for the Intent-to-Treat Population	-3%, 95% C.I. (-17.3%, 11.3%)	
Ofloxacin vs. Historical Practice by "Dry Ear" for the Clinically Evaluable Population	24%, 95% C.I. (15.1%, 32.4%)	
Ofloxacin vs. Current Practice by "Dry Ear" for the Clinically Evaluable Population	21%, 95% C.I. (6.2%, 34.6%)	
Historical vs. Current Practice by "Dry Ear" for the Clinically Evaluable Population	-3%, 95% C.I. (-18.5%, 11.8%)	

In the Intent-to-Treat Population, the 95% confidence interval (3.1%, 21.3%) for the difference in cure rates between the ofloxacin group and the historical practice group showed superiority of ofloxacin. Based on the 95% confidence intervals, the ofloxacin group showed equivalence to the Current Practice group, and the Historical Practice group showed equivalence to the Current Practice group with respect to the difference in clinical cure rates between these groups.

In the Clinically Evaluable Population, the 95% confidence interval (15.1%, 32.4%) showed ofloxacin to be therapeutically superior to the treatments employed in the Historical Practice Group. The 95% confidence interval (6.2%, 34.6%) showed ofloxacin to be therapeutically superior to the treatments employed in the Current Practice Group. The 95% confidence interval (-18.5%, 11.8%) for the difference in cure rates between the Historical Practice Group and Current Practice Group showed therapeutic equivalence between the two.

All Clinically Evaluable Ofloxacin-Treated Subjects

The following table summarizes the clinical success rates for all ofloxacin-treated subjects across all indications in this NDA.

Success Rates for All of the Medical Officer's Clinically Evaluable Ofloxacin-Treated Subjects in All Protocols	
Protocol	Clinical Success Rate
Protocol 002	76/99 (77%)
Protocol 003	78/81 (96%)
Protocol 008	103/135 (76%)
Protocol 007	119/141 (84%)
Protocol 006	148/163 (91%)
Total Clin. Eval Subjects	524/619 (85%)

Across all studies, there were 619 clinically evaluable ofloxacin-treated subjects. The clinical success rate was (85%) 524/619 for these subjects.

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MICROBIOLOGICAL EFFICACY (By Indication and Cumulative Totals in Ofloxacin-Treated Subjects)

Otitis Externa

The following table outlines the microbiological efficacy rates for the six pathogens the Applicant requested in the labeling for the indication of otitis externa.

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Six Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects Otitis Externa: Combined Protocols PRT-002 and PRT-003 (N=78)						
Pathogen	Pathogen Eradication Rates			Clinical Cure + Pathogen Eradication		
	PRT-002	PRT-003	Total	PRT-002	PRT-003	Total
<i>Enterococcus faecalis</i>	5/5	1/1	6/6	4/5 (80%)	1/1 (100%)	5/6 (83%)
<i>Staphylococcus aureus</i>	6/6	1/1	7/7	6/6 (100%)	1/1 (100%)	7/7 (100%)
<i>Enterobacter cloacae</i>	3/3	3/3	6/6	1/3 (33%)	3/3 (100%)	4/6 (67%)
<i>Klebsiella pneumoniae</i>	5/5	0/0	5/5	4/5 (80.0%)	0/0 (100%)	4/5 (80%)
<i>Proteus mirabilis</i>	3/3	0/0	3/3	2/3 (67%)	0/0 (100%)	2/3 (67%)
<i>Pseudomonas aeruginosa</i>	32/32	28/28	60/60	28/32 (88%)	28/28(100%)	56/60 (93%)

Acute Otitis Media in Pediatric Subjects with Tympanostomy Tubes

The following table outlines the microbiological efficacy rates for the seven pathogens the Applicant requested in the labeling for the indication of acute otitis media in pediatric subjects with tympanostomy tubes.

