Medical Officer's Summary Comments and Conclusions-Protocol 008

This was a well-designed and generally, well-executed study comparing the safety and efficacy of ofloxacin otic 0.3% solution to Augmentin® in the treatment of acute purulent otorrhea in pediatric subjects with tympanostomy tubes.

The primary efficacy variable was the assessment of Overall Clinical Response in the clinically evaluable population. The table below shows the Clinical Cure rates for the respective clinically evaluable populations:

Overall Clinical Cure Rates
Applicant vs. Medical Officer
Clinically Evaluable Populations-PRT008

Population	Ofloxacin	Augmentin®	95% C.I. Ofloxacin vs. Augmentin® by Cure
Applicant's	107/140 (76%)	101/146 (69%)	(-3.8%, 18.2)
Medical Officer's	103/135 (76%)	99/145 (68%)	(-3.1%, 19.2)

The Overall Microbiological Response by Subject for the Medical Officer's Microbiologically Evaluable Population is summarized in the table below:

Overall Microbiological Response by Subject for the Medical Officer's Microbiologically Evaluable Population-PRT008

Clinical Response	Ofloxacin (N=85)	Augmentin® (N=96)
Eradication	82 (96.5%)	64 (66.7%)
Persistence + Recurrence + Reinfection	3 (3.5%)	32 (33.3%)
Ofloxacin vs. Augmentin® by Eradication	29.8%, 95%CI: 18.5%, 41.1%	

The combined Overall Clinical/Microbiological Success rates for the Applicant's and MO's Microbiologically Evaluable Population are shown in the table below:

Overall Clinical/Microbiological Success Rates (all Baseline Pathogens) for the Microbiologically Evaluable Populations-PRT008

	Ofloxacin group	Augmentin® group
Applicant's Success Rates	64/83 (77%)	61/93 (66%)
Medical Officer's Success Rates	66/85 (78%)	64/96 (67%)

The Applicant requested labeling for the treatment of acute otitis media due to seven different organisms in pediatric patients with tympanostomy tubes. The following table shows the combined clinical cure and microbiological eradication rates for these seven pathogens, as assessed by the Applicant and by the Medical Officer.

Combined Clinical Cure and Microbiological Eradication (Success) Rates by Baseline Pathogen for Ofloxacin-treated subjects-PRT008 (Applicant vs. Medical Officer)

Pathogen	Applicant	Medical Officer
Staphylococcus aureus	23/28 (82%)	23/28 (82%)
Streptococcus pneumoniae	29/36 (81%)	29/36 (81%)
Enterobacter cloacae	5/5 (100%)	5/5 (100%)
Haemophilus influenzae	19/28 (68%)	21/30 (70%)
Klebsiella pneumoniae	1/1 (100%)	1/1 (100%)
Moraxella catarrhalis	10/14 (71%)	10/14 (71%)
Pseudomonas aeruginosa	6/9 (67%)	6/9 (67%)

Adverse Events

- Overall, a significantly lower percentage (p=0.041) of ofloxacin-treated subjects [42.6% (95/223)] experienced an adverse event than did Augmentin®-treated subjects [52.3% (125/239)].
- Treatment-related adverse events also occurred in a significantly lower percentage (p=<0.001)of the ofloxacin-treated subjects [5.8% (13/223)] than the Augmentin®-treated subjects [32.2% (77/239)].
- A significantly higher percentage of subjects had diarrhea (p<0.001) in the Augmentin®-treated group (29%) than in the ofloxacin-treated group (5%).
- A significantly higher percentage of subjects suffered a rash (p<0.001) in the Augmentin®-treated group (9%) than in the ofloxacin-treated group (2%).

Conclusion-Protocol 008

Ofloxacin otic 0.3% solution demonstrated clinical efficacy equivalent to Augmentin® in treating acute otitis media in pediatric subjects age ≥1 year to<12 years of age with tympanostomy tubes, and a safety profile that was at least as safe as Augmentin®.

ACUTE PURULENT OTORRHEA

Trial #2

Protocol 8280A-PRT007

"A Multicenter, Prospective with Historical and Current Practice Control, Open-Label Study to examine the Safety and Efficacy of Ofloxacin Otic Solution in the Treatment of Acute Purulent Otorrhea (Draining Ear) in Pediatric Subjects with Tympanostomy Tubes"

Study Objective/Rationale

Study Rationale

Medical Officer's Comment: *The rationale of this study was the same as for that of Protocol 008 (see page 79 of this review).*

Because there was no topical agent approved for use in middle ear which could serve as a comparator agent, this trial was designed as an open-label trial. In order to permit comparison with the efficacy of regimens that were in clinical use, data were to be collected by retrospective chart review in two control groups, an Historical and a Current Practice Group.

Study Objective

Medical Officer's Comment: *The study objective was the same as in Protocol 008, except that the safety and efficacy of ofloxacin otic solution were to be compared retrospectively to the safety and efficacy of historical and current practice regimens, rather than prospectively to Augmentin®.*

Study Design

Subjects enrolled in the ofloxacin group were evaluated as in Protocol 008 (see "Study Design" on page 80 of this review).

For the historical practice and current practice groups, investigators were to provide records for subjects via retrospective case review. The selection procedure for the Historical Practice and the Current Practice Groups is schematically shown below.

Selection Procedures for Historical Practice Group and Current Practice Group

Medical Records of all Subjects (Historical Database)	→	Meet Inclusion Criteria? (Yes)	→	Historical Registration Log	→	Meet Exclusion Criteria? (Yes)	→	Historical Practice Group		
Medical Records of all Subjects (Current Practice)	→	Enter Ofloxacin (Prospective) Group? (No)	→	Meet Inclusion Criteria? (Yes)	→	Current Registration Log	→	Meet Exclusion Criteria? (Yes)	→	Current Practice Group

Each investigator was expected to provide one evaluable historical subject for each evaluable prospective subject completed and Current Practice subjects meeting the specified inclusion and exclusion criteria, but not exceeding the number of evaluable prospective subjects enrolled in the ofloxacin group.

As originally drafted, the protocol allowed for at least 15 investigative centers and approximately 180 subjects to be enrolled to ensure data from 150 clinically evaluable subjects for the ofloxacin (prospective) group.

Study dates: December 27, 1994 to September 13, 1995

At study completion, there were 27 centers in the United States that participated in the trial. There were a total of 226 subjects enrolled into the ofloxacin group, 309 subjects fulfilled the inclusion/exclusion criteria and were included in the Historical Practice Group, and 68 subjects were enrolled in the Current Practice Group. The 27 investigative centers are listed below:

Center PRT007-702
Angelo Agro, M.D.
Professional Otolaryngology Associates
Staffordshire Professional Center
1307 Whitehorse Road, Building A, Suite 100
Voorhees, NJ 08043

Center PRT007-703
Sam Bartle, M.D.
Health First Medical Group, Research Memphis
5240 Poplar Avenue
Memphis, TN 38134

Center PRT007-704
Stephen A. Minnis, M.D.
Primecare of Southeastern Ohio, Inc.
750 Princeton Drive
Zanesville, OH 43701

Center PRT007-706
Joseph Haddad Jr., M.D.
Division of Pediatric Otolaryngology
Columbia-Presbyterian Medical Center
3959 Broadway-Babies Hospital North 108
New York, NY 10032

Center PRT007-707
Blaise Congeni, M.D.
Children's Hospital Medical Center
1 Perkins Square
Akron, OH 44308

Center PRT007-708
Joseph Dohar, M.D.
Children's Hospital of Pittsburgh
Department of Pediatric Otolaryngology
3705 5th Avenue
Pittsburgh, PA 15213

Center PRT007-709
Tasnee Chonmaitree, M.D.
Pediatric Infectious Diseases Division
University of Texas Medical Branch
9th and Market, Room C2-37
Galveston, TX 77555-0371

Center PRT007-710
Chitra Mani, M.D., FAAP
Marshall University School of Medicine
Department of Pediatrics
1801 Sixth Ave.
Huntington, WV 25701

Center PRT007-711
William Markel, M.D.
Broomfield Family Practice
1420 West Midway Blvd.
Broomfield, CO 80020

Center PRT007-712
Richard Schwartz, M.D.
Vienna Pediatric Associates, Ltd.
410 Maple Avenue, West, Suite 5
Vienna, VA 22180

Center PRT007-713
Eric Slosberg, M.D.
Pediatric Centers of Southwestern Michigan
4200 So. Westnedge
Kalamazoo, MI 49008

Center PRT007-714
Ram Yogev, M.D.
Children's Memorial Hospital
2300 Children's Plaza, Box 20
Chicago, IL 60614

Center PRT007-715
Daniel Wayman, M.D.
Medford Clinic P.C.
555 Black Oak Drive (clinical supplies)
2954 E. Barnett Road, Suite E (corres.)
Medford, OR 97504

Center PRT007-716
James A. Hedrick, M.D.
Kentucky Pediatric Research
201 South Fifth Street
Bardstown, KY 40004

Center PRT007-740
Richard V. Albery, M.D.
3825 N. 24th Street
Phoenix, AZ 85016

Center PRT007-741
Merrill Biel, M.D., Ph.D.
Minneapolis Ear Nose & Throat Clinic and
Research Foundation
2211 Park Avenue South
Minneapolis, MN 55404

Center PRT007-742
Arthur Bolz, M.D.
Jordan Diagnostics & Research, Inc.
2623 Latrobe Drive, Suite 203
Charlotte, NC 28211

Center PRT007-743
Charles I. Sheaffer, M.D.
Chapel Hill Pediatrics
901 Willow Drive, Suite 2
Chapel Hill, NC 27514

Center PRT007-744
Michael H. Fritsch, M.D.
Outpatient Clinical Research Facility
Univ. Hospital & Outpatient Center
550 University Blvd., Room 1705
Indianapolis, IN 46202-5250

Center PRT007-745
Eric T. Garner, M.D.
ENT Associates
901 N. Curtis, #401
Boise, ID 83706

Center PRT007-746
Edward L. Goldblatt, M.D.
Riverchase Clinical Research, P.C.
4517 South Lake Parkway
Birmingham, AL 35244

Center PRT007-747
R. David Glasgow, M.D.
SORRA Research Center
Medical Forum
950 22nd St., North, Suite 550
Birmingham, AL 35203

Center PRT007-749
John W. Larsen, M.D.
Chanhassen Medical Center
470 West 78th St.
Chanhassen, MN 55317

Center PRT007-750
Richard W. Nielsen, M.D.
ENT Center of Salt Lake City
22 S. 900 E.
Salt Lake City, UT 84102

Center PRT007-751
Richard J.H. Smith, M.D.
Otolaryngology Department
University of Iowa Hospitals & Clinics
200 Hawkins Drive
Iowa City, IA 52240

Center PRT007-752
J. William Wright III, M.D.
Physicians Research Group
7430 N. Shadeland Avenue, Suite 160
Indianapolis, IN 46250-5250

Center PRT007-753
William Ziering, M.D.
Ziering Allergy & Respiratory Center
4747 North First St., Suite 177
Fresno, CA 93726

No subjects were enrolled from Center 747 (Dr. Glasgow of Birmingham, Alabama), Center 749 (Dr. Larsen of Chanhassen, Minnesota), or Center 753 (Dr. Ziering of Fresno, California). Therefore, 24 of the 27 total centers contributed to this study.

