Center PRT008-852
James D. Sidman, M.D.
Minneapolis Ear, Nose & Throat Clinic
and Research Foundation
2211 Park Avenue South
Minneapolis, MN 55404

Center PRT008-853
Charles E. Smith, M.D.
Upstate Clinical Research, Inc.
552-A Memorial Drive Extension
Greer, SC 29651

Center PRT008-854
Michael Whiting, M.D.
Magan Medical Clinic
420 West Rowland Street
Covina, CA 91723

Center PRT008-855
Richard W. Nielsen, M.D.
ENT Center of Salt Lake City
22 S. 900 E.
Salt Lake City, UT 84102

Center PRT008-856
Arthur C. Jones III, M.D.
Advanced Clinical Research
1074 N. Cole Road
Boise, ID 83704

Center PRT008-857
Edward L. Goldblatt, M.D.
Riverchase Clinical Research, P.C.
4517 Southlake Parkway
Birmingham, AL 35244

Center PRT008-858
Stanley P. Galant, M.D.
1201 West La Veta, Suite 501
Orange, CA 92688

Center PRT008-859
John S. Supance, M.D.
Southern California Research Center
26732 Crown Valley Pkwy., Suite 361
Mission Viejo, CA 92691

Center PRT008-860
Eric J. Schenkel, M.D.
Valley Clinical Research Center
3729 Nazareth Road, Suite #202
Easton, PA 18045

Center PRT008-880
Elba Wu Hupat, M.D.
Miraflores 666, Depto. 405
Santiago-Centro
Santiago, Chile

Center PRT008-881
Adrianos Arguedas Mohs, M.D.
Institute Costarricense de Investigaciones
Clinicas
Frente al Cenare, Urb. Los Arboles
La Uruca, San Josè, Costa Rica

No subjects were enrolled from Center 860 (Dr. Schenkel of Easton, Pennsylvania) or from Center 881 (Dr. Mohs of Costa Rica). Therefore, 37 of the 39 total centers (36 American sites and 1 Latin American site) contributed subjects to this study.

Protocol Overview

Study Procedures

The primary efficacy parameter was the Overall Clinical Response of the subject by the Applicant for the clinically evaluable population. All other efficacy measures were considered secondary. At each visit, the clinical signs and symptoms of acute purulent otorrhea (characteristics of otorrhea, absence or presence of otorrhea, odor) were to be recorded.

Safety was to be evaluated 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 following table outlines the safety and efficacy evaluations that were to be performed at each visit.

Study Visit Schedule

	Visit Schedule			
	Visit 1, Pre-Therapy (Day 1)	Visit 2, During Therapy (Day 4-6)	Visit 3,[1] Post-Therapy (Day 11-13)	Visit 4, Test of Cure (Day 17-20)
Informed Consent	X			
Medical History	X			
Physical Examination	X	X[2]	X	X[2]
Vital Signs	X	X	X	X
Signs/Symptoms[3]	X	X	X	X
Culture	X	X[4]	X[4]	X[4]
Dispense Medication	X	X		
Collect Medication		X	X	
Medication Application	X	———	X	
Adverse Event Assessment	X[5]	X	X	X
Subject Diary	X	———	X	
Parent/Guardian Satisfaction		X	X	
Audiometry[6]	X			X[1]

1 Or upon early withdrawal.
2 Focused Physical.
3 Both ears.
4 If indicated and purulent otorrhea is present (every attempt must be made to obtain cultures and gram stains in subjects considered to be treatment failures for aerobic, anaerobic and fungal cultures).
5 After first dose administered at investigational site.
6 Audiometry on both ears was done using procedure described in Appendix C of the protocol on subjects 4 years of age or older at selected sites.

For those subjects who were withdrawn from the study prior to Visit 4, the subjects were brought into the investigator's office at which time the same procedures as performed at the Post-Therapy (Visit 3) visit were completed. In addition, an audiometry assessment was performed on those subjects who had completed a Visit 1 audiometry test, if possible. The same audiometry procedure performed at Visit 1 was followed at this early withdrawal visit.

Study Medication Dosage and Administration

- Ofloxacin otic 0.3% solution 0.25mL (5 drops) instilled into affected ear(s) every 12 hours

- Augmentin® oral suspension 40mg/kg/ day in three divided doses (every 8 hours)

Inclusion/Exclusion Criteria

Inclusion Criteria

Subjects with acute purulent otorrhea were eligible for enrollment if they met the following inclusion criteria:

- Subjects between ages of ≥1 year and <12 years;
- Females who had not reached menarche and males;
- Subjects with patent tympanostomy tube placement in the infected ear(s);
- Subjects with recent onset (<3 weeks) of purulent or mucopurulent otorrhea of presumed bacterial origin;
- Subjects whose parent or guardian 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.

Exclusion Criteria

Subjects were to be excluded or removed from the study if they met any of the following exclusion criteria:

- Subjects whose duration of purulent otorrhea was 3 weeks or longer;
- Subjects who had a known or suspected mycobacterial infection in the target ear;
- Subjects with known or suspected cholesteatoma in the target ear;
- Subjects with visible drainage surrounding the tympanostomy tube and no drainage through the lumen of the tympanostomy tube in the target ear;
- Subjects with any otologic surgery in the target ear within the previous year except for tympanostomy tube insertion in the target ear;
- Subjects with a history of cholesteatoma or mastoid surgery at any time prior to study entry in the target ear;
- Subjects who had any other condition or disease, such as chronic sinusitis and otitis externa, which could have interfered with the evaluation of the study drugs;
- Subjects with known (positive rapid strep test from oropharynx) or suspected (e.g., fever, pharyngitis, etc.) middle ear infections caused by Group A Streptococci;
- Subjects who, in the judgment of the investigator, required systemic antibiotic therapy for other infections (subjects with ear, pharyngitis, etc.);
- Subjects who had received one of the systemic antibiotics listed in Group A within 24 hours of enrollment, one of the systemic antibiotics listed in Group B within 72 hours of enrollment or any other systemic or topical antibiotics within seven days of enrollment;

Group A	Group B
Ampicillin	Trimethoprim-sulfamethoxasole
Amoxicillin	Tetracycline
Augmentin	Minocycline
Cefaclor	Doxycycline
Dicloxacillin	Cefixime
Erythromycin	Ciprofloxacin
Penicillin VK	
Chloramphenicol	
Cefuroxime axetil	
Chloramphenicol	

- Subjects who had used antiseptic otic washes (e.g., acetic acid, boric acid, etc.) within 5 days prior to study entry. Topical antibiotics for acne were allowed on a chronic basis for subjects who had been on a stable dose for at least 7 days prior to study entry;
- Subjects who had been exposed to any investigational agent within 90 days prior to study entry;
- Subjects who were receiving chemotherapy for cancer;
- Subjects whose concurrent disease was not stable for at least 2 weeks;
- Subjects with a known allergy to quinolones, penicillin, cephalosporins, ofloxacin, Augmentin®, or any of the inactive ingredients in ofloxacin otic solution or Augmentin® oral suspension;
- Subjects who were known to be immunocompromised, HIV positive (Note: HIV testing was not required), had hepatitis, or subjects with known acute or chronic renal insufficiency;
- Subjects who were receiving probenecid, allopurinol, or disulfiram;
- Subjects with a known allergy to multiple allergens;
- Subjects with mononucleosis;
- Subjects with chronic diarrhea;
- Subjects who had a high likelihood of death during the course of the study;
- Females who had reached menarche;
- Subjects who had been previously enrolled in this study;
- Subjects whose parent or guardian were considered not to be reliable in terms of use of medication as instructed, compliance in keeping scheduled appointments, or adherence to other aspects of the protocol;
- Subjects who were relatives of the investigator or other study site personnel involved in this research trial.

The reasons why any subjects were not enrolled were to be documented on the Potential Subject

Roster.

Inclusion/Exclusion Criteria for Audiometry Subjects

- Subjects at selected study sites were to meet the above inclusion/exclusion criteria with the following exceptions:

  1) Only subjects ≥4 years and <12 years of age were to be eligible for inclusion in the audiometry testing.

  2) Subjects with diagnosed sensorineural hearing impairments (defined as two or more thresholds, whether in a single ear or both ears, with bone conduction thresholds >15 dB HL) were excluded.

Protocol Amendments and Study Restrictions

Two protocol amendments were submitted to the Agency as IND Protocol Amendments, Changes in Protocol: (Serial #044, August 23, 1995 [Revision 1] and Serial #069, June 4, 1996 [Revision 2]). Among the most important provisions in these amendments were the following:

-Reasons why potential study subjects were not enrolled were to be documented on the Potential Subject Roster, various exclusion criteria were clarified, and enrollment of subjects who had received specific pre-study antibiotic therapy was permitted after a period of at least five times the drug half-life had elapsed prior to enrollment.

-Provision was made to drop a subject who had a unilateral infection at Visit 1 and who subsequently developed an infection in the contralateral ear, in order to reduce the risk of the subject not receiving an adequate number of doses to treat the infection.

-Provision was made to drop and replace subjects:

- whose baseline otorrhea cultures resulted in a *Pseudomonas aeruginosa* (2+ or greater growth) with no other pathogens,
- identified as having Group A Streptococci,
- having significant growth of fungi and no other pathogens,
- with Baseline or follow-up otorrhea cultures which demonstrated mycobacteria not considered to be a contaminant,
- whose tympanostomy tubes were not in place at Visits 2, 3, or 4.

The Study Restrictions as listed in the Final Protocol (after Revison Number 2) were as follows:

"The following restrictions will be observed for the entire term of the subject's participation in the study:

1. No medications or treatments, other than ofloxacin otic solution, are to be used in the ears;

2. No irrigation of the ears will be allowed;

3. Subject's parent or guardian must keep subject's ears dry (cotton plugs, petrolatum, ear plugs and shower caps will be provided by the Sponsor) and subjects may not swim for the entire study period (Visit 1 to Visit 4);

4. All medication(s) should be recorded on the Previous Medication and/or Concomitant Medications pages of the case report form.

5. No topical (other than study medication) or systemic antibiotics will be allowed during the entire study period (topical antibiotics for acne are allowed on a chronic basis for subjects who have been on a stable dose for at least 7 days prior to entry provided there is no change in dose during the entire study);

6. Subjects with Group A Streptococci identified from otorrhea cultures at any time during the study must be contacted and directed to return to the clinic as soon as possible for clinical evaluation. will

notify centers by phone and/or fax of any Group A Strep positive cultures.) All subjects identified with Group A Streptococci will be dropped from the study and replaced. The same procedures (including a sample for bacteriologic culture, if otorrhea is present) as in the Post-Therapy Visit should be performed at the time of study withdrawal.

7. Subjects whose baseline otorrhea culture demonstrates significant growth of fungi and no other pathogens must be dropped and replaced.

8. Subjects whose baseline otorrhea culture or follow-up visit culture demonstrates a mycobactera, not considered to be a contaminant, must be discontinued at the earliest opportunity and appropriate therapy prescribed. These subjects must be dropped from the study and replaced.

9. In cases where the subject is enrolled to the assigned treatment group and isolates a *Pseudomonas aeruginosa* (2+ or greater growth) and no other pathogens at baseline, the subject should be called back to the clinic for an immediate visit. The subject must be dropped from study and replaced. The same procedures (including a sample for bacteriologic culture, if otorrhea is present) as in the Post-Therapy Visit should be performed at the time of study withdrawal. In cases where *Pseudomonas aeruginosa* is isolated along with other pathogens, the subject may remain in the study at the investigator's discretion. These subjects do not have to be replaced."

Medical Officer's Comment: *In reviewing the protocol presented by the Sponsor/Applicant in the IND, the Medical Officer tried to arrive upon a trial design that would avoid unnecessary treatment failures in subjects with Pseudomonas aeruginosa who were randomized to the Augmentin® treatment group, yet maintain the blinding of the study. And, given concerns that an inadequately treated infection with Group A streptococcus could lead to a more severe condition such as mastoiditis, the MO felt that subjects who had Group A Streptococci isolated should be withdrawn from (or not enrolled in) the ofloxacin treatment arm.*
Because this was an evaluator-blinded, study the Medical Officer envisioned that subjects with these pathogens could be unilaterally removed from the respective treatment arms without unblinding the study. Admittedly, this was an ideal trial design, but this was an attempt to preserve the ofloxacin treatment group subjects with Pseudomonas aeruginosa without posing an undue risk to the subjects in the comparator arm who had no other pathogen to account for the infection other than Pseudomonas aeruginosa. There are no oral agents approved for use in children in the United States that are indicated for the treatment of Pseudomonas aeruginosa. Hence, the choice of any oral agent approved for use in children in the United States would have presented the same conundrum.

Evaluability Criteria

-Safety Evaluability

For a subject to be considered evaluable for the safety analysis, he or she must have been administered at least one dose of the study medication.

-Efficacy Evaluability

The criteria for evaluability for the three populations considered for efficacy analyses, as defined by the Applicant, are listed below:

- Intent-to-Treat Population: Included all subjects who received at least one dose of study drug.
- Clinically Evaluable Population: The sub-population of the intent-to-treat population that included the subjects who satisfied the following criteria:
  - Had purulent or mucopurulent otorrhea of presumed bacterial origin in the target ear which had been present for 21 days or less prior to study enrollment;
  - Had subject diary available;

- Received treatment during a period of 10 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 of ofloxacin or 7 doses of Augmentin®);
- Took no prohibited medication as listed in the protocol from Visit 1 to Visit 4;
- Had no Group A Streptococci or mycobacteria isolated during the study, and no significant growth of fungi without any other pathogen at Visit 1;
- Had no isolation of *Pseudomonas aeruginosa* with a growth index of 2+ or greater without any other valid pathogen at Visit 1;
- Did not develop contralateral ear infection after Visit 1;
- Returned for Visit 4 between Day 17 and Day 24 unless due to adverse event or clinical failure;
- Was compliant with the protocol for the entire study.

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

  - Had valid pathogen(s) isolated from the target ear at Visit 1;
  - Returned for Visit 3 between 8 hours after the last dose and Day 16;
  - 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 successful culture obtained in cases of clinical failure.

Medical Officer's Comment: *The Medical Officer agreed, in general, with the above definitions. However, the Applicant's evaluability criteria for clinical efficacy required a Test-of-Cure visit, without specifically mentioning whether a Post-Therapy (Visit 3) visit was required in cases of clinical success at Visit 4. As the Medical Officer evaluated subjects, a Post-Therapy visit was required to be considered evaluable for clinical success even if a Test-of-Cure Visit was performed. This only affected the evaluability status of two subjects, each in the ofloxacin treatment arm, who were deemed clinical cures by the Applicant but nonevaluable by the Medical Officer (812/022, and 812/070).*

Endpoint Response Definitions

-Clinical Response

At each visit, the clinical characteristics of otorrhea and the presence or absence of odor in both ears were to be assessed by the blinded evaluator using the following scales:

Characteristics of Otorrhea
0 = absent
1 = serous
2 = mucopurulent
3 = purulent
Subjects were to have mucopurulent or purulent otorrhea at baseline to qualify for entry into this trial.
Otorrhea Odor
0 = absent
1 = present
Granulation Tissue
Granulation tissue surrounding the tubes and external canal mucosa were to be evaluated at Visit 1 only according to the following scale:

0 = absent	absent
1 = mild	detectable, minimal involvement
2 = moderate	obvious, easily noted
3 = severe	quite marked, intense

The most severely affected ear (greater total score) at Baseline (or, if both ears scored equally, right ear) was designated the "target ear."

On each day of the study, the subject's parent or guardian was to assess and record in the diary the otorrhea volume relative to Baseline and the presence or absence of odor.

The investigator (or blinded evaluator) was to assess clinical response, in reference to Baseline evaluations, at the During-Therapy Visit (Visit 2, Day 4-6), the Post-Therapy Visit (Visit 3, Day 11-13), and the Test-of-Cure Visit (Visit 4, Day 17-20). Clinical response was to be defined at each visit in the target ear, as follows:

During-Therapy Visit:

Clinical Improvement:	Complete resolution or decrease in volume of otorrhea.
No Clinical Change:	No change in otorrhea from Baseline.
Clinical Failure:	Signs and symptoms of otitis media which warrant change in antimicrobial therapy (after a minimum of 3 days and a minimum of 5 doses of ofloxacin or 7 doses of Augmentin®).
Indeterminate:	Discontinued or lost to follow-up (prior to minimum of 3 days of treatment or 5 doses of ofloxacin or 7 doses of Augmentin®).

Post-Therapy Visit

Clinical Improvement:	Complete resolution or decrease in volume of otorrhea.
No Clinical Change:	No change in otorrhea from Baseline.
Clinical Failure:	Signs and symptoms of otitis media which warrant change in antimicrobial therapy (after a minimum of 3 days treatment with 75% of the dose taken).
Indeterminate:	Discontinued or lost to follow-up prior to the Post-Therapy Visit.

Test-of-Cure Visit:
Clinical Cure: Complete resolution of otorrhea at the Test-of-Cure Visit.
Clinical Failure: Presence of otorrhea at the Test-of-Cure Visit.
Indeterminate: Discontinued or lost to follow-up prior to the Test-of-Cure Visit.

Overall Clinical Response

The primary efficacy variable was to be the Overall Clinical Response of the clinically evaluable subject by the Applicant, using the following scale:

Cure: Clinical cure at the Test-of-Cure Visit.
Failure: Clinical failure at any time after receiving at least 3 days of therapy with 75% of dose taken.

Medical Officer's Comment: *In general, the Medical Officer agreed with the above definitions.*

-Microbiological Response

A Microbiological Response was to be assigned to each pathogen isolated at Baseline and to each subject at the Post-Therapy Visit and at the Test-of-Cure Visit (Visits 3 and 4, respectively).

At the Test of Cure Visit (Vistit 4), an Overall Microbiological Response was to be assigned by the Applicant, by subject and by pathogen(s), taking into consideration those individual microbiological responses assigned at Visit 3 and Visit 4.

Finally, an Overall Microbiological/Clinical Response was to be determined by the Applicant.

Outlined below are the definitions of microbiological response used by the Applicant:

Microbiological Response by Pathogen and by Subject

A Microbiological Response was assigned by the Applicant to each pathogen isolated from the target ear during the study and to each microbiologically evaluable subject infected with any valid pathogen(s), as follows:

Microbiological Response at Visit 3

Eradication Documented: Absence of all Baseline pathogen(s) from the Visit 3 culture.
Eradication Presumed: Clinical cure or clinical improvement of signs and symptoms of infection without a repeat culture because no source was present.
Persistence: Continued presence of a Baseline pathogen in Visit 3 culture (regardless of isolation of other pathogens).
Colonization: Absence of all Baseline pathogen(s) from the Visit 3 culture, but the isolation of a new pathogen(s) without a worsening of clinical signs and symptoms of infection.
Superinfection: Absence of all Baseline pathogen(s) from the Visit 3 culture, but the isolation of a new pathogen(s) with worsening signs and symptoms of infection.
Not Evaluable: Subject considered not evaluable for microbiological response under any of the following conditions:
1. Not evaluable for clinical efficacy analysis.
2. No valid pathogen(s) isolated at Baseline from the target ear.

3. No culture was performed when culture source was present.
4. Inappropriate culture submitted (i.e., culture submitted when no source to culture was reported).
5. No source to culture (i.e., no exudate/secretion) or no pathogen isolated, but a worsening of other clinical signs or symptoms relative to the Baseline condition.

Microbiological Response at Visit 4

Eradication Documented: Absence of all Baseline pathogen(s) from the Visit 4 culture.

Eradication Presumed: Sustained or subsequent clinical cure of signs and symptoms of infection without a repeat culture because no source was present.

Persistence: The same pathogen(s) that was present at the Baseline and Visit 3 cultures was also isolated in the Visit 4 culture (regardless of isolation of other pathogens).

Recurrence: Absence of all Baseline pathogen(s) and signs and symptoms (clinical cure or improvement) at Visit 3, but presence of a Baseline pathogen(s) from cultures obtained at Visit 4, accompanied by reappearance of signs and symptoms of infection.

Superinfection: Absence of all Baseline pathogen(s) with isolation at Visit 4 of the same superinfecting pathogen(s) which was isolated at Visit 3 culture.

Reinfection: Absence of all Baseline pathogen(s) and signs and symptoms at Visit 3, but presence of a different pathogen(s) in cultures obtained at Visit 4, accompanied by reappearance of signs and symptoms of infection.

Colonization: Absence of all Baseline pathogen(s) from a culture or no source to culture at Visit 3, but the isolation of a new pathogen(s) without a worsening of clinical signs and symptoms of infection.

Not Evaluable: Subject considered not evaluable for microbiological efficacy under any of the conditions cited for Microbiological Response at Visit 3, above.

Overall Microbiological Response by Subject:

Eradication: The Microbiological Responses at both Visit 3 and Visit 4 were "eradication" (documented or presumed).

Persistence: The Microbiological Response at Visit 3 and/or Visit 4 was "persistence."

Recurrence: The Microbiological Response was "eradication" (documented or presumed) at Visit 3, and "recurrence" at Visit 4.

Reinfection: The Microbiological Response was "eradication" (documented or presumed) at Visit 3 and "reinfection" at Visit 4.

Colonization: If colonization was observed at Visit 3 or Visit 4.

Superinfection: The Microbiological Response was "superinfection" at Visit 3.

Not Evaluable: The Microbiological Response was "not evaluable" at Visit 3 or Visit 4.

Overall Microbiological Response by Pathogen

Eradication Documented: Absence of all Baseline pathogen(s) from Visit 3 and Visit 4 cultures.

Eradication Presumed: Clinical cure or clinical improvement of signs and symptoms at Visit 3 and sustained clinical cure or subsequent clinical cure of signs and symptoms at Visit 4, without a repeat culture, because no source was present at both Visit 3 and Visit 4, or because Visit 3 cultures documented Baseline pathogen(s) eradication and Visit 4 cultures were not performed because no source was present.

Persistence: The same pathogen(s) that was present at Baseline was isolated at Visit 3 cultures or at Visit 3 and at Visit 4 cultures (regardless of isolation of other

pathogens).

Recurrence: Absence of all Baseline pathogen(s) and signs and symptoms (clinical cure or improvement) at Visit 3, but presence of a Baseline pathogen(s) from cultures obtained at Visit 4, accompanied by reappearance of signs and symptoms of infection.

Not Evaluable: Response at either Visit 3 or Visit 4 was "not evaluable."

Overall Microbiological/Clinical Assessment

Subjects who were evaluable for microbiological efficacy were to be classified by the Sponsor as follows:

Success: Clinical Cure at the Test-of-Cure Visit with microbiological assessment of eradication or presumed eradication (no appropriate source).

Failure: All other subjects evaluable for microbiological efficacy and clinical efficacy and not classified as Success.

***Medical Officer's Comment**: The Medical Officer agreed with the above microbiologic endpoint response definitions.*

Statistical Considerations

Sample Size

In the Applicant's development of this study, both test products were assumed to have similar efficacy and safety profiles. The goal of the trial was to establish equivalence while allowing opportunities for declaring significant differences if the disparities were sufficiently large. Overall clinical success rates of approximately 80% were anticipated for both drugs. Approximately 320 subjects were to be enrolled, and of these, 276 were expected to be evaluable. With this sample size, this study would have 80% power (alpha=0.05, 2-sided test) to detect a 15% percentage point difference in overall clinical efficacy between ofloxacin and Augmentin®-treated clinically evaluable subjects.

Analysis Planned and Populations

-Analysis

The primary efficacy analysis parameter was the Overall Clinical Response of the subject by the Applicant for the clinically evaluable population. All other efficacy measures were considered secondary.

***Medical Officer's Comment**: The Medical Officer concurred with the Applicant that the Overall Clinical Response rate is the appropriate primary efficacy analysis, and the Clinically Evaluable Population is the appropriate population on which to perform this analysis for this indication.*

-Populations: ITT, clinically evaluable, and microbiologically evaluable populations as previously defined.

Statistical Methods

Efficacy analyses were to be based on the clinical and microbiological responses at Visits 2, 3, and 4. The treatment groups were to be compared with respect to the clinical cure rate, the subject microbiological eradication rate, and the pathogen microbiological eradication rate.

Evaluation of safety data was to be based on review of adverse event within treatment groups for all subjects who received at least one dose of study drug. Audiometric testing safety data was to be presented as the change in Pure Tone Average and the change in bone and air conduction at 4000 Hz.

Study Results

Evaluability and Demographics

-Evaluability

A total of 474 subjects were enrolled and received at least one dose of medication. The following table summarizes the enrollment by center and treatment group of all subjects in this study.

PRT-008 Number of Subjects at Each Site

Investigator (Site)	Ofloxacin	Augmentin®	Total
U.S. Sites			
Asmar (801)	5	4	9
Agro (802)	16	16	32
Goldberg (804)	12	14	26
Harley (805)	2	2	4
Jordan (806)	10	8	18
Lumry (807)	3	3	6
Dohar (808)	10	13	23
Chonmaitree (809)	4	4	8
McClean (810)	8	11	19
Reisinger (811)	4	8	12
Schall (812)	6	7	13
Rosenthal (813)	2	2	4
Ibarra (814)	3	3	6
Jefferson (815)	6	6	12
Greenberg (816)	4	5	9
Rosenthal (817)	11	11	22
Silvers (818)	2	3	5
Antonelli (819)	2	3	5
Adelglass (840)	5	2	7
Barter (841)	7	7	14
DeAbate (842)	3	4	7
Drake (843)	10	7	17
Drehobl (844)	5	3	8
Fiddes (845)	5	7	12
Fries (846)	1	1	2
Obert (848)	3	4	7
Westberry (849)	1	2	3
Schaten (851)	2	4	6
Sidman (852)	11	15	26
Smith (853)	3	7	10
Whiting (854)	0	1	1
Nielsen (855)	23	22	45
Jones (856)	10	8	18
Goldblatt (857)	16	17	33
Galant (858)	1	1	2
Supance (859)	2	2	4
Schenkel (860)	0	0	0
Latin American Sites			
Hupat (880)	10	9	19
Mohs (881)	0	0	0
Total	228	246	474

A total of 228 and 246 subjects were enrolled at 37 sites in the ofloxacin-treated and Augmentin®-treated groups, respectively. Of these, 218/228 ofloxacin-treated and 237/246 Augmentin®-treated subjects were enrolled at 36 U.S. sites. At one Latin American site, 10 ofloxacin-treated subjects were enrolled and 9 Augmentin®-treated subjects were enrolled.

The following table summarizes the number of days of treatment for the two treatment groups:

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

Number of Days	Ofloxacin	Augmentin®	Total
<3	5 (2%)	9 (4%)	14 (3%)
3-6	30 (13%)	35 (14%)	65 (14%)
7-9	12 (5%)	12 (5%)	24 (5%)
10-12	178 (78%)	188 (76%)	366 (77%)
>12	1 (0.4%)	1 (0.4%)	2 (0.4%)
Missing	2 (1%)	1 (0.4%)	3 (1%)
Total	228	246	474

The majority of subjects in both treatment arms received at least ten days of therapy. The greatest portion of the remaining subjects had treatment durations of 3-6 days which would fall into the timeframe of the During-Therapy Visit (Visit 2).

The accountability of all 474 subjects, as assessed by the Applicant, is summarized in the follwoing table.

PRT-008 Subject Accountability

Parameter	Ofloxacin	Augmentin®	Total
Number of Subjects Enrolled	228	246	474
Received Drug	228	246	474
Fulfilled Inclusion/Exclusion Criteria	222	238	460
Visit 2 Procedures Completed	203	210	413
Visit 3 Procedures Completed *	210	229	439
Visit 4 Procedures Completed **	151	137	288
Intent-to-Treat Population	228	246	474
Clinically Evaluable Population	140	146	286
Microbiologically Evaluable Population	83	93	176
Audiometry Evaluable Population	30	26	56

* Includes 22 ofloxacin subjects and 30 Augmentin® subjects who completed Visit 3 procedures on their 2nd visit
** Includes 3 ofloxacin subjects and 2 Augmentin® subjects who completed Visit 4 procedures on their 3rd visit

As shown in the table above, the Applicant excluded 88 (39%) ofloxacin-treated subjects and 100 (41%) Augmentin®-treated subjects from the Intent-to-Treat Population to form the Applicant's Clinically Evaluable Population. From the Clinically Evaluable Population, the Applicant excluded 57 ofloxacin-treated subjects and 53 Augmentin®-treated subjects to form the Microbiologically Evaluable Population.

The following table outlines the Applicant's primary reasons for the exclusion of subjects from the Clinically Evaluable and Microbiologically Evaluable Populations.

Applicant's Primary Reasons for Exclusion from Analyzed Populations-PRT-008

	Ofloxacin	Augmentin®	Total
Total Number of Subjects Enrolled	228	246	474
Excluded from Intent-to-Treat Population	0	0	0
Total Intent-to-Treat Population	228	246	474
Excluded from Clinically Evaluable Population:	88 (39%)	100 (41%)	188 (40%)
Sole *Pseudomonas* Found at Baseline	20 (9%)	27 (11%)	47 (10%)
Protocol Non-Compliance	10 (4%)	20 (8%)	30 (6%)
Took Prohibited Medication	15 (7%)	15 (6%)	30 (6%)
Group A *Streptococci* Found	9 (4%)	7 (3%)	16 (3%)
Bilateral Infection after Visit 1	10 (4%)	3 (1%)	13 (3%)
Out of Visit 4 Window**	5 (2%)	8 (3%)	13 (3%)
Did Not Meet Inclusion/Exclusion Criteria	5 (2%)	7 (3%)	12 (3%)
Discontinued for Other Reason	5 (2%)	3 (1%)	8 (2%)
No Post Baseline Response*	3 (1%)	5 (2%)	8 (2%)
Fungus Found	2 (1%)	2 (1%)	4 (1%)
Pre-Existing Violation	2 (1%)	1 (0.4%)	3 (1%)
Lost to Follow-Up	1 (0.4%)	1 (0.4%)	2 (0.4%)
Not Assessed at Visit 4	1 (0.4%)	1 (0.4%)	2 (0.4%)
Total Clinically Evaluable Population	140 (61%)	146 (59%)	286 (60%)
Excluded from Microbiologically Evaluable Population:	57 (25%)	53 (22%)	110 (23%)
No Valid Baseline Pathogen	43 (19%)	42 (17%)	85 (18%)
Source Present but Culture Not Done	7 (3%)	4 (2%)	11 (2%)
Out of Visit 3 Window**	3 (1%)	2 (1%)	5 (1%)
Non Appropriate Culture Submitted	1 (0.4%)	2 (1%)	3 (1%)
No Culture Source but Symptoms Persist	1 (0.4%)	2 (1%)	3 (1%)
Not Assessed at Visit 3	2 (1%)	1 (0.4%)	3 (1%)
Total Microbiologically Evaluable Population	83 (36%)	93 (38%)	176 (37%)

* 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 reasons for exclusion from clinical evaluability were: *Pseudomonas aeruginosa* as the sole pathogen isolated at Baseline [20 (9%) ofloxacin-treated and 27 (11%) Augmentin®-treated subjects], protocol non-compliance [10 (4%) ofloxacin-treated and 20 (8%) Augmentin®-treated subjects], and took prohibited medication [15 (7%) ofloxacin-treated and 15 (6%) Augmentin®-treated subjects]. Though not statistically significant, it is noteworthy that a higher percentage (4%) of ofloxacin-treated subjects were excluded from the clinical evaluability than Augmentin®-treated subjects (1%) for bilateral infection after Visit 1.

The most common reason for exclusion from microbiological evaluability, in each treatment arm, was no valid Baseline pathogen [43 (19% of Intent-to-Treat population) ofloxacin-treated and 42 (17% of Intent-to-Treat population) Augmentin®-treated subjects].

Overall, the primary reasons for excluding subjects from clinical and microbiological evaluability appear to be similar between the two treatment groups.

A total of 80 (37 ofloxacin-treated and 43 Augmentin®-treated) subjects were enrolled in the audiometry sub-study. The distribution of these by center is shown in the following table:

Number of Subjects Enrolled and Included in Audiological Analyses at Each Site

	Ofloxacin		Augmentin®		Total	
Investigator (Site)	Enrolled	Included in Analyses*	Enrolled	Included in Analyses*	Enrolled	Included in Analyses*
U.S. Sites						
Agro (802)	9	7	9	6	18	13
Goldberg (804)	2	1	5	2	7	3
Dohar (808)	4	2	3	2	7	4
Chonmaitree (809)	0	0	1	0	1	0
McClean (810)	4	4	3	2	7	6
Greenberg (816)	1	1	2	1	3	2
Rosenthal (817)	2	1	3	1	5	2
Silvers (818)	0	0	2	1	2	1
Antonelli (819)	0	0	1	0	1	0
Drake (843)	5	5	3	1	8	6
Obert (848)	1	1	1	1	2	2
Sidman (852)	1	1	3	3	4	4
Nielsen (855)	2	1	1	1	3	2
Jones (856)	0	0	1	0	1	0
Latin American Sites						
Hupat (880)	6	6	5	5	11	11
Total	37	30	43	26	80	56

* Included subjects who had hearing threshold data for at least one frequency at both Visit 1 and Visit 4 (or post-baseline for early discontinuations) or had information on change in PTA for air or bone conduction

Of the audiometry subjects enrolled, only those subjects who had hearing threshold data for at least one frequency at both Visit 1 and Visit 4 (or post-baseline for early discontinuations) were included by the Applicant in the audiological analyses. Of the ofloxacin-treated subjects 30/37 were included in the audiological analyses, and 26/43 of the Augmentin®-treated were included.

Medical Officer's Comment: *As was true for Study 003, data from Dr. Fiddes was excluded from analyses by the Medical Officer. This was Site 45 in this study.*

There were 12 subjects, 5 ofloxacin-treated and 7 Augmentin®-treated subjects, lost from the Intent-to-Treat Population by the exclusion of this single center. Compared to the Applicant's Clinically Evaluable Population, the net effect of the Medical Officer's removal of these twelve subjects was to remove 6 evaluable subjects: 2 ofloxacin-treated clinical cures, 3 Augmentin®-treated clinical cures, and 1 ofloxacin-treated clinical failure.

None of the twelve subjects from Site #45 had been deemed microbiologically evaluable by the Applicant. So, the exclusion by the Medical Officer of these twelve subjects had no impact on the Applicant's Microbiologically Evaluable Population.

Additionally, the Medical Officer changed the clinical evaluability status of four subjects, and the microbiological evaluability status (but not the clinical evaluability status) of four other subjects.

The following table summarizes the changes in clinical and microbiological evaluability made by the Medical Officer:

Medical Officer's Changes in Clinical and Microbiological Evaluability Status PRT-008

Subject #	Applicant Clinical Eval. Status	Applicant Overall Clinical Response	Applicant Micro. Eval. Status	Applicant Micro. Response	MO Clinical Eval. Status	MO Overall Clinical Response	MO Micro. Eval. Status	MO Micro Response
Ofloxacin Group								
	Evaluable	Cure	Noneval.	-	Evaluable	Cure	Evaluable	Presumed Erad.[1]
	Evaluable	Cure	Noneval.	-	Noneval.	-	Noneval	-
	Evaluable	Cure	Noneval.	-	Noneval.	-	Noneval.	-
	Evaluable	Cure	Noneval.	-	Evaluable	Cure	Evaluable	Presumed Erad.[1]
Augmentin® Group								
	Noneval.	-	Noneval	-	Evaluable	Failure	Evaluable	Doc. Persist.[2]
	Noneval.	-	Noneval.	-	Evaluable	Cure	Noneval.	-
	Evaluable	Cure	Noneval.	-	Evaluable	Cure	Evaluable	Presumed Erad.[1]
	Evaluable	Cure	Noneval.	-	Evaluable	Cure	Evaluable	Presumed Erad.[1]

1 Presumed Eradication
2 Documented Persistence

Compared to the Applicant's Clinically Evaluable Population (after exclusion of Site #45) the net effect of the Medical Officer changes shown in the table above was to subtract two evaluable cures from the ofloxacin-treated group, and to add one evaluable cure and one evaluable failure to the Augmentin® arm. These are reviewed below:

Ofloxacin Group

Subject ____ This subject had Visit 2 on Day 4 and there was no clinical change. The subject did not return until Visit 4 on Day 18, and at that time was assessed as a clinical cure. The Medical Officer considered the two-week gap in clinical assessment between the During-Therapy Visit, where no clinical change was shown, and the Test-of-Cure Visit too long and deemed this subject "nonevaluable."

Subject ____ This subject had Visit 2 on Day 5, had no End-of-Therapy Visit (Visit 3), and was seen for the Test-ot-Cure Visit (Visit 4) on Day 17. The Medical Officer considered this subject "nonevaluable" due to the lack of an End-of-Therapy Visit.

Augmentin® Group

Subject ____ The Investigator considered this subject a clinical failure at Visit 3 and obtained the appropriate follow-up cultures. At this visit the subject was given topical antibiotics for conjunctivitis. The Applicant considered this subject "nonevaluable" due to prohibited medications, but the MO considered the subject an evaluable failure.

Subject ____ This subject required topical antibiotics for a burn on the finger at Day 13. Because this was not in the head and neck area, and the subject was called a cure with a dry ear at Visit 2 on Day 6, the MO considered this subject clinically evaluable.

Compared to the Applicant's Microbiologically Evaluable Population, the net effect of the Medical Officer's evaluability status changes was to add two ofloxacin-treated successes (Presumed Eradication), add two Augmentin®-treated successes (Presumed Eradication), and to add one Augmentin®-treated microbiologic failure (Documented Persistence). These are reviewed below:

Ofloxacin Group

Subject The Applicant considered this subject not microbiologically evaluable because the day of Visit 3 was out of the time window. However, because there was no drainage at Visit 3 or Visit 4 (which was within the proper window) and the subject was clinically cured, the Medical Officer considered this subject microbiologically evaluable.

Subject The Applicant considered this subject not microbiologically evaluable because Visit 3 on Day 10 was out of the proper time window. However, because a culture at Visit 2 showed no growth, and the subject did not have drainage at Visit 3 or 4, the MO considered this subject microbiologically evaluable.

Augmentin® Group

Subject The Applicant considered this subject not microbiologically evaluable because the day of Visit 3 was out of the time window. However, the timing of the follow-up visits looked appropriate to the Medical Officer, and there were no secretions at these follow-up visits. Therefore, the MO considered this subject microbiologically evaluable.

Subject The Applicant considered this subject not microbiologically evaluable because the day of Visit 3 was out of the time window. However, the timing of the follow-up visits looked appropriate to the Medical Officer, and there were no secretions at these follow-up visits. Therefore, the MO considered this subject microbiologically evaluable.

Of the eight subjects whose clinical and/or microbiological evaluability status the Medical Officer changed, as listed in the table above, there were only two subjects who had audiological assessments. Both were Augmentin®-treated subjects, Of these two subjects, only had audiological assessments at both Visit 1 and Visit 4 and was already included in the analyses. Site #45 was not an audiological testing site. Therefore, the Medical Officer changes in evaluability did not affect the population evaluable for the audiological analyses.

The following table summarizes the Medical Officer's Clinically Evaluable and Microbiologically Evaluable Populations by center.

Medical Officer's Clinical and Microbiological Evaluable Populations by Center

Investigator (Site)	Ofloxacin Treatment Group			Augmentin® Treatment Group		
	Intent to Treat	Clinically Evaluable	Microbiologically Evaluable	Intent to Treat	Clinically Evaluable	Microbiologically Evaluable
U.S. Sites						
Asmar (801)	5	0	0	4	2	1
Agro (802)	16	12	8	16	9	6
Goldberg (804)	12	7	5	14	10	8
Harley (805)	2	1	1	2	0	0
Jordan (806)	10	7	4	8	6	4
Lumry (807)	3	2	0	3	1	0
Dohar (808)	10	7	6	13	5	3
Chonmaitree (809)	4	3	2	4	3	3
McClean (810)	8	6	3	11	9	9
Reisinger (811)	4	2	2	8	4	3
Schall (812)	6	3	1	7	4	2
Rosenthal (813)	2	1	0	2	0	0
Ibarra (814)	3	1	0	3	1	1
Jefferson (815)	6	5	2	6	5	3
Greenberg (816)	4	4	2	5	2	1
Rosenthal (817)	11	8	4	11	5	3
Silvers (818)	2	2	1	3	2	2
Antonelli (819)	2	2	1	3	2	2
Adelglass (840)	5	2	1	2	1	1
Barter (841)	7	7	4	7	7	2
DeAbate (842)	3	1	0	4	3	1
Drake (843)	10	4	4	7	6	5
Drehobl (844)	5	2	1	3	3	2
Fiddes (845)*	0	0	0	0	0	0
Fries (846)	1	1	1	1	1	0
Obert (848)	3	2	1	4	2	1
Westberry (849)	1	1	1	2	1	0
Schaten (851)	2	0	0	4	3	1
Sidman (852)	11	8	7	15	9	5
Smith (853)	3	2	2	7	4	1
Whiting (854)	0	0	0	1	0	0
Nielsen (855)	23	13	9	22	12	9
Jones (856)	10	4	2	8	4	2
Goldblatt (857)	16	5	4	17	10	7

Medical Officer's Clinical and Microbiological Evaluable Populations by Center, continued						
Investigator (Site)	Ofloxacin Treatment Group			Augmentin® Treatment Group		
	Intent to Treat	Clinically Evaluable	Microbiologically Evaluable	Intent to Treat	Clinically Evaluable	Microbiologically Evaluable
Galant (858)	1	1	1	1	0	0
Supance (859)	2	2	1	2	2	2
Schenkel (860)	0	0	0	0	0	0
Latin American Sites						
Hupat (880)	10	7	4	9	7	6
Mohs (881)	0	0	0	0	0	0
Total	223	135	85	239	145	96

The Medical Officer excluded all subjects from this center.

The following table summarizes the various evaluable populations as presented by the Applicant, and as assessed by the Medical Officer.

Protocol 008- Acute Otitis Media Subject Populations as Presented by the Applicant and As Assessed by the Medical Officer		
	Ofloxacin	Augmentin®
Applicant's Intent-to-Treat Population	228	246
Modified Intent-to-Treat Population	223	239
Applicant's Clinically Evaluable Population	140	146
Medical Officer's Clinically Evaluable Population	135	145
Applicant's Microbiologically Evaluable Population	83	93
Medical Officer's Microbiologically Evaluable Pop.	85	96
Audiologically Evaluable Population (Applicant & Medical Officer's are the same)	30	26

The Medical Officer performed efficacy analyses on the Modified Intent-to-Treat (462 subjects), the Clinically Evaluable (280 subjects), and the Microbiologically Evaluable (176 subjects) Populations. Safety analyses were performed on the 56 subjects of the Audiologically Evaluable Population.

-Demographics

The following table summarizes the demographic information for the Applicant's Intent-to-Treat Population.

Summary of Demographic Data for the Applicant's Intent-to-Treat Population

	Ofloxacin	Augmentin®	P-value
Number of Subjects	228	246	
Age (years)			
Mean ± S.D.	3.5 ± 2.49	3.7 ± 2.73	0.59
Age Group (# subjects)			
< 2 years	81 (36%)	96 (39%)	0.456
2-12 years	147 (65%)	150 (61%)	
Sex (# subjects)			
Male	124 (54%)	150 (61%)	0.145
Female	104 (46%)	96 (39%)	
Race (# subjects)			
Caucasian	182 (80%)	192 (78%)	0.771
African American	18 (8%)	22 (9%)	
Hispanic	20 (9%)	24 (10%)	
Other	8 (4%)	8 (3%)	

Cochran-Mantel-Haenszel Test was used to compare age group, sex, and race. Age was compared using 2-way ANOVA.

There were no statistically significant differences between the ofloxacin-treated group and the Augmentin®-treated group with respect to mean age, age group distribution, sex distribution, and race distribution for the Applicant's Intent-to-Treat Population.

The Applicant compared other Baseline and target ear characteristics among the subjects in the two treatment groups in the Intent-to-Treat Population. These comparisons are summarized in the following table:

Summary of Baseline and Target Ear Characteristics for the Applicant's Intent-to-Treat Population

	Ofloxacin	Augmentin®	P-value
Number of Subjects	228	246	
Target Ear			
Right	118 (52%)	134 (55%)	0.537
Left	110 (48%)	112 (46%)	
Infection			
Unilateral	190 (83%)	207 (84%)	0.819
Bilateral	38 (17%)	39 (16%)	
Tube Placement (Days)			
Mean ± S.D.	319.0 ± 344.20	320.3 ± 358.08	0.989
Median	211	215	
Tube Type			
Short Tube	121 (53%)	113 (46%)	0.316
Long Tube	20 (9%)	20 (8%)	
Unknown	87 (38%)	112 (46%)	
Drainage (Days)			
Mean ± S.D.	4.3 ± 4.19	4.4 ± 4.22	0.868
Median	3	3	
Granulation Tissue			
Absent	198 (87%)	205 (84%)	0.209
Mild	24 (11%)	26 (11%)	
Moderate	6 (3%)	10 (4%)	
Severe	0	4 (2%)	
Organisms			
None	25 (11%)	19 (8%)	0.065
One	70 (31%)	98 (40%)	
Two	67 (30%)	71 (29%)	
Three	34 (15%)	40 (16%)	
Four or more	31 (14%)	18 (7%)	
Valid Pathogens			
None	67 (30%)	71 (29%)	0.676
One	93 (41%)	111 (45%)	
Two	51 (23%)	45 (18%)	
Three or more	16 (7%)	19 (8%)	

As shown in the table above, there were no statistically significant differences between treatment groups in the Applicant's Intent-to-Treat Population with respect to baseline and target ear characteristics such as target ear, laterality of infection, duration of tube placement, tube type, duration of drainage, granulation tissue, number of Baseline organisms, and number of Baseline pathogens.

Medical Officer's Comment:

- *In the Applicant's Clinically and Microbiologically Evaluable Populations there was a significant difference with respect to age group distribution between the two treatment groups (more children aged < 2 years in the Augmentin®-treated group). All other parameters were balanced and resembled the ITT population.*
- *In the Applicant's Microbiologically Evaluable Population a significantly higher percentage of ofloxacin-treated subjects (52%) had multiple pathogens at Baseline than Augmentin®-treated subjects (36%) (p=0.048).*
- *In the Medical Officer's Clinically and Microbiologically Evaluable Populations the two treatment groups were balanced with respect to the demographic features of age, gender, and race, as well as the pretreatment target ear characteristics. All features were similar to those of the ITT Population.*

Efficacy Results

Clinical Efficacy

The clinical response at each post-baseline visit for the Applicant's Intent-to-Treat Population is shown in the following table.

Clinical Response for the Applicant's Intent-to-Treat Population

Visit	Response	Ofloxacin	Augmentin®	P-value	95% C.I.
2	Clinical Improvement	165 (81%)	169 (81%)	0.913	(-7.5%, 8.4%)
	No Clinical Change	32 (16%)	35 (17%)		
	Clinical Failure	3 (2%)	2 (1%)		
	Indeterminate	3 (2%)	4 (2%)		
	Total	203	210		
3	Clinical Improvement	169 (81%)	155 (68%)	0.017	(1.4%, 18.1%)
	No Clinical Change	6 (3%)	9 (4%)		
	Clinical Failure	28 (13%)	47 (21%)		
	Indeterminate	7 (3%)	18 (8%)		
	Total	210	229		
4	Clinical Cure	136 (90%)	119 (87%)	0.386	(-4.7%, 10.9%)
	Clinical Failure	13 (9%)	16 (12%)		
	Indeterminate	2 (1%)	2 (2%)		
	Total	151	137		
Overall	Cure	107 (47%)	101 (41%)	0.169	(-3.7%, 18.2%)
	Failure	33 (15%)	45 (18%)		
	Not Evaluable	88 (39%)	100 (41%)		
	Total	228	246		

With respect to the Overall Clinical Response, equivalence was demonstrated between the two treatment groups in the Applicant's Intent-to-Treat Population.

Medical Officer's Comment: *The Medical Officer did not consider the sub-group analysis for the Applicant's Intent-to-Treat Population particularly important, and did not reproduce it in this review.*

The clinical response, by visit and Overall, for the subjects in the Applicant's Clinically Evaluable Population is shown in the following table.

Clinical Response for the Applicant's Clinically Evaluable Population

Visit	Response	Ofloxacin	Augmentin®	P-value	95% C.I.
2	Clinical Improvement	116 (84%)	122 (86%)	0.664	(-10.9%, 7.2%)
	No Clinical Change	21 (15%)	19 (13%)		
	Clinical Failure	1 (1%)	1 (1%)		
	Total	138	142		
3	Clinical Improvement	115 (84%)	112 (78%)	0.192	(-3.7%, 16.0%)
	No Clinical Change	2 (2%)	1 (1%)		
	Clinical Failure	20 (15%)	31 (22%)		
	Total	137	144		
4	Clinical Cure	107 (89%)	101 (89%)	0.966	(-9.0%, 8.6%)
	Clinical Failure	13 (11%)	12 (11%)		
	Total	120	113		
Overall	Cure	107 (76%)	101 (69%)	0.169	(-3.7%, 18.2%)
	Failure	33 (24%)	45 (31%)		
	Total	140	146		

The Applicant noted no statistically significant differences between treatment groups within the Clinically Evaluable Population for sub-groups analyzed by gender, race, and age.

Medical Officer's Comment: *For the Applicant's Clinically Evaluable Population, the Overall Clinical Response demonstrated equivalence: cure rates of 76% for ofloxacin-treated subjects vs. 69% for*

Augmentin®-treated subjects (p=0.17; CI_{95} [-3.7%, 18.2%]).

The Overall Clinical Response of the Medical Officer's Clinically Evaluable Population is shown in the following table:

Overall Clinical Response of the Medical Officer's Clinically Evaluable Population-PRT008		
Clinical Response	Ofloxacin (N=135)	Augmentin® (N=145)
Cure	103 (76.3%)	99 (68.3%)
Failure	32 (23.7%)	46 (31.7%)
Ofloxacin vs. Augmentin® by Cure	8.0%, 95%CI: -3.1%, 19.2%	

Medical Officer's Comment: *The 95% confidence interval (-3.1%, 19.2%) demonstrates therapeutic equivalence between the two treatment groups in the Medical Officer's Clinically Evaluable Population. The Weighted Mantel-Haenszel test was also used to compute the 95% confidence interval for the difference of the cure rate between ofloxacin and Augmentin®, and it, too, demonstrated equivalence (-1.7%, 17.1%).*

Also, the Overall Clinical cure rates in the MO Clinically Evaluable Population were consistent across subgroups anlayzed by gender, age, and race.

Summary of Clinical Efficacy

The following table outlines the Overall Clinical Cure Rates for the Applicant's and Medical Officer's 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)

-Microbiological Efficacy

Overall Microbiological Response by Subject

Microbiological Response by Subject for the Applicant's Microbiologically Evaluable Population-PRT008

Visit	Response	Ofloxacin	Augmentin®	P-value	95% C.I.
3	Eradication	82 (99%)	67 (72%)	< 0.001	(16.2%, 37.3%)
	Persistence	1 (1%)	26 (28%)		
	Total	83	93		
4	Eradication	69 (97%)	63 (91%)	0.122	(-3.2%, 15.0%)
	Persistence	0	1 (1%)		
	Recurrence	2 (3%)	4 (6%)		
	Reinfection	0	1 (1%)		
	Total	71	69		
Overall	Eradication	80 (96%)	62 (67%)	< 0.001	(18.2%, 41.2%)
	Persistence	1 (1%)	26 (28%)		
	Recurrence	2 (2%)	4 (4%)		
	Reinfection	0	1 (1%)		
	Total	83	93		

Medical Officer's Comment: *The 95% confidence interval (18.2%, 41.2%) for the difference in overall eradication rates between the ofloxacin and Augmentin® -treated groups demonstrates that in the Applicant's Microbiologically Evaluable Population, the ofloxacin-treated group had a significantly higher eradication rate than the Augmentin®-treated group.*

The Medical Officer's Overall Microbiological Response by Subject 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 eradication rates for ofloxacin (96.5%) and Augmentin® (66.7%) in the Medical Officer's Microbiologically Evaluable Population were essentially the same as those in the Applicant's Microbiologically Evaluable Population. In both the Applicant's and the Medical Officer's Microbiologically Evaluable Populations the eradication rate for ofloxacin is roughly 30% higher than that for Augmentin®. And in each population, the 95% confidence intervals suggest superiority of ofloxacin vs. Augmentin® for eradication.

Overall Microbiological Response by Pathogen

In the assessment of the organisms isolated, any bacteria from the baseline culture with the potential to cause otitis media and had a growth index of 2+ or greater was considered a valid pathogen. However, because of their high association with acute otitis media and because they are not generally known to be colonizers of the external auditory canal, *Hamemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae* were considered to be valid pathogens regardless of their growth index.

In the Applicant's Intent-to-Treat Population, there were a total of 247 isolates of 22 valid pathogens isolated at Baseline from 160/228 ofloxacin-treated subjects, and 260 isolates of 20 valid pathogens isolated at Baseline from 175/246 Augmentin®-treated subjects. The following table outlines the distribution of these Baseline pathogens.

Valid Baseline Pathogens Isolated from the Target Ear for the Applicant's Intent-to-Treat Population-PRT008

Pathogen	Ofloxacin	Augmentin®	Total
Haemophilus influenzae	55	64	119
Streptococcus pneumoniae	52	63	115
Staphylococcus aureus	41	42	83
Pseudomonas aeruginosa	37	42	79
Moraxella catarrhalis	18	17	35
Enterobacter cloacae	9	3	12
Citrobacter freundii	5	4	9
Enterococcus faecalis	4	5	9
Serratia marcescens	3	5	8
Alcaligenes xylosoxidans	3	3	6
Escherichia coli	4	2	6
A. calcoaceticus V. anitratus	3	1	4
Xanthomonas maltophilia	2	2	4
Enterobacter agglomerans	2	0	2
Klebsiella pneumoniae	1	1	2
Proteus mirabilis	2	0	2
A. calcoacet. V. haemolyticus	0	1	1
A. calcoaceticus V. lwoffi	0	1	1
Acinetobacter calcoaceticus	0	1	1
Aeromonas caviae	0	1	1
Aeromonas hydrophila	1	0	1
Alcaligenes faecalis	1	0	1
Citrobacter diversus	1	0	1
Klebsiella oxytoca	1	0	1
Leclercia adecarboxylata	0	1	1
Providencia rettgeri	1	0	1
Pseudomonas paucimobilis	1	0	1
Streptococcus anginosus	0	1	1
Total	247	260	507

The most common valid Baseline pathogens isolated from ofloxacin-treated subjects and Augmentin®-treated subjects, respectively for the Applicant's Intent-to-Treat population were: *Haemophilus influenzae* (55,64), *Streptococcus pneumoniae* (52,63), *Staphylococcus aureus* (41,42), *Pseudomonas aeruginosa* (37,42), and *Moraxella catarrhalis* (18,17).

Prior to treatment, 142 isolates of 20 valid Baseline pathogens were isolated from the 83 ofloxacin-treated subjects and 140 isolates of 16 valid Baseline pathogens were isolated from the 93 Augmentin®-treated subjects included in the Applicant's Microbiologically Evaluable Population.

The five pathogens most commonly isolated in the Applicant's Microbiologically Evaluable Population are outlined in the table below:

Most Common Valid Baseline Pathogens for the Applicant's Microbiologically Evaluable Population-PRT008

Pathogen	Ofloxacin	Augmentin®	Total
Streptococcus pneumoniae	36	38	74
Haemophilus influenzae	28	39	67
Staphylococcus aureus	28	25	53
Moraxella catarrhalis	14	10	24
Pseudomonas aeruginosa	9	7	16

Pseudomonas aeruginosa is generally resistant to Augmentin®. Subjects whose otorrhea cultures resulted in the isolation of this pathogen without any other pathogen(s) at Visit 1 were dropped from the study [20 (9%) ofloxacin-treated and 27 (11%) Augmentin®-treated subjects] and not included in the Applicant's Microbiologically Evaluable Population. As a result, the ranking of the most common valid Baseline pathogens was different for the Applicant's Microbiologically Evaluable Population (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa)* than for the Applicant's Intent-to-Treat Population (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Moraxella catarrhalis*).

The Applicant outlined the eradication rates for all the Baseline pathogens from the target ear for subjects in each treatment arm of their Microbiologically Evaluable Population. The following table shows these results.

Overall Eradication Rates by Baseline Pathogen for the Applicant's Microbiologically Evaluable Population

Pathogen	Ofloxacin	Augmentin®
Streptococcus pneumoniae	100% (36/36)	87% (33/38)
Haemophilus influenzae	93% (26/28)	77% (30/39)
Staphylococcus aureus	96% (27/28)	48% (12/25)
Moraxella catarrhalis	93% (13/14)	90% (9/10)
Pseudomonas aeruginosa	100% (9/9)	43% (3/7)
Enterobacter cloacae	100% (5/5)	67% (2/3)
Enterococcus faecalis	100% (2/2)	60% (3/5)
Citrobacter freundii	100% (3/3)	50% (1/2)
Serratia marcescens	100% (2/2)	33% (1/3)
Alcaligenes xylosoxidans	100% (3/3)	100% (1/1)
Escherichia coli	100% (2/2)	0% (0/1)
Xanthomonas maltophilia	100% (1/1)	100% (2/2)
A. calcoaceticus V. anitratus	100% (1/1)	100% (1/1)
Enterobacter agglomerans	100% (2/2)	None
A. calcoacet V. haemolyticus	None	100% (1/1)
A. calcoaceticus V. lwoffi	None	100% (1/1)
Aeromonas caviae	None	0% (0/1)
Alcaligenes faecalis	100% (1/1)	None
Klebsiella oxytoca	100% (1/1)	None
Klebsiella pneumoniae	100% (1/1)	None
Proteus mirabilis	100% (1/1)	None
Providencia rettgeri	100% (1/1)	None
Pseudomonas paucimobilis	100% (1/1)	None
Total	97% (138/142)	71% (100/140)

Medical Officer's Comment: *In the Applicant's Microbiologically Evaluable Population, the total per pathogen eradication rate for the baseline pathogens in the was 97% (138/142) for the ofloxacin-treated subjects, and 71% (100/140) for the Augmentin®-treated subjects (95% C.I.: 17.1%, 34.3%).*

The Medical Officer's Microbiologically Evaluable Population differed from the Applicant's by five subjects, 2 ofloxacin-treated and 3 Augmentin®-treated subjects. The clinical and microbiological outcomes of these subjects, as assessed by the Medical Officer, are shown in the table below:

Clinical Response and Microbiological Response of Baseline Pathogens in Additional Subjects in the Medical Officer's Microbiologically Evaluable Population

Subject #	Overall Clinical Response	Baseline Pathogen(s)	Overall Microbiological Response
Ofloxacin Treatment Group			
	Cure	*Haemophilus influenzae*	Eradication
	Cure	*Haemophilus influenzae*	Eradication
Augmentin® Treatment Group			
	Failure	*Staphylococcus aureus*	Persistence (Documented)
		Streptococcus pneumoniae	Eradication (Documented)
	Cure	*Pasterella multocida*	Eradication
		Staphylococcus aureus	Eradication
	Cure	*Staphylococcus aureus*	Eradication

Neither the Applicant nor the MO considered the *Pasteurella multocida* isolate from Subject to be a pathogen. Thus, the three organisms involved in the Medical Officer's redesignation of microbiological evaluability are: *Haemophilus influenzae, Staphylococcus aureus,* and *Streptococcus pneumoniae.*

With the additional isolates as outlined above, the Medical Officer had a per pathogen eradication rate of 97.2% (140/144) for the Baseline pathogens from ofloxacin-treated subjects, and 71.5% (103/144) for the Baseline pathogens from Augmentin®-treated subjects.

The per pathogen eradication rates for the five most commonly isolated pathogens in the Medical Officer's Microbiologically Evaluable Population are shown in the following table:

Overall Pathogen Eradication Rates of the MO Microbiologically Evaluable Population (Five Most Commonly Isolated Baseline Pathogens)

Pathogen	Ofloxacin Group	Augmentin® Group
Streptococcus pneumoniae	36/36 (100%)	34/39 (87.2%)
Haemophilus influenzae	28/30 (93.3%)	30/39 (76.9%)
Staphylococcus aureus	27/28 (96.4%)	14/28 (50.0%)
Moraxella catarrhalis	13/14 (92.9%)	9/10 (90%)
Pseudomonas aeruginosa	9/9 (100%)	3/7 (42.9%)

Compared to the Applicant's population, the Medical Officer's population had two additional *H. influenzae* isolates (both eradicated) in the ofloxacin group; 3 additional *S. aureus* isolates (1 persistent and 2 eradicated) in the Augmentin® group; and one additional *S. pneumoniae* isolate (eradicated) in the Augmentin® group.

Overall Clinical Cure Rates by Baseline Pathogen

The Applicant outlined the overall clinical cure rates by baseline pathogen as well. The following table outlines these results.

Overall Cure Rates by Baseline Pathogen for the Applicant's Microbiologically Evaluable Population

Pathogen	Ofloxacin		Augmentin®	
Streptococcus pneumoniae	81%	(29/36)	76%	(29/38)
Haemophilus influenzae	68%	(19/28)	67%	(26/39)
Staphylococcus aureus	82%	(23/28)	44%	(11/25)
Moraxella catarrhalis	71%	(10/14)	90%	(9/10)
Pseudomonas aeruginosa	67%	(6/9)	43%	(3/7)
Enterobacter cloacae	100%	(5/5)	33%	(1/3)
Enterococcus faecalis	50%	(1/2)	80%	(4/5)
Citrobacter freundii	100%	(3/3)	50%	(1/2)
Serratia marcescens	100%	(2/2)	33%	(1/3)
Alcaligenes xylosoxidans	100%	(3/3)	100%	(1/1)
Escherichia coli	50%	(1/2)	100%	(1/1)
Xanthomonas maltophilia	100%	(1/1)	50%	(1/2)
A. calcoaceticus V. anitratus	0%	(0/1)	100%	(1/1)
Enterobacter agglomerans	100%	(2/2)	None	
A. calcoacet V. haemolyticus	None		100%	(1/1)
A. calcoaceticus V. lwoffi	None		100%	(1/1)
Aeromonas caviae	None		0%	(0/1)
Alcaligenes faecalis	100%	(1/1)	None	
Klebsiella oxytoca	100%	(1/1)	None	
Klebsiella pneumoniae	100%	(1/1)	None	
Proteus mirabilis	100%	(1/1)	None	
Providencia rettgeri	100%	(1/1)	None	
Pseudomonas paucimobilis	100%	(1/1)	None	
Total	78%	(111/142)	65%	(91/140)

Medical Officer's Comment: *The total clinical cure rate by baseline pathogens for the Applicant's Microbiologically Evaluable Population was 78% (111/142) for the ofloxacin-treated subjects, and 65% (91/140) for the Augmentin®-treated subects (95% C.I.: 2.0%, 24.3%).*

APPEARS THIS WAY
ON ORIGINAL

The cure rates by baseline pathogen for the Medical Officer's Microbiologically Evaluable Population are shown in the table below:

Medical Officer's Comment: *The MO will only show the cure rates for the seven pathogens the Applicant seeks in the labeling. The results that differ from those reported by the Applicant are shown in bold print.*

Overall Cure Rates by Baseline Pathogen for the Medical Officer's Microbiologically Evaluable Population-PRT008

Pathogen	Ofloxacin	Augmentin®
Staphylococcus aureus	23/28 (82%)	**13/28 (46%)**
Streptococcus pneumoniae	29/36 (81%)	**29/39 (74%)**
Enterobacter cloacae	5/5 (100%)	1/3 (33%)
Haemophilus influenzae	**21/30 (70%)**	26/39 (67%)
Klebsiella pneumoniae	1/1 (100%)	None
Moraxella catarrhalis	10/14 (71%)	9/10 (90%)
Pseudomonas aeruginosa	6/9 (67%)	3/7 (43%)

Medical Officer's Comment: *Overall, the cure rates in the MO population were not much different than those derived by the Applicant. The Medical Officer was surprised by the relatively low clinical and microbiological success rates in the Augmentin® group, particularly for Staphylococcus aureus, but found no readily identifiable factor that might explain these results.*

Susceptility Testing of Baseline Pathogens

MIC Testing

The Applicant used NCCLS guidelines 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 sensitive if the MIC value was less than 4 µg/mL, intermediate if the MIC value was equal to 4 µg/mL , and resistant if the MIC value of ofloxacin was greater than 4 µg/mL. For subjects in the Augmentin®-treated group a pathogen was considered sensitive if the MIC value was less than 16/8 µg/mL, intermediate if the MIC value was equal to 16/8 µg/mL, and resistant if the MIC value of Amox/Clav was greater than 16/8 µg/mL.

The Overall Clinical Response by Baseline Pathogen sensitivity to the study drug received for subjects in each treatment arm of the Applicant's Microbiologically Evaluable Population is shown in the following table:

Overall Clinical Response by Baseline Pathogen Sensitivity to Drug Received for the Applicant's Microbiologically Evaluable Population

	Ofloxacin			Augmentin®		
Valid Baseline Pathogen	Cure	Failure	Total	Cure	Failure	Total
Sensitive	108 (79%)	28 (21%)	136	81 (70%)	34 (30%)	115
Intermediate	3 (60%)	2 (40%)	5	0	1 (100%)	1
Resistant	0	1 (100%)	1	9 (47%)	10 (53%)	19
Acquired Resistance	0	0	0	1 (20%)	4 (80%)	5

Note: Counts are by pathogen

Approximately 79% (108/136) and 70% (81/115) of the Baseline pathogens that were sensitive to the drug which the subject received came from subjects who had an Overall Clinical Response of cure for the ofloxacin-treated and the Augmentin®-treated groups, respectively. In the Medical

Officer's Microbiologically Evaluable Population, both of the additional H. influenzae isolates found in two subjects who were cured were sensitive to to ofloxacin. Of the two Augmentin®-treated subjects who had *S. aureus* and were cured, one had a resistant isolate and one had a sensitive isolate. The one Augmentin®-treated subject who was a treatment failure had a sensitive *S. aureus* and a sensitive *S. pneumoniae*.

No pathogens isolated from the ofloxacin-treated subjects acquired resistance during the study, but 5 isolates from the Augmentin®-treated subjects acquired resistance during the study. Three of these five isolates were *S. aureus* and all subjects were treatment failures and the pathogen was not eradicated. One was an isolate of *H. influenzae* that had an overall response of eradication and was found in a subject who was cured. The other isolate was found in a subject who was a treatment failure and it was an isolate of *Serratia marcescens* that was not eradicated.

Disc Diffusion Testing

The Applicant summarized, for the microbiologically evaluable population, the Kirby-Bauer zones of inhibition of valid Baseline pathogens along with the Overall Clinical Response of the subject in whom the valid Baseline pathogen was isolated. This is shown in the table below:

Overall Clinical Response by Kirby-Bauer Zones of Inhibition of Valid Baseline Pathogens to Ofloxacin for the Applicant's Microbiologically Evaluable Population

	Ofloxacin			Augmentin®		
	Cure	Failure	Total	Cure	Failure	Total
Zones ≥ 16 mm	103 (78%)	29 (22%)	132	87 (64%)	48 (36%)	135
Zones 13-15 mm	4 (80%)	1 (20%)	5	3 (75%)	1 (25%)	4
Zones ≤ 12 mm	0	1 (100%)	1	1 (100%)	0	1

While the response rates seem to be fairly evenly distributed accross both treatment arms, the applicability of these guidelines to topical adminstration of ofloxacin is not well-established.

Beta-Lactamase Testing

The Applicant performed beta-lactamase testing by the chromogenic cephalosporin method on all isolates of *H. influenzae* and *Moraxella catarrhalis*. The results of the test (positive or negative) for Baseline isolates in the Applicant's Microbiologically Evaluable Population, along with the Overall Clinical Response of the subjects in whom one or both of these pathogens was isolated, is shown in the table below:

Overall Clinical Response by Beta-Lactamase Result of *Haemophilus influenzae* and *Moraxella catarrhalis* Isolated from the Target Ear at Baseline for the Applicant's Microbiologically Evaluable Population

	Ofloxacin			Augmentin®		
Pathogen	Cure	Failure	Total	Cure	Failure	Total
Haemophilus influenzae						
Negative Result	13 (65%)	7 (35%)	20	17 (68%)	8 (32%)	25
Positive Result	6 (75%)	2 (25%)	8	9 (64%)	5 (36%)	14
Moraxella catarrhalis						
Negative Result	1 (100%)	0	1	1 (100%)	0	1
Positive Result	9 (69%)	4 (31%)	13	8 (89%)	1 (11%)	9

Of the *H. influenzae* isolates found in microbiologically evaluable subjects in the ofloxacin-treated group, 28.6% (8/28) were beta-lactamase positive, and 35.9% (14/39) of those from the Augmentin®-treated subjects were beta-lactamase positive. Across both treatment groups, 32.8% (22/67) of the *Haemophilus influenzae* isolates were beta-lactamase positive.

Of the two additional *H. influenzae* isolates that were added to the ofloxacin-treated cures by the

Medical Officer, one was beta-lactamase negative and the other was beta-lactamase positive.

Of the *M. catarrhalis* isolates found in microbiologically evaluable subjects in the ofloxacin-treated group, 92.9% (13/14) were beta-lactamase positive, and 90% (9/10) of those from the Augmentin®-treated subjects were beta-lactamase positive. Across both treatment groups, 91.7% (22/24) of the *Moraxella catarrhalis* isolates were beta-lactamase positive.

Overall, there does not seem to be significant differences between the two treatment groups with respect to the production of beta-lactamase and the Overall Clinical Response for subjects with *H. influenzae* or *Moraxella catarrhalis* isolated at Baseline.

Susceptibility to Penicillin and Trimethoprim/Sulfamethoxazole

The Applicant also assessed all pathogens for susceptibility to penicillin and trimethoprim/sulfamethoxazole. The following table summarizes the results of this susceptibility testing and the Overall Clinical Response for subjects in the Applicant's Microbiologically Evaluable Population who had *Streptococcus pneumoniae* isolated at baseline.

Overall Clinical Response by Susceptibility of *Streptococcus Pneumoniae* Isolated from the Target Ear at Baseline to Penicillin and Trimethoprim/Sulfamethoxazole for the Applicant's Microbiologically Evaluable Population

Drug	Ofloxacin			Augmentin®			
	Cure	Failure	Total	Cure	Failure	Total	P-value*
Penicillin							
Sensitive	22 (92%)	2 (8%)	24	17 (81%)	4 (19%)	21	0.209
Intermediate	3 (50%)	3 (50%)	6	7 (88%)	1 (13%)	8	0.181
Resistant	4 (80%)	1 (20%)	5	5 (63%)	3 (38%)	8	0.523
Acquired Resistance	0	1 (100%)	1	0	1 (100%)	1	
Trimeth/Sulfa							
Sensitive	22 (85%)	4 (15%)	26	13 (87%)	2 (13%)	15	0.86
Intermediate	2 (100%)	0	2	3 (75%)	1 (25%)	4	0.48
Resistant	5 (71%)	2 (29%)	7	13 (77%)	4 (24%)	17	0.921
Acquired Resistance	0	1 (100%)	1	0	2 (100%)	2	

* P-value comparing the difference between treatment groups with respect to cure rates

In the ofloxacin-treated subjects, 24/36 (67%) of the *Streptococcus pneumoniae* isolates were sensitive to penicillin while 21/38 (55.3%) in the Augmentin®-treated subjects were sensitive. However, there did not appear to be any significant differences in the cure rates of subjects in the two treatment groups. The Medical Officer's Microbiologically Evaluable Population differed by one *Streptococcus pneumoniae* isolate in Augmentin®-treated subject who was a treatment failure. This isolate was sensitive to both penicillin and trimethoprim/sulfamethoxazole.

In the ofloxacin-treated subjects, 26/36 (72.2%) of the *Streptococcus pneumoniae* isolates were sensitive to trimethoprim/sulfamethoxazole while 15/38 (39.5%) in the Augmentin®-treated subjects were sensitive. Despite this difference, there did not appear to be any significant differences in the overall cure rates of subjects in the two treatment groups.

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.

The following table summarizes the Overall Clinical/Microbiological Response for the subjects in the Applicant's Microbiologically Evaluable Population.

Overall Clinical/Microbiological Response for the Applicant's Microbiologically Evaluable Population

	Overall Microbiological Response by Subject	Cure Rate Ofloxacin	Cure Rate Augmentin®	95 % C.I.
Overall	Eradication	80% (64/80)	98% (61/62)	-
	Persistence	0% (0/1)	4% (1*/26)	-
	Recurrence	0% (0/2)	0% (0/4)	-
	Reinfection	None	0% (0/1)	-
Overall Clin/Micro Success Rate		77% (64/83)	66% (61/93)	(-2.8%, 25.9%)

* Subject had an Overall Microbiological Response of persistence and had an Overall Clinical Response of cure

The Applicant noted that for Augmentin®-treated subjects, clinical failure was associated with the failure to eradicate pathogens more often than was the case for the ofloxacin-treated subjects although the difference was not statistically significant.
The following table summarizes the Overall Clinical Clinical/Microbiological Response for the Medical Officer's Microbiologically Evaluable Population:

Overall Clinical/Microbiological Response for the MO's Microbiologically Evaluable Population

	Overall Microbiological Response by **Subject**	Cure Rate Ofloxacin	Cure Rate Augmentin®	95 % C.I.
Overall	Eradication	80% (66/82)	98% (63/64)	-
	Persistence	0% (0/1)	4% (1*/27)	-
	Recurrence	0% (0/2)	0% (0/4)	-
	Reinfection	None	0% (0/1)	-
Overall Clin/Micro Success Rate		78% (66/85)	66% (63/96)	(-2.1%, 26.1%)

* Subject had an Overall Microbiological Response of persistence and had an Overall Clinical Response of cure (this subject represnts the 1 in the numerator)and Subject was a clinical failure with documented persistence of *S. aureus* (this subject represents the additional subject in the numerator compared to the Applicant.)

As shown above, the Medical Officer changes did not make much difference in the overall success rate. The 95% confidence interval (-2.1%, 26.1%) indicates therapeutic equivalence of the two treatment groups in the MO's Microbiologically Evaluable Population.

Summary of Microbiological Efficacy

Microbiologic Eradication Rates per Baseline Pathogen in the Medical Officer's Microbiologically Evaluable Population-PRT008

Baseline Pathogen	Ofloxacin group	Augmentin® group
Pseudomonas aeruginosa	9/9 (100%)	3/7 (43%)
Staphylococcus aureus	27/28 (96%)	14/28 (50%)
Haemophilus influenzae	28/30 (93%)	30/39 (77%)
Streptococcus pneumoniae	36/36 (100%)	34/39 (87%)
Moraxella catarrhalis	13/14 (93%)	9/10 (90%)

Overall Clinical/Microbiological Success Rates per Selected Baseline Pathogens in the Medical Officer's Microbiologically Evaluable Population-PRT008		
Baseline Pathogen	**Ofloxacin group**	**Augmentin® group**
Pseudomonas aeruginosa	6/9 (67%)	3/7 (43%)
Staphylococcus aureus	23/28 (82%)	13/28 (46%)
Haemophilus influenzae	21/30 (70%)	26/39 (67%)
Streptococcus pneumoniae	29/36 (81%)	29/39 (74%)
Moraxella catarrhalis	10/14 (71%)	9/10 (90%)

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%)

SAFETY ANALYSES-PRT008

As presented in the NDA, the safety analyses were peformed on the Intent-to-Treat Population of 474 subjects (228 treated with ofloxacin and 246 treated with Augmentin®). However, the exclusion of one center by the Medical Officer left a total of 462 subjects in the Modified Intent-to-Treat Population. Therefore, the information presented in this section of the review is based upon the Applicant's presentation of the safety data with the differences made by the Medical Officer changes delineated where applicable.

ADVERSE EVENTS-PRT008

All Adverse Events

The following table outlines the number (%) of subjects in the Applicant's Intent-to-Treat Population who experienced adverse events during the study.

PRT-008
Adverse Events During the Study in the Intent-toTreat Population as Presented in the NDA

Parameter	Ofloxacin 0.5ml b.i.d.		Augmentin®		P-value
Number of Subjects	228		246		
Subjects with any AE	96	(42%)	127	(52%)	0.043
Subjects with Treatment-related AEs	13	(6%)	77	(31%)	<0.001
Subjects with Severe or Life-threatening AEs[1]	7	(3%)	13	(5%)	
Subjects with Serious AEs[2]	0	(0%)	2	(0.8%)	
Subjects Discontinued due to AEs	9	(3.9%)	20	(8.1%)	

1 The severity of AEs was classified by the investigator as: mild, moderate, severe, or life-threatening.
2 The sponsor classified an AE as serious if the AE: was life-threatening; resulted in hospitalization, permanent disability, or death; was cancer, congenital anomaly, or overdose; or was indicative of a systemic immediate hypersensitivity reaction (diffuse rashes) or those which might indicate CNS toxicity.

In the Applicant's Intent-to-Treat Population, adverse events occurred in a significantly lower percentage (p=0.043) of ofloxacin-treated subjects [42% (96/228)] than Augmentin®-treated subjects [52% (127/246)].

The following table shows these same parameters for the Modified Intent-to-Treat Population (after the exclusion of Center 45.)

PRT-008

Adverse Events During the Study in the Modified Intent-toTreat Population

Parameter	Ofloxacin 0.5ml b.i.d.		Augmentin®		P-value
Number of Subjects	223		239		
Subjects with any AE	95	(42.6%)	125	(52.3%)	0.041
Subjects with Treatment-related AEs	**13**	**(5.8%)**	77	(32.2%)	<0.001
Subjects with Severe or Life-threatening AEs[1]	7	(3.1%)	13	(5.4%)	0.259
Subjects with Serious AEs[2]	0	(0%)	2	(0.8%)	0.500
Subjects Discontinued due to AEs	9	(4.0%)	**19**	**(7.9%)**	

1 The severity of AEs was classified by the investigator as: mild, moderate, severe, or life-threatening.

2 The sponsor classified an AE as serious if the AE: was life-threatening; resulted in hospitalization, permanent disability, or death; was cancer, congenital anomaly, or overdose; or was indicative of a systemic immediate hypersensitivity reaction (diffuse rashes) or those which might indicate CNS toxicity.

In the Modified Intent-to-Treat Population, adverse events in general and treatment-related adverse events occurred in a significantly lower percentage of ofloxacin-treated subjects than in Augmentin®-treated subjects (p=0.041 and p=<0.001, respectively.)

No life-threatening adverse events were observed for any subject. No deaths occurred during treatment or within 30 days of the last dose of study medication. Seven ofloxacin-treated subjects and 13 Augmentin®-treated subjects were reported as having severe adverse events. Two Augmentin®-treated subjects experienced adverse events that were considered to be serious. No significant difference between treatment groups was detected in the number of subjects who discontined due to adverse events.

Of the 12 subjects who were contributed by the MO-excluded center, only 3 subjects had been reported to have had adverse events. The following is a list of all of the adverse events (and their severity and relationship to study drug) that were reported in the subjects who were excluded by the MO.

Ofloxacin-treated subjects Excluded by the Medical Officer

Subject	Adverse Event	Severity	Relationship to Study Drug
Subject	Otitis Externa	Moderate	Not Related
	Gastritis	Mild	Remote

Augmentin®-treated subjects Excluded by the Medical Officer

Subject	Pharyngitis	Mild	Not Related
Subject	Rhinitis	Mild	Not Related
	Otorrhagia	Mild	Remote*

*This adverse event led to discontinuation of the study medication.