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Seven Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects Acute Otitis Media: Combined Protocols PRT-008 and PRT-007 (N=192)						
Pathogen	Pathogen Eradication Rates			Clinical Cure + Pathogen Eradication		
	PRT-008	PRT-007	Total	PRT-008	PRT-007	Total
<i>Staphylococcus aureus</i>	27/28	26/26	53/54	23/28	25/26	48/54 (89%)
<i>Streptococcus pneumoniae</i>	36/36	28/29	64/65	29/36	24/29	53/65 (82%)
<i>Enterobacter cloacae</i>	5/5	6/6	11/11	5/5	5/6	10/11 (91%)
<i>Haemophilus influenzae</i>	28/30	30/30	58/60	21/30	25/30	46/60 (77%)
<i>Klebsiella pneumoniae</i>	1/1	4/4	5/5	1/1	4/4	5/5 (100%)
<i>Moraxella catarrhalis</i>	13/14	15/15	28/29	10/14	13/15	23/29 (79%)
<i>Pseudomonas aeruginosa</i>	9/9	32/34	41/43	6/9	30/34	36/43 (84%)

Chronic Suppurative Otitis Media

The following table outlines the microbiological efficacy rates for the pathogens the Applicant requested in the labeling for the indication of chronic suppurative otitis media in adolescents and adults with chronic perforation of the tympanic membrane.

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Six Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects (N=99) PRT-006 CSOM		
Baseline Pathogen Requested	Pathogens Eradicated	Clinical Cure + Pathogen Eradication
<i>Enterococcus faecalis</i>	7/7	6/7 (86%)
<i>Staphylococcus aureus</i>	40/40	36/40 (90%)
<i>Enterobacter cloacae</i>	4/4	4/4 (100%)
<i>Klebsiella pneumoniae</i>	2/2	2/2 (100%)
<i>Proteus mirabilis</i>	15/15	15/15 (100%)
<i>Pseudomonas aeruginosa</i>	39/39	38/39 (97%)

Efficacy of Ofloxacin versus the Pathogens Requested in the Labeling Across all Indications

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects (N=369) (All Protocols Combined)		
Baseline Pathogen Requested	Pathogens Eradicated	Clinical Cure + Pathogen Eradication
<i>Enterococcus faecalis</i>	13/13 (100%)	11/13 (85%)
<i>Staphylococcus aureus</i>	100/101 (99%)	91/101 (90%)
<i>Enterobacter cloacae</i>	21/21 (100%)	18/21 (86%)
<i>Klebsiella pneumoniae</i>	12/12 (100%)	11/12 (92%)
<i>Proteus mirabilis</i>	18/18 (100%)	17/18 (94%)
<i>Pseudomonas aeruginosa</i>	140/142 (99%)	130/142 (92%)
<i>Streptococcus pneumoniae</i>	64/65 (98%)	53/65 (82%)
<i>Haemophilus influenzae</i>	58/60 (97%)	46/60 (77%)
<i>Moraxella catarrhalis</i>	28/29 (97%)	23/29 (79%)
Total of all Pathogens Listed	396/401 (99%)	354/401 (88%)

When considering pathogens for labeling, the Medical Officer looked at both the results from the individual studies for an indication, and owing to the relatedness of these clinical entities, the overall success of ofloxacin against a given pathogen across all studies.

What one can see from the summary table above is that even when the data from all five clinical studies are pooled, there are few isolates of *Enterococcus faecalis*, *Enterobacter cloacae*, and *Klebsiella pneumoniae*. Therefore, the Medical Officer did not consider these three pathogens for labeling. *Staphylococcus aureus* and *Pseudomonas aeruginosa* were requested for all indications. When looking at the indication of otitis externa there were surprisingly few isolates of *Staphylococcus aureus*, but there were nearly 10% of the total number of subjects combined.

There were several isolates of *S. aureus* for the two other indications. In all studies, the success rate of ofloxacin against *S. aureus* was quite good. Looking at the combined totals for *S. aureus*, the Medical Officer is of the opinion that there is sufficient evidence to support labeling of this organism for all three indications. When looking at *Pseudomonas aeruginosa*, at each study and overall, there is sufficient evidence to warrant the labeling of this organism for all three indications.