Protocol Overview

Population and Procedures

-Population

- Ofloxacin Group

For the ofloxacin-treated subjects, the population studied and the study procedures were as outlined for Protocol 008 on pages 84-86 of this review.

- Historical Practice Group
- Current Practice Group

The records of historical practice at the same institutions for up to four years prior to study initiation were to serve as the source of the Historical Practice Group. The records of patients who fulfilled the inclusion/exclusion criteria, but did not participate in the prospective study arm (ofloxacin group) were also to be reviewed. Those patients were to be the source of the Current Practice Group.

-Study Procedures

For the Historical and Current Practice Groups, each subject was to be evaluated at the documented follow-up visit as having either "Dry Ear" (cure) or "Not Dry Ear" (failure). For subjects who did not have a record of a follow-up visit, up to two telephone calls were to be made to determine the clinical response of the subject. The parent or guardian of the subject was to be asked to recall whether the subject's infected ear(s) was either "Dry Ear" (cure) or "Not Dry Ear" (failure) after the completion of therapy. Those who did not remember the clinical outcome were considered "Dry Ear" (cure) and those who could not be reached by phone were considered "Not Dry Ear" (failure).

Medical Officer's Comment: *The designation of "cure" for the clinical outcome of subjects whose parent or guardian could not remember the clinical outcome, and the designation of "failure" for those who could not be reached by telephone is not necessarily unreasonable. Effectively, it is designating those subjects who would be considered "lost to follow-up" as failures while assuming a favorable outcome to those subjects who could not recollect the outcome, but were not lost to follow-up. This strategy was to be used only in the Historical and Current Practice Groups.*

Safety was to be evaluated in the ofloxacin group only, in the manner outlined in Protocol 008.

Subjects with suspected or confirmed Group A Streptococcal infection were not to be enrolled in this trial.

Study Medication and Administration

Study medication was provided for the ofloxacin group only. Dose and administration of ofloxacin was identical to that in Protocol 008.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were outlined for each group in this study: the Ofloxacin Group, the Historical Practice Group, and the Current Practice Group.

Ofloxacin Group Inclusion Criteria and Exclusion Criteria:

The inclusion and exclusion criteria for the ofloxacin group were similar to those in Protocol 008. Please refer to pages 85-86 of this review.

Historical Practice Group Inclusion and Exclusion Criteria

The historical database was to contain all the records of all the subjects visiting the study center between 01/01/90 and the date just prior to the initiation of the prospective arm (ofloxacin group) of the study for each center.

The Historical Registration Log was to list the subjects who were treated with Historical Practice in the investigator's practice at the study site between 01/01/90 and the date of study initiation for each center and who met the inclusion criteria listed below.

Historical Group Inclusion Criteria:

- Subjects between ages of ≥1 year and <12 years;
- Females who had not reached menarche and males;
- Subjects with tympanostomy tube in the target ear;
- Subjects with purulent or mucopurulent otorrhea of presumed bacterial origin.

The records of subjects meeting inclusion criteria were to be reviewed in blocks of 20 starting from the most recent case just prior to the initiation of the prospective arm (ofloxacin group) and continuing retrospectively to 1/1/90 until the required number of subject records was obtained. These subjects were to be listed in the Historical Registration Log.

The Historical Registration Log was to be documented before the Historical Practice Group was selected so that the reason for a particular subject's selection or rejection could be reviewed by the regulatory agency. The Historical Registration Log was to be submitted as part of the NDA package.

Data from the medical records of subjects on the Historical Registration Log who manifested none of the exclusion criteria were to be included in the Historical Practice Group.

Historical Group Exclusion Criteria:

These were essentially the same as for the ofloxacin group, but also included the following restriction:

- Subjects with known fungal infections in the target ear.

The exclusion criteria were to be applied to the subjects in the Historical Registration Log and a list of historical participants was to be identified. The medical records of these subjects were to be reviewed to ascertain whether the subjects fulfilled the eligibility criteria of the study.

Current Practice Group Inclusion and Exclusion Criteria:

The records of subjects who did not wish to participate in the prospective study or could not participate due to restrictions placed on them by the prospective protocol design were to be reviewed for inclusion in the Current Practice Group.

The Current Practice Registration Log was to list subjects who came to the investigator's practice for treatment during the study period and who met the inclusion criteria below.

Current Practice Group Inclusion Criteria:

Same as for the Historical Practice Group, plus the following:

- Subjects with recent onset (<3 weeks) of purulent or mucopurulent otorrhea of presumed bacterial origin.

Data from the medical records of subjects on the Current Practice Registration Log who manifested none of the following exclusion criteria were to be included in the Current Practice Group.

Current Practice Group Exclusion Criteria:

These criteria were essentially the same as for the Ofloxacin and Historical Practice Groups, plus:

- Subjects who had been previously enrolled in the Current Practice Group of this study.

Subjects in Multiple Treatment Groups

Subjects who were included in the Historical Practice Group were to be allowed to be included in either the ofloxacin group or the Current Practice Group. However, subjects were not to be allowed to be included in both the ofloxacin group and the Current Practice Group.

Evaluability Criteria

The Safety, Clinical Efficacy, and Microbiological Efficacy Evaluability Criteria for the ofloxacin-treated subjects in this study were the same as those employed in Protocol 008 (see pages 88-89 of this review) .

Endpoint Response Definitions

Ofloxacin Group

The Clinical and Microbiological Response definitions for the ofloxacin-treated subjects were the same as those used in Protocol 008 (see pages 90-93 of this review).

Historical and Current Practice Groups

- Clinical Response

The medical records of each subject in the Historical and Current Practice Groups were to be reviewed to determine the clinical response at the follow-up visit. The response was to be recorded as either of the following:

"Dry Ear" (Cure)
"Not Dry Ear" (Failure)

For subjects who did not have a record of a follow-up visit, up to two telephone calls were to be made in order to determine the subject's clinical response. The parent or guardian of the subject was to be asked whether the subject's infected ear(s) was(were) either dry or not dry.

Those who did not remember the clinical outcome were to be considered "Dry Ear" (Cure)
Those who could not be reached by telephone were to be considered "Not Dry Ear" (Failure).

Medical Officer's Comment: *The Medical Officer agreed with the above clinical response definitions. No microbiological data was collected for the HP and CP groups.*

Statistical Considerations

Analyses Planned and Populations

-Analysis of Clinical Response

The primary efficacy parameter was to be the comparison of the Overall Clinical Response of the clinically evaluable ofloxacin-treated 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. The definitions of these groups were essentially the same as in Protocol 008, and these 3 populations were: Intent-to-Treat Population, Clinically Evaluable Population, and the Microbiologically Evaluable Population.

- 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, mkcrobiologically 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

Evaluabiltiy and Demographics

-Evaluability

Medical Officer's Comment: *The Medical Officer did not exclude any centers or change any clinical or microbiological efficacy assessments in this study.*

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

Number of Subjects in Each Center-PRT007

Investigator (Center)	Ofloxacin Enrolled	Ofloxacin Met Inc/Exc	Historical Practice Met Inc/Exc	Current Practice Met Inc/Exc
Agro (702)	19	19	20	14
Bartle (703)	5	5	18	4
Minnis (704)	5	4	10	0
Haddad (706)	8	7	0	0
Congeni (707)	2	2	12	2
Dohar (708)	19	19	16	0
Chonmaitree (709)	11	11	13	9
Mani (710)	17	17	17	9
Markel (711)	2	1	1	0
Schwartz (712)	9	8	12	3
Slosberg (713)	10	7	16	7
Yogev (714)	3	1	21	4
Wayman (715)	6	6	19	0
Hedrick (716)	7	6	10	2
Albery (740)	3	3	3	0
Biel (741)	13	13	17	1
Bolz (742)	4	3	4	11
Sheaffer (743)	3	3	18	1
Fritsch (744)	1	1	0	0
Garner (745)	30	27	16	0
Goldblatt (746)	11	11	15	0
Glasgow (747)	0	0	0	0
Larsen (749)	0	0	0	0
Nielsen (750)	23	22	35	0
Smith (751)	11	11	11	1
Wright (752)	4	4	5	0
Ziering (753)	0	0	0	0
Total	226	211	309	68

Ofloxacin Group

All 226 subjects enrolled in the ofloxacin arm received study medication at Visit 1, thereby constituting the Intent-to-Treat population. The following table gives the ranges of treatment days the subjects received.

Number of Days on Treatment for the Ofloxacin Intent-to-Treat Population-PRT007

Number of Days	Ofloxacin 0.25ml b.i.d.	
<3	4	(2%)
3-6	26	(12%)
7-9	15	(7%)
10-12	172	(76%)
>12	6	(3%)
Missing	3	(1%)
Total	226	

The majority (76%) of the subjects received at least 10 days (a full course) of treatment, and the bulk of the remaining subjects (19%) received between 3 to 9 days of treatment.

The following table summarizes the accountability of the 226 subjects enrolled in the ofloxacin group.