Adverse events that occurred in 5 or more subjects in the Applicant's Intent-to-Treat Population are listed in the following table:

Adverse Events that Occurred in Five[1] or More Subjects in the Applicant's Intent-to-Treat Population

	Ofloxacin (N=228)		Augmentin® (N=246)		
Adverse Events by Body System	Subjects(%)	Events[2]	Subjects(%)	Events[2]	P-value
Respiratory System Disorders					
Rhinitis	25 (11%)	28	21 (9%)	22	0.438
Coughing	11 (5%)	12	7 (3%)	7	0.338
Upper resp tract infection	11 (5%)	11	3 (1%)	3	0.028
Pharyngitis	3 (1%)	3	2 (1%)	2	0.675
Sinusitis	2 (1%)	2	3 (1%)	3	1
Gastrointestinal Sys Disorders					
Diarrhea	12 (5%)	13	70 (29%)	76	<0.001
Vomiting	8 (4%)	8	11 (5%)	11	0.646
Body as a Whole - Gen Disorders					
Fever	17 (8%)	22	13 (5%)	14	0.351
Pain	2 (1%)	2	4 (2%)	4	0.687
Hearing and Vestibular Disorders					
Earache	6 (3%)	6	8 (3%)	8	0.231
Otorrhagia	3 (1%)	3	4 (2%)	4	0.481
Vision Disorders					
Conjunctivitis	5 (2%)	5	4 (2%)	4	0.744
White Cell and Res Disorders					
Lymphadenopathy	5 (2%)	6	1 (0.4%)	1	0.11
Skin and Appendages Disorders					
Rash	4 (2%)	5	23 (9%)	24	<0.001
Centr & Periph Nerv Sys Disorders					
Headache	4 (2%)	4	3 (1%)	3	0.715
Psychiatric Disorders					
Nervousness	4 (2%)	4	2 (1%)	2	0.434
Resistance Mechanism Disorders					
Moniliasis	2 (1%)	2	7 (3%)	7	0.178

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.

A significantly higher percentage of subjects had diarrhea ($p<0.001$) in the Augmentin®-treated group (29%) than in the ofloxacin-treated group (5%), and 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%). A significantly higher percentage of subjects suffered upper respiratory tract infections ($p=0.028$) in the ofloxacin-treated group (5%) than in the Augmentin®-treated group (1%).

The Modified Intent-to-Treat Population would have the same listing of commonly-occurring adverse events for the ofloxacin-treated subjects as shown in the Applicant's table above. However, the relative percentages would rise slightly due to the smaller denominator (N=223 in the Modified ITT.)

Severe Adverse Events

Most adverse events were mild or moderate in severity. However, 7 (3%) of 228 ofloxacin-treated subjects and 13 (5%) of 246 Augmentin®-treated subjects were reported by the investigator as having severe (Grade 3) adverse events. These were the same for the Applicant and the Modified ITT Populations. Severe adverse events are summarized in the following table:

Severe Adverse Events in Applicant and Modified ITT Populations-PRT008

	Ofloxacin		Augmentin®	
Adverse Events by Body System	Subjects(%)	Events*	Subjects(%)	Events*
Respiratory System Disorders				
Rhinitis	2 (1%)	2	0	0
Coughing	2 (1%)	2	0	0
Pharyngitis	1 (0.4%)	1	1 (0.4%)	1
Bronchospasm	1 (0.4%)	1	0	0
Body as a Whole - Gen Disorders				
Fever	3 (1%)	3	0	0
Condition aggravated**	0	0	1 (0.4%)	1
Hearing and Vestibular Disorders				
Otorrhea	1 (0.4%)	1	0	0
Gastrointestinal Sys Disorders				
Diarrhea	0	0	8 (3%)	8
Vomiting	0	0	1 (0.4%)	1
Skin and Appendages Disorders				
Rash	0	0	4 (2%)	4
Special Senses Other, Disorders				
Taste Perversion	0	0	1 (0.4%)	1

* Subjects may experience more than one event during the study.
**Exacerbation of chronic respiratory insufficiency

Eight (3%) Augmentin®-treated subjects experienced a severe case of diarrhea compared to none for the ofloxacin-treated group, and 4 (2%) Augmentin®-treated subjects had a severe rash compared to none for the ofloxacin-treated group.

APPEARS THIS WAY
ON ORIGINAL

Treatment-Related Adverse Events

The Applicant summarized the treatment-related adverse events that occurred in two or more subjects in the following table:

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

	Ofloxacin		Augmentin®		
Adverse Events by Body System	Subjects(%)	Events[2]	Subjects(%)	Events[2]	P-value
Gastrointestinal System Disorders					
Diarrhea	3 (1%)	4	66 (27%)	72	<0.001
Vomiting	1 (0.4%)	1	6 (2%)	6	0.124
Abdominal Pain	1 (0.4%)	1	2 (1%)	2	1
Special Senses Other, Disorders					
Taste perversion	3 (1%)	3	1 (0.4%)	1	0.355
Hearing and Vestibular Disorders					
Earache	2 (1%)	2	0	0	0.231
Skin and Appendages Disorders					
Rash	2 (1%)	2	11 (5%)	12	0.022
Centr & Periph Nerv Sys Disorders					
Paresthesia	2 (1%)	2	0	0	0.231
Resistance Mechanism Disorders					
Moniliasis	0	0	7 (3%)	7	0.015

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.

A significantly higher percentage of subjects suffered treatment-related diarrhea ($p<0.001$) in the Augmentin®-treated group (27%) than in the ofloxacin-treated group (1%); a significantly higher percentage of subjects suffered a treatment-related rash ($p=0.022$) in the Augmentin®-treated group (5%) than in the ofloxacin-treated group (1%); and a significantly higher percentage of subjects suffered treatment-related moniliasis ($p=0.015$) in the Augmentin®-treated group (3%) than in the ofloxacin-treated group (0%).

There were only three treatment-related adverse events that are not listed in the table above. These were all in ofloxacin-treated subjects. There was one subject and event each of: rhinitis, sinusitis, and pruritus.

The majority of treatment-related adverse events were mild to moderate in severity. Eleven Augmentin®-treated subjects experienced treatment-related adverse events that were considered by the investigator to be severe, but no ofloxacin-treated subjects did. No treatment-related adverse events were considered by the Sponsor to be serious.

Subject Discontinuations due to Adverse Events

Nine (4%) ofloxacin-treated subjects and 20 (9%) Augmentin®-treated subjects experienced adverse events that resulted in discontinuation of study medication.

One subject was discontinued from the study after all study medication was administered but prior to the Test-of-Cure Visit (Visit 4) .

Capsule Summaries were provided by the Applicant for all subjects who discontinued due to adverse events. The following table, compiled by the Applicant, lists the subjects who discontinued study medications due to an adverse event(s).

Subjects Discontinuing Study Medication Due to Adverse Event-PRT008

Subject	Treatment	Discontinued Study Medication	Adverse Event
	ofloxacin	Yes	U.R.I.
	ofloxacin	Yes	U.R.I.
	ofloxacin	Yes	Vomiting, diarrhea, fever, sinusitis
	ofloxacin	Yes	Otorrhea
	ofloxacin	Yes	U.T.I.
	ofloxacin	Yes	Conjunctivitis
	ofloxacin	Yes	Pneumonia
	ofloxacin	Yes	Rhinitis
	ofloxacin	Yes	Bronchitis
	Augmentin®	Yes	Exacerbation of BPD
	Augmentin®	Yes	Diarrhea, rash
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Fever, earache
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Diarrhea, vomiting
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Vomiting, diarrhea
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Conjunctivitis
	Augmentin®	Yes	Otorrhea
	Augmentin®	Yes	Otorrhagia
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Moniliasis, diarrhea
	Augmentin®	Yes	Diarrhea
	Augmentin®	Yes	Diarrhea

*The Data Listings incorrectly identified Subject as discontinuing the study due to a pre-existing condition.

Medical Officer's Comment: *In the footnote to the table above, the Applicant notes that in the Data Listings of the NDA it was incorrectly listed that subject was discontinued from the study due to a pre-existing condition. Presumably the abbreviation "BPD," listed in this table as the Adverse Event, refers to bronchopulmonary dysplasia. It should be noted that this subject died 71 days after the last dose of study medication. The available information about this subject is presented below.*

As previously mentioned, only one subject from the excluded center, Subject treated with Augmentin®, had an adverse event (otorrhagia) that resulted in the discontinuation of study medication.

Deaths and Other Serious Adverse Events

Two Augmentin®-treated subjects experienced adverse events that were considered by the Sponsor to be serious:

- Subject was hospitalized due to an exacerbation of chronic respiratory insufficiency. The condition started 3 days after initiation of treatment and required hospitalization. Protocol therapy was discontinued without unblinding. The condition lasted for 3 days, but the subject improved and was discharged from the hospital. The investigator considered the event unrelated to study drug therapy.
  In the Capsule Summary this subject was described as having been a 21-month old female who

was born prematurely (27 weeks 1 lpound, 9 ounces). She required intensive care and ventilatory support from birth through age three months, nasal oxygen from age four months through eighteen months, and tracheostomy and feeding gastrostomy at age twenty months. She had had multiple hospital admissions for respiratory distress and failure to thrive. A reported relapse of the respiratory insufficiency occurred resulting in the death of this subject 71 days after the last dose of study medication.

-Subject was hospitalized after the study was completed (13 days after last dose of study medication) due to a mild case of otorrhea. The subject recovered and the event was considered by the investigator to be unrelated to drug therapy.

No life-threatening adverse event was observed for any subject.

No deaths occurred during treatment or within 30 days of the last dose of study medication.

Medical Officer's Comment: *The Applicant, noting that the death of Subject occurred more than two months after discontinuation of the study medication (Augmentin®), felt that this death was unrelated to the study medication. The Medical Officer concurred with the Applicant.*

AUDIOMETRY RESULTS

The purpose of audiometric testing in this study was to assess whether topical administration of 0.3% ofloxacin otic solution 0.25mL b.i.d. for ten days in children with acute otorrhea and tympanostomy tubes adversely affected auditory function compared to Augmentin® oral suspension dosed at 40mg/kg/day [13.3 mg/kgt.i.d.] for ten days.

When audiometric testing is performed, each ear is assessed independently for bone and air conduction of sound at a variety of frequencies. Bone conduction thresholds reflect the integrity and function of the inner ear whereas air conduction thresholds are affected by both middle and inner ear function.

The primary outcome variable for the audiometry sub-study of this protocol was change in bone conduction pure tone average (PTA) between Baseline (Visit 1) and the Test-of-Cure Visit (Visit 4). PTA is defined as the average of hearing thresholds at 500, 1000 and 2000Hz. The difference in bone conduction PTA was calculated by subtracting the Visit 4 PTA from the Visit 1 PTA. The target and non-target ears of subjects were categorized as having a positive change (improvement in hearing), a negative change (decrease in hearing), or no change. Changes in PTA or in conduction thresholds (at any frequency) of 10 dB or greater were considered significant changes in hearing.

Changes in sensorineural hearing for bone conduction thresholds at 4000 Hz were also analyzed. The 4000 Hz frequency threshold is considered a more sensitive indicator of change in sensorineural hearing.

A total of 30 ofloxacin-treated subjects and 26 Augmentin®-treated subjects were included in the audiometry analyses. However, a few subjects in each arm were discontinued before Visit 4 and did not have final audiometry testing. The additional test of bone conduction at 4000 Hz was conducted on a fewer number of subjects in each arm than the primary testing of bone conduction PTA. The Medical Officer's population for audiometry was the same as that of the Applicant.

In summary the results of audiometry showed:

- No significant difference between treatment groups for bone conduction PTA for the target or non-target ears.
- No significant difference between treatment groups for bone conduction threshold changes at 4000 Hz for the target or non-target ears.

- A statistically significant difference between treatment groups in air conduction PTA. In the ofloxacin group, 19/28 (68%) showed a positive air conduction change (improvement in hearing) vs. only 9/26 (35%) in the Augmentin®-treated group (p=0.029).

Medical Officer's Comment: The tables summarizing this information can be found on pages 101-105 of the Applicant's Study Report in Volume 82 of the NDA.

SUMMARY OF SAFETY

The main findings of the general safety analyses are:

- Adverse events occurred in a significantly lower percentage (p=0.041) of ofloxacin-treated subjects [42.6% (95/223)] than Augmentin®-treated subjects [52.3% (125/239)].
- 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%).
- Ofloxacin 0.3% otic solution instilled twice daily was at least as safe as Augmentin® oral suspension in the treatment of acute purulent otorrhea in subjects between ≥ 1 and < 12 years of age with tympanostomy tubes.