The three organisms requested only for the indication of acute otitis media in pediatric subjects with tympanostomy tubes are: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. As shown above in the table for this indication, there were numerous isolates of each of these organisms, and the success rates for ofloxacin against these pathogens were acceptable. The Medical Officer believes there is sufficient evidence to support the labeling of these three organisms for the indication of AOM.

The Applicant requested the labeling of *Proteus mirabilis* for the indications of otitis externa and CSOM. There were insufficient isolates to warrant the labeling of this for otitis externa. The success rate of ofloxacin and the number of isolates were sufficient to warrant the labeling of this for CSOM.

SUMMARY OF CLINICAL AND MICROBIOLOGICAL EFFICACY-ALL PHASE III NDA PROTOCOLS

The Medical Officer is of the opinion that sufficient evidence of safety and efficacy has been demonstrated to warrant the labeling of ofloxacin otic 0.3% solution for all three requested indications with the pathogens as listed below:

Otitis Externa

Pseudomonas aeruginosa
Staphylococcus aureus

Acute Otitis Media

Staphylococcus aureus
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Pseudomonas aeruginosa

Chronic Suppurative Otitis Media

Staphylococcus aureus
Proteus mirabilis
Pseudomonas aeruginosa

Overview of Safety-All Phase III NDA Protocols

Significant/Potentially Significant Events

-Deaths

There were no deaths during the study or within 30 days of the last dose of study medication in any of the protocols.

-Serious Adverse Events and Study Withdrawals

The following lists delineate the number of ofloxacin-treated subjects per study who had serious adverse events, and the number of ofloxacin-treated subjects who were withdrawn due to an adverse event (irrespective of the relationship to study drug in either case.) For details, please see the individual study reviews.

Serious Adverse Events

Protocol 002- 3 subjects
 Protocol 003- 2 subjects
 Protocol 008- 0 subjects
 Protocol 007- 3 subjects
 Protocol 006- 0 subjects
 TOTAL 8 subjects

Withdrawn due to Adverse Events

Protocol 002- 4 subjects
 Protocol 003- 2 subjects
 Protocol 008- 9 subjects
 Protocol 007- 6 subjects
 Protocol 006- 5 subjects
 TOTAL 26 subjects

Other Safety Findings

-Adverse Event Incidence Tables

In general, ofloxacin otic 0.3% solution was well-tolerated in both and pediatric subjects. Most of the adverse events were of mild to moderate severity.

The following table outlines the treatment-related adverse events seen in $\geq 1\%$ of the ofloxacin-treated subjects in the otitis externa studies, Protocols 002 & 003.

Treatment-Related Adverse Events Seen in $\geq 1\%$ of the Ofloxacin-Treated Subjects with Otitis Externa (PRT002 and PRT003 Combined)	
<u>Adverse Event</u>	<u>Frequency (N=229)</u>
Pruritus	4.4%
Application Site Reaction	2.6%
Dizziness	1.0%
Earache	1.0%
Vertigo	1.0%

The adverse events shown in the above table represent the adverse events seen in $\geq 1\%$ of the subjects with intact tympanic membranes. The following treatment-related adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing, and otorrhagia.

The following table outlines the treatment-related adverse events seen in $\geq 1\%$ of the ofloxacin-treated subjects in the acute otitis media studies, Protocols 008 and 007.

Treatment-Related Adverse Events Seen in $\geq 1\%$ of the Ofloxacin-Treated Subjects with Tympanostomy Tubes and Acute Otitis Media (PRT008 and PRT007 Combined)	
<u>Adverse Event</u>	<u>Frequency (N=449)</u>
Rash	1.1%
Diarrhea	1.0%
Paraesthesia	1.0%
Earache	1.6%
Otorrhagia	1.0%
Taste Perversion	1.8%

The following table outlines the treatment-related adverse events seen in $\geq 1\%$ of the ofloxacin-treated subjects with chronic suppurative otitis media in Protocol 006.