Subject Accountability for the Ofloxacin-Treated Subjects-PRT007

Parameter	Ofloxacin 0.25ml b.i.d.
Number of Subjects Enrolled	226
Received Drug	226
Fulfilled inclusion/exclusion criteria	211
Visit 2 Procedures Completed	204
Visit 3 Procedures Completed*	201
Visit 4 Procedures Completed**	158
Intent-to-Treat Population	226
Clinically Evaluable Population	143
Microbiologically Evaluable Population	107

* Includes 16 subjects that completed Visit 3 procedures on their 2nd visit
**Includes 3 subjects that completed Visit 4 procedures on their 3rd visit

Fifteen subjects did not fulfill the inclusion/exclusion criteria, 22 subjects did not have Visit 2 procedures completed, 25 subjects did not have Visit 3 procedures completed, and 68 subjects did not have Visit 4 procedures completed.

Eighty-three ofloxacin-treated subjects in the Intent-to-Treat population were excluded from the clinically evaluable population. Thirty-six subjects in the clinically evaluable population were excluded from the microbiologically evaluable population. The primary reasons for exclusion from these populations is summarized in the table below:

Primary Reasons for Exclusion from Analyzed Populations for the Ofloxacin-Treated Subjects PRT007-AOM

	Ofloxacin 0.25ml b.i.d.	
Total Number of Subjects Enrolled	226	
Excluded from Intent-to-Treat	0	
Total Intent-to-Treat Population	226	
Excluded from Clinically Evaluable Population:	83	(37%)
Took Prohibited Medication	15	(7%)
Group A Streptococci Found	12	(5%)
Inclusion/exclusion criteria not met	11	(5%)
Bilateral Infection after Visit 1	11	(5%)
Protocol Non-Compliance	10	(4%)
No Post Baseline Response*	5	(2%)
Fungus Found	5	(2%)
Discontinued for Other Reason	5	(2%)
Out of Visit 4 Window**	5	(2%)
Lost to Follow-up	4	(2%)
Total Clinically Evaluable Population	143	(63%)
Excluded from Microbiologically Evaluable Population:	36	(16%)
No Valid Baseline Pathogen	28	(12%)
Out of Visit 3 Window**	4	(2%)
Source Present but Culture Not Done	3	(1%)
No Culture Source but Symptoms Persist	1	(0.4%)
Total Microbiologically Evaluable Population	107	(47%)

* Subjects who dropped out of the study before Visit 2 or had no clinical response after Baseline
** Visit 3 window is from 8 hours after last dose to Day 16, Visit 4 window is Day 17-24

The most common primary reasons for exclusion from the clinically evaluable population were: took prohibited medication (15 subjects), Group A Streptococci isolated (12 subjects), inclusion/exclusion criteria not met (11 subjects), development of bilateral infection after Visit 1 (11 subjects), and protocol non-compliance (10 subjects).

Of the 36 subjects excluded from the microbiologically evaluable population, 28 had no pathogen isolated at Baseline, 4 subjects did not have the Visit 3 assessment within the defined window of time (but were seen within the Visit 4 window if they had a Visit 4), 3 subjects had a source present but no culture was taken, and one subject had presistent symptoms without a culture source present.

Historical and Current Practice Groups

The medical records of each subject in the Historical (HP) and Current Practice (CP) Groups were to be reviewed to determine the clinical response at the follow-up visit. The response was to be recorded as either of the following:

"Dry Ear" (Cure)
"Not Dry Ear" (Failure)

For subjects who did not have a record of a follow-up visit, up to two telephone calls were to be made in order to determine the subject's clinical response. The parent or guardian of the subject was to be asked whether the subject's infected ear(s) was(were) either dry or not dry. According to the protocol the outcomes were to be assigned as follows:

> Those who were contacted by telephone but did not remember the clinical outcome were to be considered "Dry Ear" (Cure).
> Those who could not be reached by telephone were to be considered "Not Dry Ear" (Failure).

Of 354 subjects reviewed for inclusion in the Historical Practice Group, 309 met the inclusion/exclusion criteria. Of 69 subjects listed for the Current Practice Group, 68 met the inclusion/exclusion criteria. The follow-up experience of the 309 subjects in the Historical Practice Group and the 68 subjects in the Current Practice Group is outlined in the table below:

Summary of Follow-Up Experience for the Historical and Current Practice Arms of Protocol 007-AOM

	Historical Practice Group		Current Practice Group
Fulfilled Inclusion/Exclusion Criteria	309		68
Had Follow-up Visit	218/309	(71%)	48/68 (71%)
Had Attempted Phone Contact	91/309	(29%)	20/68 (29%)
Successful Phone Contact	53/91	(58%) (17%of 309)	17/20 (85%) (25% of 68)
Remembered Outcome	51/53	(96%) (16.5%of 309)	17/17
Did Not Remember Outcome	2/53	(4%)	0/17
Could Not Be Reached	38/91	(41%)(12% of 309)	3/20 (15%) (4% of 68)
Reached But Could Not Recall Outcome so Assigned "Dry Ear" (Cure) per Protocol	2/309	(0.6%)	0
Could Not Be Reached therefore Outcome of a "Wet Ear" (Failure) Assigned per Protocol without actual documentation/recollection of such	38/309	(12% of 309)	3/20 (4% of 63)
Had Follow-up Visit so Considered Clinically Evaluable Population	218		48

As shown in the table above, in the Intent-to-Treat Population only 38/309 (12%) of the HP group were assigned "failure" without actual documentation of such, and only 3/68 (4%) of the CP group had the assigned outcome of "failure" without actual documentation of such. Only 2 subjects in the HP group (2/309=0.6%) and no subjects in the CP arm had the assigned outcome of "dry ear" (cure) without recollection or actual 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.

-Demographics

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

Demographic Data for the Ofloxacin (Intent-to-Treat Population), Historical Practice and Current Practice Groups-PRT007

	Ofloxacin	Historical	Current	P-value[1]	P-value[2]	P-value[3]
Number of Subjects	226	309	68			
Age (yrs.)						
Mean ± S.D.	3.8 ± 2.8	3.6 ± 2.5	3.7 ± 2.4	0.349	0.747	0.780
Age Group (# subjects)						
<2	79 (35%)	104 (34%)	24 (35%)	0.754	0.959	0.796
2-12	147 (65%)	205 (66%)	44 (65%)			
Gender (# subjects)						
Male	133 (59%)	175 (57%)	45 (66%)	0.609	0.278	0.148
Female	93 (41%)	134 (43%)	23 (34%)			
Race (# subjects)						
Caucasian	188 (83%)					
African American	18 (8%)					
Hispanic	11 (5%)					
Other	9 (4%)					

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

In the Intent-to-Treat Population, the ofloxacin group was comparable to the Historical Practice and Current Practice Groups with respect to age, age distribution, and gender distribution. Race was only presented for the ofloxacin group, so no between-group comparisons can be made for race.

Medical Officer's Comment: *In the Clinically Evaluable Population, the ofloxacin group was comparable to the Historical Practice and Current Practice Groups with respect to age, age distribution, and gender distribution. Also, these demographic features of the respective clinically evaluable populations resembled those of the ITT Population.*

The Microbiologically Evaluable Population of ofloxacin-treated subjects was comparable to the ofloxacin-treated ITT Population, as well as the HP and CP groups, with respect to age, age distribution, and gender distribution.

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 tube placement, drainage assessment, granulation tissue assessment, number of organisms isolated at Baseline, and the number of valid pathogens at Baseline.

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.*

The following table summarizes the additional baseline and target ear characteristics data recorded for the Intent-to-Treat Population of ofloxacin-treated subjects.

Summary of Baseline and Target Ear Characteristics for the Ofloxacin-Treated Intent-to-Treat Population-PRT007

Characteristic		Characteristic		Characteristic	
Number of subjects	226	Drainage*		Valid pathogens**	
Target ear		Mean ± S.D.	4.5 ± 4.4	None	54 (24%)
Right	125 (55%)	Granulation tissue**		One	110 (49%)
Left	101 (45%)	Absent	192 (86%)	Two	47 (21%)
Infection		Mild	21 (9%)	Three or more	14 (6%)
Unilateral	182 (81%)	Moderate	7 (3%)		
Bilateral	44 (20%)	Severe	4 (2%)		
Tube placement*		Organisms			
Mean ± S.D.	328.7 ± 335.5	None	27 (12%)		
Tube type		One	75 (33%)		
Short tube	107 (47%)	Two	64 (28%)		
Long tube	26 (12%)	Three	44 (20%)		
Unknown	92 (41%)	Four or more	15 (7%)		
No tube	1 (0.4%)				

* Measured in days
** Subject did not have lab data and subjects had missing granulation tissue info for the target ear.

Of the Intent-to-Treat Population, 81% had a unilateral infection and 76% had one or more valid pathogens at Baseline. Most subjects (86%) did not have granulation tissue.

Medical Officer's Comment: *In the clinically evaluable ofloxacin-treated population, the distribution of subjects by baseline and target ear characteristics was similar to that seen for subjects in the Intent-to-Treat Population. One exception was that the mean duration of tube placement was slightly less in the Clinically Evaluable Population (307.3 days) than in the Intent-to-Treat Population (328.7 days).*

The distribution of the subjects in the Microbiologically Evaluable Population with respect to the baseline and target ear characteristics resembled that of the Intent-to-Treat Population. The infections were mostly unilateral (81%), granulation tissue was absent (86%), and the tube had been in place for a mean duration of at least 300 days.

The duration of drainage was similar in all three populations,

Efficacy Results

Clinical Efficacy

The primary efficacy variable was 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. All other efficacy measures were to be considered secondary.

The Applicant presented outline of the clinical responses for each post-baseline visit for the Intent-to-Treat, and Clinically Evaluable Populations, 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.

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 007-AOM
Comparison of Clinical Response for the
Ofloxacin,Historical Practice, and Current Practice Groups

	Ofloxacin-Treated	Historical Practice	Current Practice
All Subjects	224	309	67
(Intent-to-Treat)			
Dry Ear	135 (60%)	187 (61%)	47 (70%)
Not Dry Ear	89 (40%)	122 (40%)	20 (30%)
Total	224	309	67
Subjects w/ F/U Visit	141	218	47
(Clinically Evaluable)			
Dry Ear	119 (84%)	140 (64%)	33 (70%)
Not Dry Ear	22 (16%)	78 (36%)	14 (30%)
Total	141	218	47

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 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.

The following table shows the subset analyses by gender and age for the Overall Clinical Response of Success in the clinically evaluable ofloxacin-treated subjects and the Historical Practice Group subjects with a follow-up visit.

Subset Analyses by Demographic Aspects of the Overall Clinical Success Rates of the Clinically Evaluable Ofloxacin-Treated Subjects and the Historical Practice Group Subjects with a Follow-Up Visit-PRT007

Subset	Ofloxacin (N=141)	Historical Practice (N=218)	95% Confidence Interval	Breslow-Day's P-value
Gender				
Male	78/87 (89.7%)	80/124 (64.5%)	(13.6%, 36.7%)	0.074
Female	41/54 (75.9%)	60/94 (63.8%)	(-4.3%, 28.5%)	
Age				
1 yr. - 2 years	39/50 (78.0%)	51/76 (67.1%)	(-6.4%, 28.2%)	0.068
2 yrs. - 7 years	62/73 (84.9%)	72/114 (63.2%)	(8.6%, 35.0%)	
7 yrs. - 12 years	18/18 (100%)	17/28 (60.7%)	(16.6%, 61.9%)	
Race		Not Available	Not Applicable	Not Applicable
White	100/116 (86.2%)			
Black	9/12 (75.0%)			
Hispanic	10/12 (83.3%)			
Other	0/1 (0%)			

As shown in the table above, significant heterogeneity of treatment effects was detected for male subjects and subjects ages 2 to 12 years. In each of these sub-groups, the treatment effects more favored ofloxacin than the treatments employed in the Historical Practice Group.

Secondary Clinical Efficacy Parameters

The Applicant presented the shift from Baseline in otorrhea and odor scores for subjects in the Intent-to-Treat and Clinically Evaluable Population ofloxacin-treated subjects. In each population the scores improved with each sequential visit in most subjects. This is what would be expected given that these scores should correlate with the overall clinical response. The Medical Officer did not reproduce these tables.

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.

Medical Officer's Comment: *Included in the total of 107 subjects in the Microbiologically Evaluable Population are the two subjects, Subjects who had first been enrolled in the Current Practice Group. The Medical Officer did not consider the inclusion of the data from these two subjects to make a substantial difference in the overall results. As such, the Medical Officer presented the data as reported by the Applicant.*

Microbiological Response by Subject

The overall microbiological response by subject was derived from the microbiological response of the subjects at Visits 3 and 4. One hundred and six subjects were assessed for microbiological response at Visit 3. One subject did not return for a Visit 3, but returned at Visit 4 and was given an overall microbiological response of eradication. (However, this subject had an Overall Clinical/Microbiological response of failure.)

The following table outlines the microbiological responses by subject for the microbiologically evaluable ofloxacin-treated subjects at Visit 3, Visit 4, and Overall.

Microbiological Response by Subject for the Ofloxacin-Treated Microbiologically Evaluable Population-PRT007

Response	Visit 3	Visit 4	Overall
Eradication	102 (96%)	99 (100%)	103 (96%)
Persistence	3 (3%)	0	3 (3%)
Superinfection	1 (1%)	0	1 (1%)
Total	106	99	107

All 107 subjects in the microbiologically evaluable population were given an overall microbiological response. Eradication occurred in 96% (103/107) of the microbiologically evaluable subjects. (This total includes the 102 subjects seen at Visit 3 and Subject who was seen at Visit 4, but not Visit 3.) Persistence occurred in three subjects , and superinfection occurred in one subject

Microbiological Response by Pathogen

Prior to treatment, there were a total of 160 isolates of 17 valid baseline pathogens from the 107 subjects in the Microbiologically Evaluable Population. The following table shows the correlation of microbiologic response and clinical response by pathogen.

Overall Microbiological Response and Clinical Response by Pathogen for the Ofloxacin-Treated Microbiologically Evaluable Population-PRT007

Pathogen	Eradication		Persistence		Total # Isolates	Cure		Failure		Total # Isolates
Pseudomonas aeruginosa	32	(94%)	2	(6%)	34	30	(88%)	4	(12%)	34
Haemophilus influenzae	30	(100%)	0		30	25	(83%)	5	(17%)	30
Streptococcus pneumoniae	28	(97%)	1	(3%)	29	24	(83%)	5	(17%)	29
Staphylococcus aureus	26	(100%)	0		26	25	(96%)	1	(4%)	26
Moraxella catarrhalis	15	(100%)	0		15	13	(87%)	2	(13%)	15
Enterobacter cloacae	6	(100%)	0		6	5	(83%)	1	(17%)	6
Klebsiella pneumoniae	4	(100%)	0		4	4	(100%)	0		4
Escherichia coli	3	(100%)	0		3	3	(100%)	0		3
A. calcoaceticus V. anitratus	2	(100%)	0		2	2	(100%)	0		2
Citrobacter freundii	2	(100%)	0		2	1	(50%)	1	(50%)	2
Enterococcus faecalis	2	(100%)	0		2	2	(100%)	0		2
Serratia marcescens	2	(100%)	0		2	2	(100%)	0		2
A. calcoaceticus V. lwoffi	1	(100%)	0		1	1	(100%)	0		1
Enterobacter aerogenes	1	(100%)	0		1	1	(100%)	0		1
Enterococcus faecium	1	(100%)	0		1	0	(0%)	1	(100%)	1
Providencia rettgeri	1	(100%)	0		1	1	(100%)	0		1
Pseudomonas fluorescens	1	(100%)	0		1	1	(100%)	0		1
Total	157		3		160	140		20		160

The most common pathogens isolated were: *Pseudomonas aeruginosa* (34), *Haemophilus influenzae* (30), *Streptococcus pneumoniae* (29),*Staphylococcus aureus* (26), and *Moraxella catarrhalis* (15).

Three pathogens isolated at Baseline, two isolates of *Pseudomonas aeruginosa* and one isolate of *Streptococcus pneumoniae* were persistent at Visit 3 and received an overall microbiological response of persistence. These were seen in the following subjects:

Subject	*Pseudomonas aeruginosa*
Subject	*Pseudomonas aeruginosa*
Subject	*Streptococcus pneumoniae*

Subject had an Overall Clinical Response of cure since the subject was not discontinued from the study or placed on alternative therapy and had complete resolution of otorrhea. Subjects who were discontinued from the study and placed on systemic antibiotics, had an Overall Clinical Response of failure. Due to their persisting pathogens at Visit 3, all three of these subjects had an Overall Clinical/Microbiological response of failure.

All other baseline pathogens were eradicated. The overall clinical response of cure in subjects with the pathogens usually associated with acute otitis media in patients with intact membranes was: 83% (25/30) for *Haemophilus influenzae*, 83% (24/29) for *Streptococcus pneumoniae*, and 87% (13/15) for *Moraxella catarrhalis*. The overall clinical response of cure in subjects with the pathogens usually associated with otitis externa was: 88% (30/34) for *Pseudomonas aeruginosa*, and 96% (25/26) for *Staphylococcus aureus*.

Overall Clinical/Microbiological Assessment

The Overall Clinical/Microbiological response was "success" if the subject had an Overall Microbiological Response of eradication and an Overall Clinical Response of cure. All other subjects were given an Overall Clinical/Microbiological response of failure. The Overall Clinical/Microbiological success rate was 86% (92/107).

The following table outlines the clinical response by the microbiological response for the 107 microbiologically evaluable ofloxacin-treated subjects.

Clinical Response by Microbiological Response for the Ofloxacin-Treated Microbiologically Evaluable Population-PRT007

		Microbiological Response by Subject						
Visit	Clinical Response	Eradication		Persistence		Superinfection		Total
3	Clinical Improvement	96	(94%)	1	(33%)	0		97
	No Clinical Change	1	(1%)	0		0		1
	Clinical Failure	5	(5%)	2	(67%)	1	(100%)	8
	Total	102		3		1		106
4	Clinical Cure	93	(94%)	0		0		93
	Clinical Failure	6	(6%)	0		0		6
	Total	99		0		0		99
Overall	Cure	92	(89%)	1	(33%)	0		93
	Failure	11	(11%)	2	(67%)	1	(100%)	14
	Total	103		3		1		107

Approximately 89% (92/103) of subjects with an overall microbiological response of eradication had an Overall Clinical Response of cure, while the other 11 subjects were clinical failures. As previously noted, Subject had an overall microbiological response of persistence and an Overall Clinical Response of cure, and Subjects each had an overall microbiological response of persistence and an Overall Clinical Response of failure. Subject had an overall microbiological response of superinfection and an Overall Clinical Response of failure. One subject who did not return for a Visit 3 assessment, returned at Visit 4 and was given an overall microbiological response of eradication, but received an Overall Clinical/Microbiological response of failure.

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 are 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, and intermediate if the MIC value was equal to 4 µg/mL. All other pathogens were considered to be sensitive.

The following table outlines the correlation of the Overall Clinical Response by pathogen sensitivity to ofloxacin for the 160 valid Baseline pathogens isolated from the 107 subjects in the Microbiologically Evaluable Population. The percentages shown reflect the percentage of the isolates that had that susceptibility status, not of the 160 total isolates.

Overall Clinical Response by Pathogen Sensitivity for the Ofloxacin-Treated Microbiologically Evaluable Population-PRT007

	Overall Clinical Response				
Valid Baseline Pathogen	Cure		Failure		Total
Sensitive	137	(88%)	19	(12%)	156
Intermediate	1	(50%)	1	(50%)	2
Resistant	1	(100%)	0		1
Acquired Resistance	1	(100%)	0		1

Of the 160 valid pathogens isolated at Baseline, 156 (97.5%) were considered to be sensitive to ofloxacin. Approximately 88% (137/156) of sensitive pathogens isolated at Baseline came from subjects who had an overall clinical response of cure, and approximately 12% (19/156) of the sensitive pathogens isolated at Baseline were found in subjects who were clinical failures. There were a total of four pathogens that had intermediate, resistant, or acquired resistance sensitivity patterns to ofloxacin.

Of the nineteen sensitive pathogens that were isolated at Baseline from subjects who were clinical failures, most (17/19) were eradicated. The following table outlines these pathogens and identifies the subjects from whom they were isolated.