Treatment-Related Adverse Events Seen in $\geq 1\%$ of the Ofloxacin-Treated Subjects with Chronic Suppurative Otitis Media (PRT006)	
<u>Adverse Event</u>	<u>Frequency (N=207)</u>
Taste Perversion	16.9%
Pruritis	2.4%
Dizziness	2.4%
Paraesthesia	1.0%
Vertigo	1.4%
Earache	1.0%
Dry Mouth	1.4%

It should be noted that unlike the other protocols, in Protocol 006 the subjects were specifically asked to record in their diary whether they had a bitter taste after the first dose of medication.

Pooling the subjects from Protocols 008, 007, and 006 this represents all of the subjects who were dosed with ofloxacin otic solution in the presence of a non-intact tympanic membrane. The following table represents the treatment-related adverse events seen in $\geq 1\%$ of this pooled population.

Treatment-Related Adverse Events Seen in $\geq 1\%$ of the Ofloxacin-Treated Subjects with Non-Intact Tympanic Membranes (PRT008, PRT007, and PRT006 pooled)	
<u>Adverse Event</u>	<u>Frequency (N=656)</u>
Taste Perversion	6.6%
Earache	1.4%
Pruritus	1.1%
Paraesthesia	1.0%
Rash	1.0%
Dizziness	1.0%

Other treatment-related adverse events reported in subjects with non-intact tympanic membranes included: diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). The following treatment-related adverse events were each reported in a single subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

-Laboratory Findings, Vital signs, ECGs

The only laboratory tests that were performed in any of the Phase III studies were the microbiology tests. There was no clinical reason to perform electrocardiograms as a part of any of these protocols, and in the opinion of the Medical Officer there were no clinically significant alterations of vital signs in subjects in these protocols.

-Special Studies (Audiometry)

In Protocol 008 a subset of subjects had an audiometry testing performed to assess whether topical administration of ofloxacin otic 0.3% solution twice daily for ten days in children with acute otorrhea and tympanostomy tubes adversely affected auditory function more than Augmentin® (dosed at 40mg/kg/day for 10 days) which is not known to be ototoxic.

Audiometry demonstrated no statistically significant differences between treatment groups with respect to changes in Pure Tone Average (PTA) for bone conduction or for changes at 4000 Hz for both bone conduction and air conduction in the target and non-target ears. Though air conduction PTA is not as good an indicator of inner ear hearing function as bone conduction, a statistically significant higher percentage of ofloxacin-treated subjects (68%) than Augmentin®-treated subjects showed a positive air conduction change (improvement in hearing).

-Human Reproduction Data

There is no information available on the use of ofloxacin otic 0.3% solution and its impact on human reproduction.

120-Day Safety Review

In addition to the NDA submission of December 18, 1996, the Applicant submitted a 120-day Safety Update report on April 24, 1997. The additional safety data from IND trials, not previously reported but included in this update, are derived from subjects in an ongoing Phase IIIB clinical trial, Protocol 013. This protocol was initiated in November, 1996 and safety data on all subjects enrolled in that trial as of February 7, 1997 was included in this update. This information is summarized below.

All data included in the original NDA were derived from studies that had been completed prior to that submission, thus there is no new information from the trials submitted in the NDA. Other than Protocol 013, no other new Phase I, Phase II, Phase III, or Phase IIIB IND studies have been initiated.

The cutoff date for foreign data included in this Safety Update was February 1 1997. Data from one Japanese trial and updated information on spontaneous reports of adverse events from Japan were included in this Update. This information is summarized below.

Protocol 013-Protocol Summary and Safety Information

Title: "A Phase IIIB, Multicenter, Randomized, Parallel Group, Evaluator Blinded, Comparative Study to Evaluate the Effectiveness of Prophylactic Ofloxacin Otic Solution versus Control (No Prophylaxis) in Decreasing the Incidence of Early Post-Tympanostomy Otorrhea in Pediatric Subjects"

Subjects as of February 7, 1997:

One hundred seventy (170) subjects had been enrolled. This represented an estimated 85 subjects treated with ofloxacin and 85 in the comparative arm, but the study was still blinded at the time of this report.

Indication: Prophylaxis

Subject Population:

Children age equal to or greater than 6 months of age to 6 years of age undergoing tympanostomy tube insertion.