Sensitive Pathogens Isolated at Baseline from Ofloxacin-Treated Microbiologically Evaluable Subjects who were Clinical Failures-PRT007

Pathogen	Count	Subjects	Eradicated
Streptococcus pneumoniae	5		4
Haemophilus influenzae	5		5
Pseudomonas aeruginosa	4		3
Moraxella catarrhalis	2		2
Staphylococcus aureus	1		1
Enterobacter cloacae	1		1
Citrobacter freundii	1		1
Total	19		17

* Subject had persistent pathogen

Subject had a sensitive *Streptococcus pneumoniae* isolate that persisted, and Subject had a sensitive *Pseudomonas aeruginosa* isolate the persisted. In Subject the *Streptococcus pneumoniae* was the only pathogen isolated at Baseline and at early withdrawal. Subject had *Pseudomonas aeruginosa* and *Citrobacter freundii* isolated from both ears at Baseline, but only *Pseudomonas aeruginosa* was isolated from the target ear at early withdrawal. In both of these subjects, the pathogens that persisted retained their original sensitivity to ofloxacin.

The following table outlines the four pathogens, of the 160 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-PRT007

	Count	Subject (MIC)	Clin Resp	Eradicated
Pathogens with Intermediate Sensitivity				
Pseudomonas aeruginosa	1	(4 µg/mL)	Cure	1
Enterococcus faecium	1	(4 µg/mL)	Failure	1
Total	2			2
Resistant Pathogens				
Pseudomonas aeruginosa	1	(8 µg/mL)	Cure	1
Pathogens that Acquired Resistance				
Pseudomonas aeruginosa	1	(4 µg/mL at Baseline) (8 µg/mL at Visit 3)	Cure	0
Total	4			3 of 4

* Subject had persistent pathogen

Two subjects each had a pathogen (both eradicated) with intermediate sensitivity at Baseline. Subject had a resistant pathogen at Baseline, but because the patient was clinically cured the microbiological assessment was eradication. Subject had an intermediate pathogen at Baseline that acquired resistance and persisted at Visit 3, but at Visit 4 the subject had no otorrhea and was considered a clinical cure. Subject was a clinical failure, but the culture taken at the post-therapy visit only grew 1+ *Candida parapsilosis*. The Gram's stain showed no neutrophils, and no bacteria. This subject also had a sensitive *Pseudomonas aeruginosa* as a pathogen at Baseline, but this was a sensitive isolate.

Beta-lactamase Testing of *H. influenzae* and *M. catarrhalis* isolates

Beta lactamase testing by the chromogenic cephalosporin method was performed for all isolates of *Haemophilus influenzae* and *Moraxella catarrhalis.* The results of the test (positive or negative) for baseline isolates along with the overall clinical response of the subject in whom *Haemophilus influenzae* or *Moraxella catarrhalis* was isolated are presented, for the ofloxacin-treated microbiologically evaluable population, in the table below.

Overall Clinical Response by Beta Lactamase Result of Valid Baseline Pathogen for Target Ear for the Ofloxacin-Treated Microbiologically Evaluable Population-PRT007

	β Lactamase Negative Result			β Lactamase Positive Result		
Pathogen	Cure	Failure	Total	Cure	Failure	Total
Haemophilus influenzae	14 (78%)	4 (22%)	18	11 (92%)	1 (8%)	12
Moraxella catarrhalis	1 (100%)	0	1	12 (86%)	2 (14%)	14

Twelve of the thirty (40%) *Haemophilus influenzae* and 14/15 (93%) of the *Moraxella catarrhalis* isolates at Baseline in microbiologically evaluable subjects were β–lactamase positive. Cure rates of 92% and 86% were achieved in subjects with β–lactamase positive *Haemophilus influenzae* and *Moraxella catarrhalis*, respectively. The cure rate of 78% (14/18) for subjects with beta-lactamase negative *H. influenzae* seems low in comparison to that for the beta-lactamase positive isolates, but all four subjects who failed had documented eradication of the *H. influenzae*. The one subject with beta-lactamase positive *H. influenzae* who failed also had documented eradication of the isolate despite clinical failure. Overall, 25/30 (83%) of the *H. influenzae* isolates were from subjects who were clinical cures. The two subjects with beta-lactamase positive *M. catarrhalis* who failed also had documented eradication of the pathogen despite the determination of treatment failure. Overall, 13/15 (87%) of the Baseline *Moraxella catarrhalis* isolates were from subjects who were clinical cures.

Further Susceptibility Testing of *Streptococcus pneumoniae* isolates

Susceptibility testing of all *Streptococcus pneumoniae* to penicillin and trimeth/sulfa was also performed. The results of the susceptibility testing, along with the overall clinical response of the subjects (in the ofloxacin-treated microbiologically evaluable population) in whom *Streptococcus pneumoniae* was isolated, is presented in the following table:

Overall Clinical Response by Susceptibility of *Streptococcus Pneumoniae* at Baseline to Penicillin and Trimeth/Sulfa for Target Ear for the Ofloxacin-Treated Microbiologically Evaluable Population-PRT007

		Overall Clinical Response		
Drug	Susceptibility	Cure	Failure	Total
Penicillin	Sensitive (MIC ≤ 0.12 µg/mL)	16 (80%)	4 (20%)	20
	Intermediate	6 (100%)	0	6
	Resistant (MIC ≥ 4 µg/mL)	2 (67%)	1 (33%)	3
Trimeth/Sulfa	Sensitive (MIC ≤ 2/38 µg/mL)	12 (75%)	4 (25%)	16
	Intermediate	5 (100%)	0	5
	Resistant (MIC ≥ 8/152 µg/mL)	7 (88%)	1 (13%)	8

Three of the twenty-nine (10%) Baseline isolates of *Streptococcus pneumoniae* were resistant to penicillin and 28% (8/29) were resistant to trimethoprim/sulfamethoxazole. Two of the three (67%) subjects with penicillin-resistant *Streptococcus pneumoniae* and 7/8 (88%) with trimethoprim/sulfa-resistant *Streptococcus pneumoniae* were cured.

Medical Officer's Comment: *While the data above show a good overall clinical response rate (24/29=83%) in subjects with S. pneumoniae irrespective of penicillin or TMP/SMZ susceptibility, no generalizations can be made regarding possible therapeutic outcomes with penicillin or TMP/SMZ in comparison to topical ofloxacin.*

Summary of Clinical and Microbiological Efficacy-PRT007

Summary of 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 (84%) (119/141) with "Dry Ear" was significantly higher than for subjects in the Historical Practice Group (64%) (140/218). The 95% Confidence Interval (10.9%, 29.5%) suggests superiority of ofloxacin vs. the treatments employed in the Historical Practice Group in this study for the outcome of "Dry Ear."

Summary of Microbiological Efficacy

The Medical Officer did not make any substantiative changes to the data presented by the Applicant. Microbiological data were collected only for the subjects in the ofloxacin group. The Microbiologically Evaluable Population consisted of 107 subjects from whom160 isolates of 17 valid baseline pathogens were collected.

By Subject Response

On a per subject basis, eradication occurred in 96% (103/107) of the microbiologically evaluable subjects. Persistence occurred in three subjects, and superinfection occurred in one subject.

By Pathogen Response

The five most commonly isolated pathogens were: *Pseudomonas aeruginosa* (34), *Haemophilus influenzae* (30), *Streptococcus pneumoniae* (29),*Staphylococcus aureus* (26), and *Moraxella catarrhalis* (15).

Three pathogens isolated at Baseline, two isolates of *Pseudomonas aeruginosa* and one isolate of *Streptococcus pneumoniae* were persistent at Visit 3 and received an Overall Microbiological response of persistence. All other baseline pathogens were eradicated.

The overall clinical response of cure in subjects with the five most commonly isolated pathogens was: 83% (25/30) for *Haemophilus influenzae*; 83% (24/29) for *Streptococcus pneumoniae*; 87% (13/15) for *Moraxella catarrhalis*; 88% (30/34) for *Pseudomonas aeruginosa*, and 96% (25/26) for *Staphylococcus aureus*.

Overall Clinical/Microbiological Response

The Overall Clinical/Microbiological response was "Success" if the subject had an overall microbiological response of eradication and an Overall Clinical Response of cure. All other subjects were given an Overall Clinical/Microbiological response of failure. Microbiological data were only collected for the ofloxacin-treated subjects.

The Overall Clinical/Microbiological success rate for ofloxacin was 86% (92/107).

SAFETY ANALYSES-Protocol 007

GENERAL ASSESSMENTS

The safety data were collected, and analyses performed, for only the ofloxacin-treated subjects. Analyses were performed for the 226 subjects in the Intent-to-Treat Population.

Medical Officer's Comment: *The safety assessments have an Intent-to-Treat Population of 226 rather than 224 as was used for clinical efficacy assessments because the two subjects who were in both the Current Practice Group and the ofloxacin group were treated with ofloxacin. Hence, they must be included in the safety analyses.*

ADVERSE EVENTS

All Adverse Events

Adverse event data were collected for the ofloxacin group only. The following table outlines the number (%) of subjects who experienced adverse events during the study.

PRT007-Clinical Adverse Event Rates in the Ofloxacin-Treated Subjects

Parameter	Ofloxacin Group (N=226)
Subject with any Adverse Event (AE)	120 (53.1%)
Subject with Treatment-Related AE	29 (12.8%)
Subject with Severe Adverse Event(s)	7 (3.1%)
Subject with Serious Adverse Event(s)	3 (1.3%)
Subject Discontinued due to AE(s)	6 (2.7%)

Adverse events occurred in 53% (120/226) of the subjects. No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication. Most adverse events were of mild to moderate severity.

Summarized in the following table are the adverse events that were seen in 5 or more subjects, and the intensity of these events.

Adverse Events that Occurred in Five[1] or More Ofloxacin-Treated Subjects

	Mild or Moderate		Severe		
Adverse Event by Body System	Subjects (%)	Events[2]	Subjects (%)	Events[2]	Total Subjects
Respiratory System Disorders					
Rhinitis	35 (16%)	37	0	0	35 (16%)
Coughing	14 (6%)	14	0	0	14 (6%)
Upper Resp Tract Infection	10 (4%)	11	1 (0.4%)	1	11 (5%)
Pharyngitis	8 (4%)	8	0	0	8 (4%)
Gastrointestinal System Disorders					
Vomiting	14 (6%)	14	2 (1%)	2	16 (7%)
Diarrhea	9 (4%)	9	0	0	9 (4%)
Body as a Whole - Gen Disorders					
Fever	22 (10%)	24	1 (0.4%)	1	23 (10%)
Skin and Appendages Disorders					
Rash	13 (6%)	13	1 (0.4%)	1	14 (6%)
Hearing and Vestibular Disorders					
Earache	11 (5%)	11	0	0	11 (5%)
Otorrhagia	7 (3%)	8	0	0	7 (3%)
White Cell and Res Disorders					
Lymphadenopathy	6 (3%)	6	0	0	6 (3%)
Special Senses Other. Disorders					
Taste Perversion	4 (2%)	4	1 (0.4%)	1	5 (2%)

1 The number 5 was chosen to separate the more common AEs from the less frequent AEs in the study.
2 Subjects may experience more than one event during the study.

Adverse events most frequently involved the respiratory system, the gastrointestinal system, and the body as a whole. Rhinitis was the most common event of the respriatory system and overall (16%). Fever occurred in 10% (23/226) of the subjects and vomiting was seen in 7% (16/226).

There were eight adverse events in seven subjects that were considered by the respective investigators to be severe in nature. Five of these eight events are listed in the table above. The only severe adverse event that was seen in more than one subject was vomiting, which was considered to be severe in 2 of the 16 subjects affected. One subject, had three events which were considered to be severe in nature, fever, vomiting, and nausea.

The severe adverse events and the subjects in whom they were seen are listed below.

Severe Adverse Events

Respiratory System Disorders:	Upper Respiratory Tract Infection (Subject
Gastrointestinal System Disorders:	Vomiting (Subjects
	Nausea (Subject
Body as a Whole-General Disorders:	Fever (Subject
Skin and Appendages Disorders:	Rash* (Subject
Hearing and Vestibular Disorders:	Otorrhea (Subject
Special Senses and Other Disorders:	Taste Perversion* (Subject
	Halitosis* (Subject

*This adverse event was considered by the Investigator to be treatment-related.

Treatment-Related Adverse Events

The following table summarizes the treatment-related adverse events that occurred in two or more subjects: There was no designation as "definitely" related to study drug.

Treatment-Related Adverse Events that Occurred in Two[1] or More Ofloxacin-Treated Subjects

	Possible			Probable			
Adverse Event by Body System	Subjects	(%)	Events[2]	Subjects	(%)	Events[2]	Total Subjects
Hearing and Vestibular Disorders							
Earache	4	(2%)	4	1	(0.4%)	1	5 (2%)
Otorrhagia	3	(1%)	3	0		0	3 (1%)
Tinnitus	2	(1%)	2	0		0	2 (1%)
Special Senses Other, Disorders							
Taste perversion	2	(1%)	2	3	(1%)	3	5 (2%)
Skin and Appendages Disorders							
Rash	3	(1%)	3	0		0	3 (1%)
Body as a Whole - Gen Disorders							
Fever	2	(1%)	2	0		0	2 (1%)
Centr & Periph Nerv Sys Disorders							
Paraesthesia	1	(0.4%)	1	1	(0.4%)	1	2 (1%)

[1] The number 2 was chosen to separate the more common AEs from the less frequent AEs in the study
[2] Subjects may experience more than one event during the study.

There were no treatment-related adverse events that were considered by the Applicant to be serious.

Subjects Discontinued due to Adverse Events

There were 6 of the 226 subjects (2.7%) who experienced adverse events that caused them to discontinue study medication. These six subjects and the event(s) are listed below:

Subject This subject experienced Streptococcal pharyngitis of moderate severity deemed by the Investigator to be unrelated to the study medication.

Subject This subject experienced Streptococcal pharyngitis of moderate severity deemed by the Investigator to be unrelated to the study medication.

Subject This subject experienced tonsillitis of moderate severity deemed by the Investigator to be remotely related to the study medication,

Subject This subject experienced bronchitis of moderate severity deemed by the Investigator to be unrelated to study medication.

Subject This subject experienced burning (paraesthesia) after the instillation of the study drug and pain. She also experienced fever and otitis externa. The Investigator assessed the paraesthesia as probably drug-related, and the fever, pain, and otitis externa as possibly drug-related.

Subject This subject experienced bronchitis of moderate severity which the Investigator deemed not related to the study drug.

Medical Officer's Comment: *Both the Medical Officer and the Applicant concurred with the respective investigator's assessments of relationship of these adverse events to the study drug.*

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 the study or within 30 days of the last dose of study medication.

The serious adverse events (none treatment-related) experienced by three subjects are outlined below:

Subject This subject was a 14-month-old female who had recurrent otorrhea who received ten days of ofloxacin otic without resolution of otorrhea. She was then treated with Augmentin® and Cortisporin® eardrops. Nine days after completion of the ofloxacin study, and approximately 8 days after starting the alternative therapies, the subject was admitted to the hospital for intravenous therapy of persistent otorrhea. She was treated and discharged from the hospital on what was the 18th day after completion of the study drug. The Investigator considered this adverse event to be unrelated to the study drug. The Applicant concurred with this assessment. The Medical Officer agrees with this assessement.

Subject This subject was a 5 year 9 month-old female who was treated with ofloxacin otic solution from 5/19-5/28/95 for purulent otorrhea. On 6/6/95 she was admitted to the hospital for treatment of dehydration and upper respiratory tract infection. She was discharged from the hospital on 6/9/95. The adverse event was felt by the Investigator and the Applicant to be unrelated to study drug therapy. The Medical Officer agrees with this assessment.

Subject This subject was a 14-month old male with congenital cleft palate associated with Pierre Robin syndrom who was enrolled in the ofloxacin-arm of the study on 8/10/95 and was discontinued on 8/23/95. On 9/8/95 the patient was electively hospitalized for surgical repair of cleft palate and was discharged on 9/11/95. The Investigator considered the event unlikely to be related to study drug therapy. The Applicant noted that the event was serious that it resulted in hospitalization (and unexpected), but in the view of the Applicant it was unrelated to the study medication. The Medical Officer does not consider hospitalization for elective surgical repair of cleft palate to be related to the study drug therapy.

SUMMARY OF SAFETY

- Adverse events occurred in 53% (120/226) of the ofloxacin-treated subjects, and most were of mild or moderate severity.
- Three subjects (1%) experienced serious adverse events, but none of the events were considered treatment-related.
- Treatment-related adverse events were seen in 12.8% (29/226) of the ofloxacin-treated subjects.
- The treatment-related adverse events that were seen in greater than or equal to 1% of the population were: earache, otorrhagia, tinnitus, taste perversion, rash, fever, and paraesthesia.

Medical Officer's Summary Comments and Conclusions-Protocol 007

The objective of this study was to demonstrate the safety and efficacy of ofloxacin otic solution in the treatment of acute purulent otorrhea (draining ear) in pediatric subjects with tympanostomy tubes. This was conducted as an open-label study with Historical and Current Practice Groups serving as the controls.

The following table outlines success rates ("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 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%)

***Medical Officer's Comment**: Because there was not sufficient information available to ensure that the Historical and Current Practice Groups were similar to the Ofloxacin group, both with respect to disease conditions and treatments, the Medical Officer did not consider 95% confidence intervals for treatment outcome comparisons appropriate for this study. Essentially, the MO viewed this study as an uncontrolled trial.*

On a per subject basis, eradication occurred in 96% (103/107) of the microbiologically evaluable subjects. Persistence occurred in three subjects, and superinfection occurred in one subject.

The Overall Clinical/Microbiological success rate for ofloxacin was 86% (92/107).

The following table shows the combined clinical cure and microbiologic eradication rates for the seven pathogens requested in the labeling.

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Seven Requested Pathogens
Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects (N=107)
PRT-007 Acute Otitis Media
Open Label Trial

Baseline Pathogen Requested	Pathogens Eradicated	Clinical Cure + Pathogen Eradication
Staphylococcus aureus	26/26	25/26 (96%)
Streptococcus pneumoniae	28/29	24/29 (83%)
Enterobacter cloacae	6/6	5/6 (83%)
Haemophilus influenzae	30/30	25/30 (83%)
Klebsiella pneumoniae	4/4	4/4 (100%)
Moraxella catarrhalis	15/15	13/15 (87%)
Pseudomonas aeruginosa	32/34	30/34 (88%)

- The safety analyses showed ofloxacin to be generally well-tolerated. Most adverse events were of mild to moderate severity.
- Treatment-related adverse events were seen in 12.8% (29/226) of the ofloxacin-treated subjects.
- The treatment-related adverse events that were seen in greater than or equal to 1% of the population were: earache, otorrhagia, tinnitus, taste perversion, rash, fever, and paraesthesia.

Indication Summary

Acute Otitis Media in Pediatric Patients with Tympanostomy Tubes

Summary of Clinical and Microbiological Efficacy in AOM

For this indication, the Applicant conducted two studies: PRT-008, a randomized, evaluator-blinded comparative trial of ofloxacin otic 0.3% solution versus Augmentin®; and PRT-007, an open-label study with historical and current practice controls.

- **Clinical Efficacy**

The following table outlines the primary efficacy variable in PRT008, the Overall Clinical Response, in the clinically evaluable subjects.

Overall Clinical Cure Rates
Applicant vs. Medical Officer
Clinically Evaluable Populations-PRT008

Population	Ofloxacin	Augmentin®	95% C.I. Ofloxacin vs. Augmentin® by Cure
Applicant's	107/140 (76%)	101/146 (69%)	(-3.8%, 18.2)
Medical Officer's	103/135 (76%)	99/145 (68%)	(-3.1%, 19.2)

Medical Officer's Comment: *In PRTO008, the 95% confidence interval (-3.1%, 19.2%) demonstrated therapeutic equivalence between the two treatment groups in the Medical Officer's Clinically Evaluable Population.*

In Protocol 007 the primary efficacy variable was 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.