Number of Sites/Region: 17 United States Sites

Ofloxacin Dose/Duration of Treatment: 0.3% otic solution 0.25mL b.i.d. for 3 days

Comparator Agent: No therapy

Demographics:

Caucasian subjects predominated, accounting for 88% of the subjects, and 12% fell into other race categories.

All Adverse Events:

The most common adverse events in subjects enrolled in Protocol 013 were rhinitis which occurred in 21.8% of the subjects (37 subjects, 38 events); earache which occurred in 15.3% of subjects (26 subjects, 29 events); and fever which occurred in 11.8% of subjects (20 subjects, 22 events). In order to maintain the blinding of the evaluator, investigators were instructed to evaluate the relationship of adverse events to study drug as though all subjects were receiving drug.

Severe Adverse Events:

In this study, there were 10 subjects (5.9%) who experienced 11 severe adverse events. The only severe adverse event that occurred in more than one subject was fever which occurred in three subjects. One subject experienced a severe earache that was considered probably treatment-related. All other severe adverse events were considered unrelated to the study treatment. Two of these subjects experienced severe adverse events which were also considered serious but were not considered treatment-related. These will be reviewed in the following section. The other severe adverse events reported in this study were similar to the types of adverse events seen reported in the studies in the NDA.

Deaths and Serious Adverse Events:

As of the cut-off date for reporting in this Safety Update, no deaths had occurred during the study or within 30 days of the end of treatment in Protocol 013. The Applicant also noted that there was no evidence of the uncommon but worrisome adverse events which have been associated with systemic quinolone therapy such as seizures, psychotic reactions, arthropathy, or photoreactions.

As noted above, two of the ten subjects experiencing severe adverse events had events that were considered serious but not treatment related. One subject had post-operative adenoidal bleeding which required surgical cauterization. While under general anesthesia for the myringotomy and tympanostomy tube insertion, the other subject had an additional surgical procedure of upper GI endoscopy and banding of gastric and esophageal varices. This subject experienced the serious adverse events of upper gastrointestinal bleeding and difficulty awakening from anesthesia.

The Applicant reported the information on two other subjects who experienced serious adverse events that occurred after the cut-off date for this Update. One subject experienced post-operative atelectasis which was unexpected and required hospitalization. The other subject developed diarrhea and dehydration approximately 4 hours after the last dose of study therapy. This condition was considered serious in that it was unexpected and required hospitalization. Neither the post-operative atelectasis nor the diarrhea with dehydration were considered related to the study drug.

Subject Discontinuation Due to Adverse Events:

As noted above, in order to maintain the blinding of the evaluator, investigators were instructed to evaluate the relationship of adverse events to study drug as though all subjects were receiving drug. Thus, even subjects in the "no treatment" arm of Protocol 013 could have been "discontinued from therapy due to AE." The incidence of adverse events which resulted in discontinuation of study drug in subjects enrolled in Protocol 013 (4.1%) did not substantially differ from ofloxacin-treated subjects enrolled in the NDA trials of AOM (3.3%) or all NDA trials (2.8%).

Foreign Marketing Approvals, Foreign Post-Marketing and Phase IV Studies, Spontaneous Reports, and Foreign Studies

Foreign Marketing Approvals:

Marketing approval for ofloxacin otic solution has been obtained in two more countries in addition to those listed in the NDA. These are Thailand in December, 1995 and the Phillipines in June of 1996. Thus, the complete list of countries in which ofloxacin otic solution is marketed as of this Safety Update is as follows: Japan, Hong Kong, People's Republic of China, France, Thailand, and the Phillipines.

Foreign Post-Marketing Studies and Spontaneous Reports of Adverse Experiences:

No additional data subsequent to the NDA submission were available from the Japanese Post-Marketing Phase IV Study as of the February 1, 1996 cut-off date for the preparation of this Safety Update. One serious adverse event and two subjects with non-serious adverse events were spontaneously reported in Japan between March 27, 1996 and December 31, 1996. The serious adverse event was an aggravated hepatic disorder and this was reported to the Agency on July 3, 1996 in IND Serial #071. The non-serious adverse events reported in the two Japanese subjects included headache and burning sensation in the ear in one subject, and the "feeling of ear closed" and "hearing decreased" in the other.