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%)

Medical Officer's Comment: *The limitation of this study was the lack of information available to ensure that the Historical and Current Practice Groups were similar to the Ofloxacin group, both with respect to disease conditions and treatments. Essentially, the Medical Officer viewed this study as an uncontrolled trial supportive of the controlled trial, Protocol 008.*

- **Microbiological Efficacy**

Per Subject Basis

Overall Microbiological Response by Subject for the Medical Officer's Microbiologically Evaluable Population-PRT008		
Clinical Response	Ofloxacin (N=85)	Augmentin® (N=96)
Eradication	82 (96.5%)	64 (66.7%)
Persistence + Recurrence + Reinfection	3 (3.5%)	32 (33.3%)
Ofloxacin vs. Augmentin® by Eradication	29.8%, 95%CI: 18.5%, 41.1%	

On a per subject basis, in Protocol 007, eradication occurred in 96% (103/107) of the microbiologically evaluable subjects.

Overall Clinical/Microbiological Response

Overall Clinical/Microbiological Success Rates (all Baseline Pathogens) for the Microbiologically Evaluable Populations-PRT008		
	Ofloxacin group	Augmentin® group
Applicant's Success Rates	64/83 (77%)	61/93 (66%)
Medical Officer's Success Rates	66/85 (78%)	64/96 (67%)

The Overall Clinical/Microbiological success rate for ofloxacin in Protocol 007 was 86% (92/107).

Per Pathogen Basis

The Applicant requested labeling for the treatment of acute otitis media due to seven different organisms in pediatric patients with tympanostomy tubes. The following table summarizes the pathogen eradication rates and Overall Clinical/Microbiological Success rates for the ofloxacin-treated subjects in the Medical Officer's Microbiologically Evaluable Population in each of these two studies and combined.

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
Staphylococcus aureus	27/28	26/26	53/54	23/28	25/26	48/54 (89%)
Streptococcus pneumoniae	36/36	28/29	64/65	29/36	24/29	53/65 (82%)
Enterobacter cloacae	5/5	6/6	11/11	5/5	5/6	10/11 (91%)
Haemophilus influenzae	28/30	30/30	58/60	21/30	25/30	46/60 (77%)
Klebsiella pneumoniae	1/1	4/4	5/5	1/1	4/4	5/5 (100%)
Moraxella catarrhalis	13/14	15/15	28/29	10/14	13/15	23/29 (79%)
Pseudomonas aeruginosa	9/9	32/34	41/43	6/9	30/34	36/43 (84%)

Summary of Safety in AOM

- The safety analyses of each study showed ofloxacin to be generally well-tolerated. In each study, most of the adverse events were of mild to moderate severity.
- A significantly lower percentage (p=0.041) of ofloxacin-treated subjects [42.6% (95/223)] experienced an adverse event than did Augmentin®-treated subjects [52.3% (125/239)].
- Treatment-related adverse events also occurred in a significantly lower percentage (p=<0.001)of the ofloxacin-treated subjects [5.8% (13/223)] than the Augmentin®-treated subjects [32.2% (77/239)].
- Rash (1.1%), diarrhea (1.0%), paraesthesia (1.0%), earache (1.6%), otorrhagia (1.0%), and taste perversion (1.8%) were the only treatment-related adverse events seen in ≥ 1.0% of all ofloxacin-treated subjects (N=449.)
- There were no life-threatening or serious adverse events seen in the ofloxacin-treated subjects in either study.
- There were no deaths during treatment or within 30 days of the last dose of study medication in either study.

Medical Officer's Recommendation-AOM with Tympanostomy Tubes

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 acute otitis media due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa* in pediatric patients (ages 1 year to 12 years) with tympanostomy tubes.

Indication #3

Chronic Suppurative Otitis Media

There was one study conducted for this indication:
8280A-PRT006-An Open-Label Study with
Historical and Current Practice Group Controls

CHRONIC SUPPURATIVE OTITIS MEDIA

Trial #1 of 1

Protocol 8280A-PRT006

"A Multicenter, Prospective with Historical and Current Practice Control, Open-Label Study to Examine the Safety and Efficacy of Ofloxacin Otic Solution in the Treatment of Purulent Otorrhea (Draining Ear) in Adolescents and Adults with Chronic Perforation of Tympanic Membranes"

Study Rationale and Objective

Study Rationale

The Applicant did not outline a specific "study rationale," but did provide an introductory section with an overview of the disease entity to be studied and the reasoning behind the approach taken in this study. The following information was excerpted from the Applicant's study report:

> If untreated or inadequately treated, otitis media can produce sufficient pressure to rupture the tympanic membrane (TM). In-growth of squamous epithelial cells may occur from the external canal. Within the middle ear, lymphoid and other mononuclear cell infiltration may lead to fibrosis of the wall of the middle ear.
>
> Chronic suppurative otitis media (CSOM) is usually associated with perforation of the anterior or central portions of the tympanic membrane. In these patients, there exists a persisting communication between the middle ear and the external auditory canal, allowing organisms which have access to the canal to pass into the middle ear. Thus, in any one patient, the pathogen(s) responsible for CSOM may have gained access to the middle ear from either the pharynx or the external canal or both.
>
> The organisms most commonly associated with CSOM in adults with perforated tympanic membranes include Staphylococcus *aureus*, *Pseudomonas aeruginosa* and other enteric pathogens. Infections with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are less common in adults than in children.
>
> Because the pathogens associated with CSOM in patients with chronic perforation of the tympanic membrane may be more like those seen in otitis externa, anti-infectives active against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other enteric pathogens are essential.
>
> Therapy of CSOM in adults with perforated TMs is not standardized. No agent is approved specifically for this indication. Some physicians treat with oral antibiotics while others use a variety of topical agents. While many oral agents are generally effective in treating AOM in children and adults with intact tympanic membranes, they may not be effective in patients with chronically perforated TMs because of the different spectrum of pathogens associated with this disorder.
>
> As noted above, there is no topical agent approved for use in middle ear which could serve as a comparator in this trial. This trial was therefore designed as an open-label trial. In order to permit comparison with the efficacy of regimens that were in clinical use, data was to be collected by retrospective chart review in two control groups, an Historical and a Current Practice Group.

Study Objective

The objective of this study was to demonstrate the safety and efficacy of ofloxacin otic solution in the treatment of purulent otorrhea (draining ear) in adolescents and adults with chronic perforation of tympanic membranes.

***Medical Officer's Comment**: The design of this trial, including how the historical control group was to be developed, was reviewed by the Division.*

Study Design

This was a multicenter, prospective , open-label study with a historical control arm (Historical Practice Group) and a current control arm (Current Practice Group) to demonstrate the safety and efficacy of ofloxacin otic solution in the treatment of purulent otorrhea (draining ear) in adolescent and adult subjects (≥ 12 years of age) with chronic perforation of tympanic membranes. Purulent otorrhea was defined as any purulent or mucopurulent secretion through the external canal from a perforated tympanic membrane.

Subjects were to have had perforation of the tympanic membrane(s) for at least 21 days. Subjects in the ofloxacin group (prospective arm) who met all on the inclusion criteria and none of the exclusion criteria were to receive ofloxacin 0.3% otic solution 0.5 mL b.i.d. (approximately 12 hours apart) for 14 days. These subjects were to be evaluated at the following timepoints:

Visit	Period	Window (Day of Study)
1	Baseline (Pre-therapy)	Day 1
2	During Therapy	Day 4-6
3	Post-Therapy	Day 15-17
4	Test-of-Cure	Day 21-24

The During Therapy Visit was to be after a minimum of 5 doses of ofloxacin. The Post-Therapy Visit was to be 1-3 days after completion of therapy, and the Test-of-Cure Visit was to be 7 to 10 days post-treatment.

***Medical Officer's Comment**: In this study, unlike the others in this NDA, the duration of therapy with ofloxacin was to be 14 days. Therefore, the Post-Therapy, and Test-of-Cure visits were at different timepoints in terms of "Study Day."*

The Historical and Current Practice Groups were to be derived from a retrospective review of cases from the respective centers from records dated between 01/01/90 and the day just prior to the initiation of the prospective arm (ofloxacin group) at each center. The selection procedure for these subjects was similar to that in Protocol 007, as shown schematically on page 128 of this review.

As originally drafted, the protocol allowed for at least 15 investigative centers and approximately 150 appropriately targeted subjects to be enrolled to ensure clinically evaluable data from 126 subjects in the ofloxacin group. One protocol amendment was submitted to the FDA on August 23, 1995 as an IND Protocol Amendment, Change in Protocol (Serial #044). The protocol was amended to allow for the inclusion of investigative centers in Latin America. Of a total of at least 15 investigative centers, no more than five centers could be located in Latin America. The Latin American centers could provide a maximum of 50 subjects (of a total of approximately 150

subjects) to yield a maximum of 42 clinically evaluable subjects (of a total of 126 clinically evaluable subjects). The analysis plan for the study was also clarified, incorporating a plan for analysis of data from Latin American centers. This amendment was reviewed with the agency prior to implementation.