Foreign Studies:

Data from one published Japanese study which was not included in the NDA was summarized in this Safety Update. This was study 8280J-CLN-089. This was a retrospective study conducted by among patients treated between January, 1993 and April, 1994. Patients with otorrhea and chronic suppurative otitis media without cholesteatoma who had been treated with ofloxacin otic 0.3% solution b.i.d. alone were compared to those who had received ofloxacin otic 0.3% solution b.i.d. in combination with a non-quinolone oral antibiotic. Bacterial cultures were obtained prior to therapy and following therapy if otorrhea persisted. Clinical responses were scored as "very effective," "effective," "slightly effective," and "not effective." Audiometry was performed before treatment and was to be repeated if the patient complained of decreased hearing. Eighty-four patients fulfilled the inclusion criteria: 46 received ofloxacin otic solution alone and 38 received ofloxacin otic solution in combination with an oral antibiotic. The overall clinical efficacy (including "very effective" and "effective") was 67% for ofloxacin otic solution alone and 71% for ofloxacin otic

solution combined with oral antibiotic therapy. No information regarding adverse events or audiometric findings was reported.

Non-Clinical Studies:

No non-clinical studies have been performed by the Sponsor/Applicant other than those reported in the NDA, and no new reports of non-clinical studies relevant to this submission have been found in the published literature beyond those already summarized in the NDA.

**APPEARS THIS WAY
ON ORIGINAL**

MEDICAL OFFICER'S OVERALL SAFETY CONCLUSIONS

In the five Phase III clinical studies in this NDA, ofloxacin otic 0.3% solution was generally well-tolerated and most of the adverse events seen were of mild to moderate severity and infrequently required discontinuation of therapy. The most common treatment-related adverse events reported were: pruritus, application site reaction, dizziness, earache, vertigo, taste perversion, paraesthesia, and rash.

The data suggest that ofloxacin otic 0.3% solution is at least as safe as Cortisporin® in the treatment of otitis externa in subjects age 1 year or older, and at least as safe as Augmentin® in the treatment of acute otitis externa in pediatric subjects age 1 year and older who have tympanostomy tubes.

There was no evidence of adverse events which have been associated with systemic quinolone therapy such as seizure, psychotic reactions, arthropathy, or photoreactions in the NDA studies or reported in the 120-Day Safety Update.

The Medical Officer is of the opinion that when used at the doses studied in this NDA, and for the same clinical indications studied, ofloxacin otic 0.3% solution should be reasonably safe.

**APPEARS THIS WAY
ON ORIGINAL**

5.) With one exception, the Medical Officer's recommendations with respect to the Proposed Medication Guide for FLOXIN® Otic are in concurrence with those of the DDMAC Reviewer, Jo Ann Spearmon. The Medical Officer believes that the word _____ and the arrow on the diagram in _____ of the section _____ are sufficiently clear and do not need to be moved. —

This concludes the Medical Officer's Review of NDA 20-799

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Cheryl L. McDonald, M.D.
Medical Officer, HFD-520
12/31/1997

cc: Original NDA #20-799
HFD-340
HFD-520/Division Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/DepDir/L. Gavrilovich
HFD-520/MO/C. McDonald
HFD-520/Pharm/A. Ellis
HFD-520/Micro/R. King
HFD-520/Chem/B.V. Shetty
HFD-880/Biopharm/J. Zheng
HFD-725/Biostat/J. Jiang

Concurrence Only:
HFD-520/DivDir/G. Chikami
HFD-520/SMO/J. Soreth

2/20/98
3/23/98

Date of Completion of Drafts:
MO Review of Protocols 002 and 003: July 31, 1997
MO Review of Protocol 008: August 22, 1997
MO Review of Protocol 007: September 12, 1997
MO Review of Protocol 006: October 3, 1997
MO Review of NDA: December 31, 1997