Study dates were: December 23, 1994 to February 23, 1996

At study completion, there were 35 total centers: 33 centers in the United States, and 2 centers in Latin America. These are listed below:

Center PRT006-602
Angelo Agro, M.D.
Professional Otolaryngology Associates
Staffordshire Professional Center
1307 White Horse Road, Building A, Suite 100
Voorhees, NJ 08043

Center PRT006-604
Trevor Goldberg, M.D.
Charlotte Eye, Ears, Nose and Throat
Research Department
1600 East Third Street
Charlotte, NC 28204

Center PRT006-605
Kazem Golshan, M.D.
Dayton Area Research Associates, Inc.
1900 Wayne Avenue
Dayton, OH 45410

Center PRT006-606
Joseph Haddad Jr., M.D.
Division of Pediatric Otolaryngology
Columbia-Presbyterian Medical Center
3959 Broadway-Babies Hospital North 108
New York, NY 10032

Center PRT006-607
Barry Hirsch, M.D.
University of Pittsburgh
Eye and Ear Institute Building
203 Lothrop Street, Suite 519
Pittsburg, PA 15213

Center PRT006-608
John S. Huff, M.D.
ENT Professional Associates
6545 France Avenue South
Suite 650
Edina, MN 55435

Center PRT006-609
Anthony Jahn, M.D.
556 Eagle Rock Avenue
Roseland, NJ 07068

Center PRT006-612
David Schall, M.D.
Madigan Army Hospital
3315 South 23rd Street, Suite 108
Tacoma, WA 98405

Center PRT006-613
Fred Telischi, M.D.
University of Miami
1666 Northwest 10th Ave., Room 314
Miami, FL 33136

Center PRT006-614
Jeff Vrabec, M.D.
University of Texas Medical Branch
7.104 John Sealy Annex
301 University Boulevard
Galveston, TX 77555-0521

Center PRT006-615
Daniel Wayman, M.D.
Medford Clinic P.C.
555 Black Oak Drive (clinical supplies)
2954 E. Barnett Road, Suite E (corres.)
Medford, OR 97504

Center PRT006-616
Roy Arthur Greenberg, M.D.
5525 Dewey Drive, Suite 210 (corres.)
Fair Oaks, CA 95628
1600 Creekside Drive, Suite 2100 (clinical supplies)
Folsom, CA 95630

Center PRT006-617
Murray Hal Rosenthal, D.O.
The Center for Primary-Care Research
9449 Balboa Ave., Suite #205
San Diego, CA 92123-4342

Center PRT006-618
Patrick Hugh McClean, M.D.
11820 Northup Way, Suite 108
Bellevue, WA 98005

Center PRT006-610
Sam Levine, M.D.
University of Minnesota Health Center
Department of Otolaryngology
420 Delaware Street, S.E., Box 396
Minneapolis, MN 55455

Center PRT006-640
Richard V. Albery, M.D.
3825 N. 24th Street
Phoenix, AZ 85016

Center PRT006-641
Merrill A. Biel, M.D., Ph.D.
Minneapolis Ear, Nose & Throat Clinic and Research Foundation
2211 Park Avenue South
Minneapolis, MN 55404-3753

Center PRT006-651
Richard J.H. Smith, M.D.
Otolaryngology Department
University of Iowa Hospital & Clinics
200 Hawkins Drive
Iowa City, IA 52240

Center PRT006-642
Arthur Bolz, M.D.
Jordan Diagnostics & Research, Inc.
3623 Latrobe Drive, Suite 203
Charlotte, NC 28211

Center PRT006-652
J. William Wright III, M.D.
Physicians Research Group
7430 N. Shadeland Avenue, Suite 160
Indianapolis, IN 46250-5250

Center PRT006-643
Amelia Fischer Drake, M.D.
Univ. of North Carolina School of Medicine
610 Burnett Womack Bldg., CB#7070
Chapel Hill, NC 27599-7070

Center PRT006-653
William Ziering, M.D.
Ziering Allergy & Respiratory Ctr.
4747 North First Street, Suite 177

Center PRT006-644
Michael H. Fritsch, M.D.
Univ. Hospital & Outpatient Center
550 N. University Blvd., Room 1705
Indianapolis, IN 46202-5250

Center PRT006-654
King Foon Yee, M.D.
Magan Medical Clinic
420 West Rowland Street
Covina, CA 91723

Center PRT006-645
Eric T. Garner, M.D.
1074 N. Cole Rd.
Boise, ID 83704

Center PRT006-655
Quang T. Tran, M.D.
Jordon Diagnostics & Research Inc.
300 Lindsay Street, Suite 200
High Point, NC 27262

Center PRT006-646
Edward L. Goldblatt, M.D.
Riverchase Clinical Research, P.C.
4517 South Lake Parkway
Birmingham, AL 35244

Center PRT006-656
Eric J. Schenkel, M.D.
Allergy & Asthma Specialists
3213 Nazereth Road
Easton, PA 18045

Center PRT006-647
Carl M. Nechtman, M.D.
SORRA Research Center
Medical Forum
950 22nd Street North, Suite 550
Birmingham, AL 35203

Center PRT006-657
Rickey G. Love, M.D.
The Otorhinolaryngology Associates, P.C.
2173 Normandie Drive
Montgomery, AL 36111

Center PRT006-649
John w. Larsen, M.D.
Chanhassen Medical Center
470 West 78th Street
Chanhassen, MN 55317

Center PRT006-658
Michael H. Bertino, M.D.
South Tex Applied Clin. Trials
85 NE Loop 410, Sta. 612
San Antonio, TX 78216

Center PRT006-650
Richard W. Nielsen, M.D.
ENT Center of Salt Lake City
22 S. 900 E.
Salt Lake City, UT 84102

Latin American Sites
Center PRT006-680
Irma Caballeros de Escobar, M.D.
5a. Avenida 3-09 Zona 1, 2º nivel
Guatemala, Guatemala

Center PRT006-681
Byron Villeda, M.D.
8ª Avenida 2-48 Zona 1
Guatemala, Guatemala

Protocol Overview

Population and Procedures

-Population

- Ofloxacin Group

For the ofloxacin-treated subjects, the population studied was to be subjects ≥ 12 years of age with Chronic Suppurative Otitis Media (CSOM).

- Historical Practice Group
- Current Practice Group

The records of historical practice at the same institutions for up to four years prior to study initiation were to serve as the source of the Historical Practice Group. The records of patients who fulfilled the inclusion/exclusion criteria, but did not participate in the prospective study arm (ofloxacin group) were also to be reviewed. Those patients were to be the source of the Current Practice Group.

-Study Procedures

The primary efficacy parameter was the overall clinical assessment of the subject by the Sponsor for the ofloxacin-treated clinically evaluable population. All other efficacy measures were considered secondary. At each visit, the clinical signs and symptoms of purulent otorrhea (characteristics of otorrhea, presence or absence of otorrhea odor) were recorded.

Safety was evaluated in the ofloxacin group based on observed and spontaneously reported adverse events recorded at Baseline and at all post-baseline visits, and on changes from Baseline in the physical examinations and vital signs. The presence of any bitter taste in the mouth at any time during the first six hours following the first dose was noted.

Subjects with suspected or confirmed Group A Streptococcal infection were not to be enrolled in this trial.

No safety data were collected on the Historical or Current Practice Group subjects.

- Historical and Current Practice Groups

The study procedures for the HP and CP groups were same as those described for these groups in Protocol 007. Please see page 131 of this review for details.

- Ofloxacin Group

The the safety and efficacy assessments that were to be performed at each visit for subjects in the ofloxacin group were similar to those outlined for subjects in Protocol 008, found on Page 84 of this review. The three differences in the study visit schedule for this protocol are:

- Visit 3 was to be between Days 15-17; Visit 4 was to be between Days 21-24
- At Visit 1, subjects were to be asked whether they experienced a bitter taste sensation after medication administration.
- Females of childbearing potential were to have a urine pregnancy test performed at Visit 1.

Study Medication and Administration

Study medication was provided for the ofloxacin group only. The regimen was:

- Ofloxacin otic solution 0.3%- Instill 0.5mL (10 drops) into the affected ear(s) twice daily approximately 12 hours apart for 14 consecutive days (28 doses of ofloxacin otic solution).

No adjustments in dose were permitted.

Ofloxacin Group Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were outlined for each group in this study: the Ofloxacin Group, the Historical Practice Group, and the Current Practice Group.

Ofloxacin Group Inclusion Criteria:

Adolescent and adult subjects ≥ 12 years of age with purulent otorrhea (draining ear) with chronic perforated tympanic membranes were eligible for enrollment if they met the following criteria:

- Subjects ≥12 years of age;
- Males and non-pregnant, non-lactating females;
- Subjects with chronic perforations of the tympanic membrane in the affected ear(s);
- Subjects with purulent or mucopurulent otorrhea of presumed bacterial origin;
- Subjects who had read and signed a written informed consent to participate (approved by the reviewing IRB) and California Experimental Subject's Bill of Rights, if appropriate.

Inclusion Criteria for the Historical and Current Practice Groups

- Subjects ≥12 years of age;
- Subjects with chronic perforation of tympanic membrane;
- Subjects with purulent or mucopurulent otorrhea of presumed bacterial origin.

Exclusion Criteria:

The exclusion criteria for all groups in this study were similar, in general, to those outlined for the ofloxacin group in Protocol 008 (found on pages 85-86 of this review). Some additional exclusion criteria unique to this study include the following:

- Subjects whose perforation of the tympanic membrane is considered acute (< 21 days);

- Subjects with tympanostomy tubes in the affected ear(s);
- Subjects with any otologic surgery in the target ear within the previous year
- Subjects who had been previously enrolled in this study (subjects who were included in the Historical Practice Group were eligible for enrollment in the ofloxacin group);
- Subjects who had been previously enrolled in the Current Practice Group of this study.

Subjects in Multiple Treatment Groups

Subjects who were included in the Historical Practice Group were to be allowed to be included in either the ofloxacin group or the Current Practice Group. However, subjects were not to be allowed to participate in both the ofloxacin group and the Current Practice Group.

Evaluability Criteria

-Safety Evaluability

To be evaluable for safety analyses, a subject must have received at least one dose of the study medication. Safety was to be evaluated for the ofloxacin group only.

-Clinical and Microbiological Evaluability

The following outlines clinical and microbiological evaluability criteria the Applicant used to define the respective populations:

Clinically Evaluable Population: The subpopulation of the intent-to-treat population that included the subjects who satisfied the following criteria:

- Had perforated tympanic membranes for more than 21 days prior to enrollment;
- Had purulent or mucopurulent otorrhea of presumed bacterial origin in the target ear and satisfied the other inclusion/exclusion criteria
- Had subject diary available;
- Received treatment during a period of 14 consecutive days with a minimum of 75% and a maximum of 120% of doses or were judged a clinical failure by the investigator and received at least three days of medication (minimum of 5 doses);
- Took no prohibited medication as listed in the protocol from Visit 1 to Visit 4;
- Had no Group A Streptococci or mycobacteria during the study, and no significant growth of fungi without any other pathogen at Visit 1;
- Did not develop contralateral ear infection after Visit 1;
- Returned for Visit 4 between Day 21 and Day 28 unless due to adverse event or clinical failure;
- Was compliant with the protocol for the entire study.

Microbiologically Evaluable Population: The subpopulation of the clinically evaluable population that included all clinically evaluable subjects satisfying the following additional criteria: