

Most of these adverse events were mild and not-related to the study drug. There were only two that were possibly treatment-related: one event of a headache in an ofloxacin-treated subject and one event of pruritus in a Cortisporin®-treated subject.

Medical Officer's Comment: None of the excluded subjects had a serious AE, and none had been withdrawn due to an AE.

The following table outlines the adverse events that were seen in five or more subjects in the Intent-to-Treat Population presented in the NDA:

Adverse Events that Occurred in Five¹ or More Subjects in the Intent-to-Treat Population Presented in the NDA-PRT002

<u>Adverse Event by Body System</u>	<u>Ofloxacin 0.5ml b.i.d. (N=158)</u>		<u>Cortisporin® 0.2ml q.i.d (N=156)</u>		<u>P-value³</u>
	<u>Subjects (%)</u>	<u>Events²</u>	<u>Subjects (%)</u>	<u>Events²</u>	
<u>Skin and Appendages Disorders</u>					
Pruritus	14 (8.9%)	14	11 (7.1%)	11	0.678
Rash Erythematous	4 (2.5%)	5	1 (0.6%)	1	Not Done
<u>Respiratory System Disorders</u>					
Rhinitis	7 (4.4%)	8	4 (2.6%)	4	0.542
Pharyngitis	6 (3.8%)	6	1 (0.6%)	1	Not Done
<u>Centr & Periph Nerv Sys Disorders</u>					
Headache	10 (6.3%)	11	3 (1.9%)	4	0.086
Dizziness	2 (1.3%)	2	3 (1.9%)	3	0.683
<u>Hearing and Vestibular Disorders</u>					
Earache	6 (3.8%)	6	8 (5.1%)	9	0.597
<u>Application Site Disorders</u>					
Application Site Reaction	6 (3.8%)	7	6 (3.8%)	7	1.000
<u>Body as a Whole - Gen Disorders</u>					
Fever	4 (2.5%)	4	3 (1.9%)	3	1.000
<u>Resistance Mechanism Disorders</u>					
Otitis Media	4 (2.5%)	4	3 (1.9%)	3	1.000
<u>White Cell and Res Disorders</u>					
Lymphadenopathy Cervical	3 (1.9%)	5	3 (1.9%)	3	1.000

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.

³ Treatment comparison of the number of subjects with the AE. P-values were not computed when the number of subjects was less than 2 in either arm.

Pruritus was the most commonly seen adverse event in each treatment arm of the ITT Population presented in the NDA. And, as noted above, headache was the next most commonly seen AE in the ofloxacin-treated subjects, and earache was for the Cortisporin®-treated subjects in the ITT Population presented in the NDA.

Medical Officer's Comment: In the modified ITT, the events that had an different number of subjects actually experiencing the event, not just a different percentage of the population, are bolded in the table below:

**Adverse Events that Occurred in Five¹ or More Subjects in the
Modified Intent-to-Treat Population-PRT002
(Excludes Centers 15 & 22)**

<u>Adverse Event by Body System</u>	<u>Ofloxacin 0.5ml b.i.d. (N=129)</u>		<u>Cortisporin® 0.2ml q.i.d. (N=127)</u>		<u>P-value³</u>
	<u>Subjects (%)</u>	<u>Events²</u>	<u>Subjects (%)</u>	<u>Events²</u>	
<u>Skin and Appendages Disorders</u>					
Pruritus	14 (10.9%)	14	10 (7.9%)	10	0.521
Rash Erythematous	4 (3.1%)	5	1 (0.8%)	1	0.370
<u>Respiratory System Disorders</u>					
Rhinitis	6 (4.7%)	7	4 (3.1%)	4	0.749
Pharyngitis	5 (3.9%)	5	0 (0%)	0	0.060
<u>Centr & Periph Nerv Sys Disorders</u>					
Headache	4 (3.1%)	5	3 (2.4%)	4	1.000
Dizziness	2 (1.6%)	2	3 (2.4%)	3	0.683
<u>Hearing and Vestibular Disorders</u>					
Earache	6 (4.7%)	6	8 (6.3%)	9	0.595
<u>Application Site Disorders</u>					
Application Site Reaction	6 (4.7%)	7	6 (4.7%)	7	1.000
<u>Body as a Whole - Gen Disorders</u>					
Fever	4 (3.1%)	4	3 (2.4%)	3	1.000
<u>Resistance Mechanism Disorders</u>					
Otitis Media	4 (3.1%)	4	3 (2.4%)	3	1.000
<u>White Cell and Res Disorders</u>					
Lymphadenopathy Cervical	3 (2.3%)	5	2 (1.6%)	2	1.000

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.

³ Treatment comparison of the number of subjects with the AE. P-value calculated by the Fisher's Exact Test

Medical Officer's Comment: The two treatment groups were similar with respect to all of the adverse events listed, with the exception of pharyngitis (4% for ofloxacin-treated patients compared to 0% for Cortisporin®-treated subjects; p=0.06). In general, the incidence of AEs increased slightly in the modified ITT safety analysis.

Subjects Withdrawn due to Adverse Events

There were four ofloxacin-treated subjects who were discontinued from the study due to adverse events. Six adverse events were reported from these four subjects. Two subjects from the Cortisporin® arm were discontinued due to an adverse event. These are outlined below:

Ofloxacin-treated subjects withdrawn due to adverse events:

- withdrawn due to a rash
- withdrawn due to a fractured ankle
- withdrawn due to an earache and fever
- withdrawn due to pneumonia and otitis media

Cortisporin®-treated subjects withdrawn due to adverse events:

- withdrawn due to an application site reaction
- withdrawn due to an erythematous rash

Severe Adverse Events

Most of the adverse events were mild or moderate in severity, but nine subjects had adverse events that the investigator rated as severe. There was no single adverse event that was reported as severe in more than one subject. There were six subjects in the ofloxacin group and three Cortisporin® group subjects who experienced severe adverse events (p=0.502). These are listed below:

Ofloxacin-treated subjects with severe adverse events:

- pruritis
- pharyngitis
- ulcerative stomatitis
- otitis media
- earache
- pneumonia

Cortisporin®-treated subjects with severe adverse events:

- application site reaction
- myocardial infarction
- fatigue

Medical Officer's Comment: *On the pages of the case report forms designed for the reporting of adverse events, there was not a distinction between the intensity and gravity of an event. The only category listed was "severity" (i.e., intensity) which could be scored as mild, moderate, severe, or life-threatening. No events seen in this study were deemed "life-threatening." The assessment of whether an adverse event was "serious" (i.e., gravity) was made by the Applicant.*

The Applicant noted that a "highly conservative" definition of serious adverse events was used in this study because it was one of the first two studies of this compound using the otic route in humans in the U.S. In addition to the events usually considered serious (life-threatening; resulting in hospitalization, permanent disability, or death; cancer, congenital anomalies; and overdose), the Applicant considered two other events as serious. Those events which might be indicative of a systemic immediate hypersensitivity reaction (diffuse rashes) or those which might indicate CNS toxicity were also considered to be serious.

Five subjects (3 ofloxacin, 2 Cortisporin®) experienced adverse events that the Applicant considered to be serious. These are listed below:

Ofloxacin-treated subjects with serious adverse events:

- rash
- broken ankle
- pneumonia

Cortisporin®-treated subjects with serious adverse events:

- myocardial infarction
- erythematous rash

Of these events, only the rash in subject _____ and the erythematous rash of subject _____ were felt to be possibly treatment-related. The other serious adverse events were deemed by the respective investigator to be "not related" to treatment with the study drug.

Treatment-Related Adverse Events

The number of subjects with treatment-related adverse events was similar (p=0.325) for the two treatment groups: 25/158 (15.8%) ofloxacin-treated subjects and 18/156 (11.5%) Cortisporin®-treated subjects in the Intent-to-Treat Population in the NDA.

The adverse events, occurring in two or more subjects in the ITT Population as presented in the NDA which were considered by the respective investigators to be possibly or probably related to study drug treatment, are listed in the following table:

Treatment-Related Adverse Events that Occurred in Two¹ or More Subjects in the Intent-to-Treat Population in the NDA-PRT002

<u>Adverse Event by Body System</u>	<u>Ofloxacin 0.5ml b.i.d.</u> (N=158)		<u>Cortisporin® 0.2ml q.i.d.</u> (N=156)		<u>P-value³</u>
	<u>Subjects (%)</u>	<u>Events²</u>	<u>Subjects (%)</u>	<u>Events²</u>	
<u>Skin and Appendages Disorders</u>					
Pruritus	10 (6.3%)	10	6 (3.8%)	6	0.443
Rash Erythematous	1 (0.6%)	1	1 (0.6%)	1	Not Done
<u>Application Site Disorders</u>					
Application Site Reaction	6 (3.8%)	7	6 (3.8%)	7	1.000
<u>Centr & Periph Nerv Sys Disorders</u>					
Dizziness	1 (0.6%)	1	2 (1.3%)	2	Not Done
Vertigo	2 (1.3%)	2	0		Not Done
<u>Hearing and Vestibular Disorders</u>					
Earache	2 (1.3%)	2	3 (1.9%)	3	0.683

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.

³ Treatment comparison of the number of subjects with the AE. P-values were not computed when the number of subjects was less than 2 in either arm.

Of the treatment-related adverse events shown in the table above, there were two subjects, one in each arm, who had severe events that were considered to possibly be study drug-related. Ofloxacin subject had a severe case of pruritis limited to his ear canal and Cortisporin® subject had a severe application site reaction. (Neither of these two subjects was excluded by the MO.) The intensity of these reactions was deemed "severe" however, this should be distinguished from the two cases described above, who had reactions of moderate intensity but the gravity of which was deemed "serious" by the Applicant.

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The adverse events, occurring in two or more subjects in the Modified ITT Population, which were considered by the respective investigators to be possibly or probably related to study drug treatment, are listed in the following table:

Treatment-Related Adverse Events that Occurred in Two¹ or More Subjects in the Modified Intent-to-Treat Population-PRT002

Adverse Event by Body System	Ofloxacin 0.5ml b.i.d. (N=129)		Cortisporin® 0.2ml q.i.d. (N=127)		P-value ³
	Subjects (%)	Events ²	Subjects (%)	Events ²	
<u>Skin and Appendages Disorders</u>					
Pruritus	10 (7.8%)	10	5 (3.9%)	5	0.287
Rash Erythematous	1 (0.8%)	1	1 (0.8%)	1	1.000
<u>Application Site Disorders</u>					
Application Site Reaction	6 (4.7%)	7	6 (4.7%)	7	1.000
<u>Centr & Periph Nerv Sys Disorders</u>					
Dizziness	1 (0.8%)	1	2 (1.6%)	2	0.621
Vertigo	2 (1.6%)	2	0		0.498
<u>Hearing and Vestibular Disorders</u>					
Earache	2 (1.6%)	2	3 (2.4%)	3	0.683

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.

³ Treatment comparison of the number of subjects with the AE. P-values were calculated by the Fisher's Exact Test.

Medical Officer's Comment: *There was no statistically significant differences between the two treatment groups with respect to any of the adverse events listed in the table above.*

The Applicant performed subgroup analyses for the adverse events by body system and the groups of age, race, and gender for any adverse event and the treatment-related adverse events.

With respect to any adverse event (i.e., irrespective of relationship to study drug), the two treatment groups were similar for the majority of the body systems. The few exceptions are shown in the table below:

Adverse Events for Subgroups of the Intent-to-Treat Population in the NDA with Significant Treatment Group Comparison-PRT002

Subgroup	Adverse Event or Body System	Ofloxacin	Cortisporin®	P-value*
Male	Skin and Appendages	15 / 82 (18.3%)	2 / 71 (2.8%)	0.003
Female	Centr & Periph Nervous System	12 / 76 (15.8%)	4 / 85 (4.7%)	0.032
	Headache	8 / 76 (10.5%)	2 / 85 (2.4%)	0.047
Caucasian	Skin and Appendages	18 / 115 (15.7%)	7 / 118 (5.9%)	0.020
Age 17-45	Centr & Periph Nervous System	14 / 97 (14.4%)	3 / 82 (3.7%)	0.020

* Treatment comparison of the number of subjects with the AE.

Medical Officer's Comment: *All but one of the reactions in these subgroups, Caucasian male subject with severe pruritis, were mild or moderate in severity. As these adverse events were not analyzed by treatment attribution, the Medical Officer believes the clinical significance of the statistical differences in the select subgroups described above is difficult to discern.*

In the subgroup analyses of the treatment-related adverse events, in both the ITT and the Modified ITT, the number of subjects in each treatment group experiencing an adverse event was similar for all individual adverse events and most body systems. The two exceptions are shown in the following two tables:

**Treatment-Related Adverse Events for
Subgroups of the Intent-to-Treat Population in the NDA
with Significant Treatment Group Comparison-PRT002**

<u>Subgroup</u>	<u>Adverse Event or Body System</u>	<u>Ofloxacin</u>	<u>Cortisporin®</u>	<u>P-value*</u>
Caucasian	Skin and Appendages	10 / 115 (8.7%)	3 / 118 (2.5%)	0.048
Age 17-45	Treatment-related AEs	17 / 97 (17.5%)	6 / 82 (7.3%)	0.046

*Treatment comparison of the number of subjects with the AE.

**Treatment-Related Adverse Events for
Subgroups of the Modified Intent-to-Treat Population
with Significant Treatment Group Comparison-PRT002
(Excludes Centers 15 & 22)**

<u>Subgroup</u>	<u>Adverse Event or Body System</u>	<u>Ofloxacin</u>	<u>Cortisporin®</u>	<u>P-value*</u>
Caucasian	Skin and Appendages	10 / 114 (8.8%)	3 / 115 (2.6%)	0.050
Age 17-45	Treatment-related AEs	16 / 81 (19.8%)	5 / 66 (7.6%)	0.056

*Treatment comparison of the number of subjects with the AE. The P-value was calculated using the Fisher's Exact Test.

Medical Officer's Comment: *This subgroup analysis was performed with respect to adverse events assessed to be treatment-related, and for these two subgroups the difference approaches statistical significance. However, the Medical Officer does not necessarily understand whether this is of any clinical significance.*

SAFETY SUMMARY-Adult Otitis Externa Study

The intent-to-treat population of 314 subjects was composed of two treatment groups that were of similar demographic and baseline characteristics. There were 158 ofloxacin-treated subjects and 156 Cortisporin®-treated subjects.

Most of the adverse events seen were of mild or moderate severity. There were two subjects (one in each group) withdrawn due to serious adverse events possibly related to the study drug, but the events were each of moderate severity. There were no deaths during the study or within 30 days of the last dose of study medication.

Overall, the number of subjects experiencing any adverse event (p=0.081), severe adverse events (p=0.502), and treatment-related adverse events (p=0.325) were similar between the ofloxacin and Cortisporin® treatment groups

The data suggest that overall, ofloxacin 0.3% otic solution instilled in the external auditory canal twice daily is as safe as Cortisporin® otic solution instilled four times daily for the treatment of acute otitis externa in subjects 12 years of age and older.

Medical Officer's Summary Comments and Conclusions- Protocol 002

This was a well-designed study comparing the safety and efficacy of ofloxacin otic solution with that of Cortisporin® otic solution in the treatment of acute otitis externa of presumed bacterial origin in subjects 12 years of age and older.

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

Overall Clinical Response MO Clinically Evaluable Subjects-PRT002 (after the Exclusion of Two Centers)		
<u>Clinical Response</u>	Ofloxacin (N=99)	Cortisporin® (N=98)
Cure	76 (76.8%)	79 (80.6%)
Failure	23 (23.2%)	19 (19.4%)
Ofloxacin vs. Cortisporin® by cure	-3.8%, 95%CI; -16.3%, 8.6%	

The Overall Microbiological Assessment by Subject for the MO's Microbiologically Evaluable Population is shown in the table below:

**Overall Microbiological Assessment by Subject
Medical Officer's Microbiologically Evaluable Population-PRT002**

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.	
Eradication	44	(97.8%)	46	(97.9%)
Persistence	0		1	(2.1%)
Recurrence	1	(2.2%)	0	
Total	45		47	

Ofloxacin vs. Cortisporin® by Eradication -0.1%, 95%: -8.2%, 8.0%

The following table shows the combined clinical cure and microbiological eradication rates, as assessed by the Applicant and by the Medical Officer, for the six pathogens requested in the labeling.

Combined Clinical Cure and Microbiological Eradication (Success) Rates by Pathogen for Ofloxacin-treated subjects-PRT002 (Applicant vs. Medical Officer)		
Baseline Pathogen Requested in Labeling	Applicant	Medical Officer
<i>Pseudomonas aeruginosa</i>	28/32 (87.5%)	28/32 (87.5%)
<i>Staphylococcus aureus</i>	6/6 (100%)	6/6 (100%)
<i>Enterococcus faecalis</i>	5/6 (83.3%)	4/5 (80.0%)
<i>Klebsiella pneumoniae</i>	4/5 (80.0%)	4/5 (80.0%)
<i>Proteus mirabilis</i>	2/3 (66.7%)	2/3 (66.7%)
<i>Enterobacter cloacae</i>	1/3 (33.3%)	1/3 (33.3%)

The safety analyses showed ofloxacin otic to be generally well-tolerated. Most of the adverse events were of mild to moderate severity. The most common adverse events in both treatment arms were: pruritus, headache, rhinitis, earache, and application site reaction. The most common treatment-related adverse events were: pruritus, erythematous rash, application site reaction, dizziness, vertigo, and earache. These were similar between the two treatment groups.

Based on the data in this study, the Medical Officer is of the opinion that ofloxacin otic 0.3% solution demonstrated adequate safety and clinical effectiveness in the treatment of otitis externa in subjects age 12 and older to support approval of this requested indication.

With respect to the organisms requested for this indication, the Medical Officer will tally the number of organisms in both the adult and pediatric studies, for a final count. But, in this study the only two organisms that were seen in greater than 10% of the microbiologically evaluable population were *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

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Otitis Externa Trial #2

8280A-PRT-003

“A Multicenter, Randomized, Evaluator-Blind Study to Compare the Safety and Efficacy of Ofloxacin Otic Solution with that of Cortisporin® Otic Solution in the Treatment of Acute Otitis Externa in Pediatric Patients”

Study Objective and Design

The study objectives and design were identical to the adult otitis externa protocol with the exception of age of patients (< 12 years of age) and the dose of drugs administered:

- Ofloxacin 0.3% otic solution 0.25 ml (5 drops) every 12 hours
- Cortisporin® otic solution 0.15 ml (3 drops) every 6 hours

Investigators in Protocol 003

<u>CENTER #/ SITE</u>	<u>INVESTIGATOR</u>
51 Little Rock, AR	Gordon Schutze, MD
52 Sellersville, PA	Henry Bernstein, MD
53 Atlanta, GA	Wilson Andrews, MD
54 St. Petersburg, FL	Thomas White, MD
55 Dallas, TX	Scott Manning, MD
56 Fresno, CA	Joseph Ibarra, MD
57 Vienna, VA	Richard Schwartz, MD
58 Scottsdale, AZ	Samuel McLinn, MD
59 Whittier, CA	Robert Fiddes, MD
60 Denver, CO	Kenny Chan, MD
61 Little Rock, AR	Terry Jefferson, MD
62 Houston, TX	Alfred Phillips, MD
63 Shreveport, LA	Thomas Latiolais, MD
64 Cleveland, OH	Jeffrey Blumer, MD
65 Charlotte, NC	Barry Golembe, MD
66 Birmingham, AL	Kenneth Elmer, MD
67 Savannah, GA	Blair Christensen, MD
68 Augusta, GA	Ned Rupp, MD
69 Dallas, TX	Jeffrey Adelglass, MD
70 Orlando, FL	Thomas Marbury, MD
71 San Diego, CA	Margaret Drehobl, MD
72 Bayamon, PR	Eduardo Caro Acevedo, MD
73 Harvey, LA	Eric Jacobs, MD

Study Dates: July 16, 1994 to June 9, 1995

Study Results

Evaluability and Demographics

-Evaluability

~~A total~~ of 287 subjects were enrolled and each received at least one dose of medication. The distribution of these subjects and their evaluability status according to the Applicant is shown in the following table.

Investigator	Center Number	OFLOXACIN			CORTISPORIN®		
		Intent to Treat	Clinically Evaluable	Micro. Evaluable	Intent to Treat	Clinically Evaluable	Micro. Evaluable
Schutze	51	1	0	0	0	0	0
Bernstein	52	0	0	0	1	1	1
Andrews	53	8	8	4	8	6	4
White	54	8	6	1	10	7	5
Manning	55	0	0	0	1	1	1
McCarty	56	5	4	3	4	3	1
Schwartz	57	5	5	3	7	6	4
McLinn	58	32	26	7	32	26	10
Fiddes	59	15	9	4	15	7	1
Chan	60	0	0	0	0	0	0
Jefferson	61	14	10	7	12	8	6
Phillips	62	3	3	3	1	1	1
Latiolais	63	4	3	0	4	3	1
Blumer	64	0	0	0	0	0	0
Golembe	65	0	0	0	2	1	1
Elmer	66	2	2	0	1	1	1
Christensen	67	0	0	0	2	1	1
Rupp	68	3	1	0	4	4	2
Adelglass	69	4	4	2	5	4	3
Marbury	70	5	5	1	4	2	0
Drehobl	71	6	3	2	4	3	2
Caro Acevedo	72	20	19	7	20	20	8
Jacobs	73	8	8	1	7	6	0
Totals	23	143	116	45	144	111	53

The accountability of these 287 subjects, as assessed by the Applicant, is summarized in the following table:

Subject Accountability			
<u>Parameter</u>	<u>Ofloxacin 0.25ml b.i.d.*</u>	<u>Cortisporin® 0.15ml q.i.d.</u>	<u>Total</u>
Number of Subjects Enrolled	143	144	287
Received Drug	143	144	287
Completed Visit 2	140	142	282
Completed Visit 3	136	130	266
Completed Visit 4	128	123	251
Intent-to-Treat Population	143	144	287
Clinically Evaluable Population	116	111	227
Microbiologically Evaluable Population	45	53	98

* Subject completed Visit 3, but did not complete Visit 2 and 4. Therefore, the subject is counted twice in the totals.

The following table summarizes the number of days of treatment for the two treatment groups of the Intent-to-Treat Population:

Number of Days on Treatment Intent-to-Treat Population					
<u>Days</u>	<u>Ofloxacin 0.25ml b.i.d.</u>		<u>Cortisporin® 0.15ml q.i.d.</u>		<u>P-value</u>
<10	8	(5.6%)	15	(10.4%)	0.662
10	115	(80.4%)	105	(72.9%)	
>10	20	(14.0%)	24	(16.7%)	
Total	143		144		

As shown above, the two treatment groups were similar ($p=0.662$) with respect to the number of days on treatment medication, and the majority of subjects in each group received the protocol-defined duration of ten days.

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The primary reasons the Applicant excluded subjects from the clinically evaluable and microbiologically evaluable populations are summarized in the following table.

Primary Reasons for Exclusion from Applicant's Analyzed Populations

	Ofloxacin 0.25ml b.i.d.		Cortisporin® 0.15ml q.i.d.	
Total Number of Subjects Enrolled	143		144	
Excluded from Intent-to-Treat	0		0	
Total Intent-to-Treat Population	143		144	
Excluded from Clinically Evaluable:	27	(18.9%)	33	(22.9%)
<3 Days of Treatment	1	(0.7%)	0	
<75% Compliance	0		3	(2.1%)
Concomitant Medication	11	(7.7%)	5	(3.5%)
Inclusion/Exclusion	8	(5.6%)	5	(3.5%)
No Visit 2, 3 and 4	1	(0.7%)	2	(1.4%)
No Visit 3 and 4	2	(1.4%)	10	(6.9%)
No Visit 4 only	4	(2.8%)	4	(2.8%)
Visit Spacing	0		4	(2.8%)
Total Clinically Evaluable Population	116		111	
Excluded from Microbiologically Evaluable:	98	(68.5%)	91	(63.2%)
Not Clinically Evaluable	27	(18.9%)	33	(22.9%)
No Baseline Pathogen	69	(48.3%)	54	(37.5%)
Follow-up Culture Missing	1	(0.7%)	2	(1.4%)
Inappropriate Culture	0		1	(0.7%)
Clin. Failure & No Pathogen Present	1	(0.7%)	1	(0.7%)
Total Microbiologically Evaluable Population	45		53	

In the review of this data, the Medical Officer made very few changes in the evaluability status or outcome assessment of the subjects. There were three subjects that the Medical Officer changed. These are summarized in the table below:

Medical Officer Changes in Subject Clinical Evaluability and Overall Clinical Assessment

Subject	Treatment	Applicant Evaluability	Applicant Assessment	MO Evaluability	MO Assessment
	Ofloxacin	Not Evaluable	Failure	Evaluable	Failure
	Cortisporin®	Not Evaluable	Failure	Evaluable	Failure
	Cortisporin®	Evaluable	Cure	Not Evaluable	-

Compared to the Applicant's clinically evaluable population, the net effect of these MO changes was to add one ofloxacin failure and one Cortisporin® failure, and to subtract one Cortisporin® cure.

Medical Officer's Comment:

The two investigators whose data the MO excluded from analyses in Protocol 002, Drs. Jacobs and Caro Acevedo, were also investigators in this study. Therefore, the data from Site 73 (Dr. Jacobs) and Site 72 (Dr. Caro Acevedo) were excluded from the analyses of efficacy and safety in this study.

Another investigator who participated in this study, Dr. Fiddes, was undergoing an unrelated investigation by the Division of Scientific Investigations at the time of this review. However, due to serious questions about the integrity of Dr. Fiddes' data, the MO also excluded Site 59 from analyses of safety and efficacy in this study.

Therefore, the MO changed the status of the three subjects listed in the table above, and excluded all subjects from Sites 59, 72, and 73. The following table shows the Medical Officer's resultant evaluability per center.

PRT-003 Medical Officer's Evaluability Per Center

Investigator	Center Number	OFLOXACIN			CORTISPORIN		
		Intent to Treat	Clinically Evaluable	Micro. Evaluable	Intent to Treat	Clinically Evaluable	Micro. Evaluable
Schutze	51	1	0	0	0	0	0
Bernstein	52	0	0	0	1	1	1
Andrews	53	8	8	4	8	6	4
White	54	8	7	1	10	7	5
Manning	55	0	0	0	1	1	1
McCarty	56	5	4	3	4	3	1
Schwartz	57	5	5	3	7	6	4
McLinn	58	32	26	7	32	26	10
Fiddes	59	0	0	0	0	0	0
Chan	60	0	0	0	0	0	0
Jefferson	61	14	10	7	12	8	6
Phillips	62	3	3	3	1	1	1
Latiolais	63	4	3	0	4	3	1
Blumer	64	0	0	0	0	0	0
Golembe	65	0	0	0	2	1	1
Elmer	66	2	2	0	1	1	1
Christensen	67	0	0	0	2	1	1
Rupp	68	3	1	0	4	4	2
Adelglass	69	4	4	2	5	4	3
Marbury	70	5	5	1	4	2	0
Drehobl	71	6	3	2	4	3	2
Caro Acevedo	72	0	0	0	0	0	0
Jacobs	73	0	0	0	0	0	0
Totals		100	81	33	102	78	44
Total Number of Centers Providing Evaluable Data							
		18	14	13	17	17	16

The exclusion of three centers by the Medical Officer resulted in a loss of 85 total subjects from the Intent-to-Treat Population, 43 from the ofloxacin arm and 42 from the Cortisporin® arm. Of these subjects, the Applicant had considered 69/85 clinically evaluable. The following table outlines how those subjects had been assessed by the Applicant.

Protocol 003- Pediatric Otitis Externa Evaluable Subjects Lost from Excluded Investigators			
	Ofloxacin	Cortisporin®	Total
Total Subjects Excluded from ITT Pop.	43	42	85
Total Clinically Evaluable Subjects Lost	36	33	69
Subjects Lost per Excluded Investigator			
Caro Acevedo	19 Evaluable Cures	20 Evaluable Cures	
Fiddes	7 Evaluable Cures 2 Evaluable Failures	6 Evaluable Cures 1 Evaluable Failure	
Jacobs	8 Evaluable Cures	6 Evaluable Cures	
Total Loss from Applicant's Clinically Evaluable Population	34 Evaluable Cures 2 Evaluable Failures	32 Evaluable Cures 1 Evaluable Failure	

In summary, there was a 30% decrease in the Intent-to-Treat Population, from 287 subjects to 202 subjects in the Modified Intent-to-Treat Population. The Clinically Evaluable Population also decreased 30%, from the Applicant's 227 subjects to the Medical Officer's 158 subjects. The Microbiologically Evaluable Population decreased 21%, from the Applicant's total of 98 subjects to 77 in the Medical Officer's population.

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-Demographics

The demographics of the Applicant's Intent-to-Treat Population are presented in the following table:

Summary of Demographic Data for the Applicant's Intent-to-Treat Population-PRT-003

	<u>Ofloxacin 0.25ml b.i.d.</u>		<u>Cortisporin® 0.15ml q.i.d.</u>		<u>P-value*</u>
<u>Number of Subjects</u>	143		144		
<u>Age (yrs.)</u>					
Mean ± S.D.	7.0 ± 2.9		7.7 ± 2.9		0.024
<u>Gender (no. subjects)</u>					
Male	72	(50%)	60	(42%)	0.166
Female	71	(50%)	84	(58%)	
<u>Race (no. subjects)</u>					
Caucasian	98	(69%)	98	(68%)	0.734
African American	9	(6%)	9	(6%)	
Asian	1	(1%)	0		
Hispanic	35	(25%)	36	(25%)	
Other	0		1	(1%)	
<u>Infection</u>					
Unilateral	117	(82%)	129	(90%)	0.055
Bilateral	26	(18%)	15	(10%)	
<u>Reference Ear</u>					
Right	82	(57%)	88	(61%)	
Left	61	(43%)	56	(39%)	
<u>Reference Ear Status</u>					
Exacerbating	94	(66%)	92	(64%)	0.777
Stable	49	(34%)	52	(36%)	
<u>Duration of Otitis Externa (Days)</u>					
Mean ± S.D.	2.9 ± 1.9		3.1 ± 2.2		0.315
<u>Total Signs/Symptoms Score</u>					
Mean ± S.D.	8.1 ± 1.4		8.0 ± 1.5		0.952
<u>Number of Organisms**/Subjects</u>					
Polymicrobial	28	(20%)	38	(26%)	0.261
Monomicrobial	48	(34%)	49	(34%)	
None	67	(47%)	57	(40%)	
<u>Organism Type</u>					
Single Pathogen	40	(28%)	50	(35%)	
Multiple Pathogens	18	(13%)	18	(13%)	
Fungi Only	0		1	(1%)	
Normal Flora only	18	(13%)	18	(13%)	
None	67	(47%)	57	(40%)	

* Cochran-Mantel-Haenszel General Association Test was used to compare gender, race, infection, reference ear status, and number of organisms; age, duration of otitis externa and total signs/symptoms score were compared using 2-way ANOVA test.

** Regardless of pathogenicity.

The two treatment groups were comparable with respect to demographic and baseline characteristics at Baseline with the exception of age. The mean age of 7.0 years for the ofloxacin group was less than the mean age of 7.7 years for the group of Cortisporin®-treated subjects (p=0.024).

Medical Officer's Comment:

Looking more closely at the distribution of subjects in the Applicant's Intent-to-Treat Population with respect to age, the two treatment groups were similar with the following distributions:

<u>Age (years)</u>	<u>Ofloxacin (N=143)</u>		<u>Cortisporin® (N=144)</u>	
	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>
< 1	2	(1.4)	0	(0.0)
1	3	(2.1)	6	(4.2)
2-11	136	(95.1)	135	(93.8)
>11	2	(1.4)	3	(2.1)

For the Applicant's Clinically Evaluable Population, the treatment groups were, with one exception, balanced with respect to demographics and baseline disease characteristics. The mean age for subjects in the ofloxacin arm was slightly less (7.1 years) than that of subjects in the Cortisporin®-treated subjects (7.8 years) ($p=0.042$).

Similarly, in the Medical Officer's Clinically Evaluable Population the only notable difference in the baseline demographics and disease characteristics for the two treatment groups was age. The mean age of the Cortisporin®-treated subjects was 8.5 years versus 7.3 years for the ofloxacin-treated subjects ($p=0.003$).

The baseline disease characteristics of both clinically evaluable populations were similar to the ITT population; however, the mean ages of subjects in both treatment arms were slightly higher than those in the ITT population. Also, the racial composition of the MO's Clinically Evaluable Population differed from that of the ITT due to the loss of subjects from Puerto Rico.

In the Applicant's Microbiologically Evaluable Population the only significant difference in demographics or disease characteristics between groups was the mean duration of the current episode of otitis externa. The subjects in the Cortisporin®-treated population had a slightly greater mean duration of the current episode (3.8 days) than subjects in the ofloxacin-treated group (2.6 days) ($p=0.007$).

In the MO's Microbiologically Evaluable Population the demographics were balanced between treatment arms and similar to the ITT population with the exception of racial composition and age. Each arm of the MO population had fewer Hispanic subjects due to the loss of the Center in Puerto Rico. And, the mean ages (8.0 and 8.5 years) of ofloxacin- and Cortisporin®-treated subjects, respectively were higher than for the ITT population (7.0 and 7.7 years).

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Efficacy

-Clinical Efficacy

As described above, the Applicant presented an Intent-to-Treat Population of 287 subjects, and a Clinically Evaluable Population of 227 subjects. In reviewing the data as presented in the NDA, the Medical Officer made so few changes that had no other information come to light, the conclusions drawn by the Applicant would have been accepted by the MO. However, because the MO excluded three investigative centers the population sizes derived by the MO are much different than those of the Applicant. Therefore, the Medical Officer will present the efficacy analyses for the Applicant's clinically and microbiologically evaluable populations, and for the Medical Officer's clinically and microbiologically evaluable populations.

The subject populations now break down as shown in the table below:

Study PRT-003 Subject Populations Before and after the Exclusion of Three Centers		
Treatment Group for Clinical Response	Subjects Included	
	Ofloxacin	Cortisporin®
Intent-to-Treat Population	143	144
Modified ITT Population*	100	102
Applicant Clinically Evaluable	116	111
MO Clinically Evaluable	81	78
Applicant's Microbiologically Evaluable Population	45	53
MO's Microbiologically Evaluable Population	33	44

*Excludes centers 59, 72, and 73.

The following tables show the Overall Clinical Assessment for the Applicant's Intent-to-Treat Population and Clinically Evaluable Populations:

Overall Clinical Assessment for the Applicant's Intent-to-Treat Population PRT-003				
Assessment	Ofloxacin 0.25ml b.i.d.	Cortisporin® 0.15ml q.i.d.	P-value	95% C.I.
Cure	117 (81.8%)	116 (80.6%)	0.832	(-8.5%, 11.0%)
Failure	26 (18.2%)	28 (19.4%)		
Total	143	144		

Overall Clinical Assessment for the Applicant's Clinically Evaluable Population PRT-003				
Assessment	Ofloxacin 0.25ml b.i.d.	Cortisporin® 0.15ml q.i.d.	P-value	95% C.I.
Cure	112 (96.6%)	105 (94.6%)	0.482	(-4.3%, 8.2%)
Failure	4 (3.4%)	6 (5.4%)		
Total	116 (100%)	111 (100%)		

Medical Officer's Comment: Regardless of patient population analyzed, the Applicant showed comparable clinical success rates for ofloxacin otic and Cortisporin solutions in pediatric patients with OE. And, the 95% CI demonstrated equivalence in each case.

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

Overall Clinical Response MO Clinically Evaluable Population PRT-003 (after the Exclusion of Three Centers)		
Clinical Response	Ofloxacin (N=81)	Cortisporin® (N=78)
Cure	78 (96.3%)	72 (92.3%)
Failure	3 (3.7%)	6 (7.7%)
Ofloxacin vs. Cortisporin® by cure	4.0%, 95%CI; -4.5%, 12.4%	

Even with the exclusion of the investigative centers and the loss of a significant number of subjects from each treatment arm, the distribution of subjects (and the cure rates) remained balanced for gender, age, and race. The cure rates remained above 90% for both treatment groups. The 95% Confidence Interval (-4.5%, 12.4%) for the Medical Officer's Clinically Evaluable Population demonstrates, by the DAIDP Guidelines, therapeutic equivalence between the two treatment groups.

Using the sample sizes of the Medical Officer's Clinical Evaluable Population, the study has 66.5% power of detecting a statistically significant difference under the presumption that success rates for both groups are 80.0%, lower bound delta is 0.15, and 2-tailed alpha is 0.05.

-Microbiological Efficacy

The Applicant identified 98 subjects who fit the definition of the microbiologically evaluable population; 45 ofloxacin-treated subjects and 53 who were treated with Cortisporin®. This population was, with only one exception as discussed above, the same as that for the Medical Officer.

However, the exclusion of data from three centers decreased the number of microbiologically evaluable subjects to a total of 77 subjects-33 ofloxacin-treated subjects and 44 Cortisporin®.treated subjects. Because the MO essentially agreed with the Applicant prior to the exclusion of three centers, the Medical Officer will present the microbiological data the Applicant presented and how the data were affected by the exclusion of three centers. These two datasets will be referred to as the Applicant's Microbiologically Evaluable Population and the Medical Officer's Microbiologically Evaluable Population.

The Applicant presented microbiological assessments for Visit 3 and Visit 4 on a per subject and per pathogen basis, and an overall combined clinical/microbiological outcome. Each of these assessments will be presented for the Applicant's and the Medical Officer's Microbiologically Evaluable Populations.

Microbiological Assessment by Subject

The Applicant reported the following microbiological responses, by subject at Visit 3.

Microbiological Assessment by Subject at Visit 3 for the Applicant's Microbiologically Evaluable Population-PRT003					
Assessment	Ofloxacin 0.25ml b.i.d.		Cortisporin® 0.15ml q.i.d.		95% C.I.
Documented Eradication	2	(4.5%)	1	(1.9%)	(-2.1%, 2.1%)
Presumed Eradication	42	(95.5%)	52	(98.1%)	
Not Evaluable*	1		0		
Total	45		53		

* Not Evaluable (Subject is excluded from the calculation of percentages.

In the Applicant's Microbiologically Evaluable Population submitted in the NDA, total of 98 subjects (45 ofloxacin-treated and 53 Cortisporin®-treated subjects) were assessed for microbiological response at Visit 3. The one ofloxacin-treated subject shown above as "Not Evaluable," Subject _____ was considered a clinical failure by the investigator at Visit 2 and was withdrawn from the study. Hence, this subject was not evaluable at Visit 3. But, this subject was microbiologically evaluable overall (persistence). Other than this one subject, all subjects in both treatment groups had eradication of all pathogens isolated at Baseline at Visit 3 (95% C.I. =[-2.1%,2.1%])

Because there were only two instances of "documented eradication", and all others were "presumed eradication," the Medical Officer will only list "eradication" for the Medical Officer's population. The responses seen in the MO's Microbiologically Evaluable Population at Visit 3 are summarized in the table below:

Microbiological Assessment by Subject at Visit 3 for the Medical Officer's Microbiologically Evaluable Population-PRT003		
Clinical Response	Ofloxacin (N=33)	Cortisporin® (N=44)
Eradiation	33 (100%)	44 (100%)
Persistence + Recurrence	0 (100%)	0 (0%)
Ofloxacin vs. Cortisporin® for Eradiation	0%, 95%CI: -2.7%, 2.7%	

Medical Officer's Comment: The above table shows that the exclusion of three centers did not substantially affect the microbiological assessment rates in either arm at Visit 3.

The following two tables show the microbiological response, by subject at Visit 4, in the Applicant and MO Microbiologically Evaluable Populations, respectively:

Microbiological Assessment by Subject at Visit 4 for the Applicant's Microbiologically Evaluable Population-PRT003					
Assessment	Ofloxacin 0.25ml b.i.d.		Cortisporin® 0.15ml q.i.d.		95% C.I.
Presumed Eradication	44	(100%)	53	(100%)	(-2.1%, 2.1%)
Not Evaluable*	1		0		
Total	45		53		

* Not Evaluable is excluded from the calculation of percentages.

Microbiological Assessment by Subject at Visit 4 for the Medical Officer's Microbiologically Evaluable Population-PRT003		
Clinical Response	Ofloxacin (N=33)	Cortisporin® (N=44)
Eradication	33 (100%)	44 (100%)
Persistence + Recurrence	0 (100%)	0 (0%)
Ofloxacin vs. Cortisporin® for Eradication	0%, 95%CI: -2.7%, 2.7%	

As shown above, the response rates and the 95% confidence interval for subjects in the Medical Officer's Microbiologically Evaluable Population are the same at Visit 4 as at Visit 3. By subject assessment, there was complete eradication in both treatment arms. The 95% confidence interval suggests therapeutic equivalence of the two treatment groups for eradication.

The Overall Microbiological Assessment by Subject, in the Applicant's and in the MO's Microbiologically Evaluable Population, is summarized in tables below:

Overall Microbiological Assessment by Subject for the Applicant's Microbiologically Evaluable Population-PRT003

Assessment	Ofloxacin 0.25ml b.i.d.	Cortisporin® 0.15ml q.i.d.	P-value	95% C.I.
Eradication	44 (97.8%)	53 (100%)	0.386	(-8.6%, 4.1%)
Persistence	1 (2.2%)	0		
Total	45	53		

Overall Microbiological Assessment by Subject for the Medical Officer's Microbiologically Evaluable Population-PRT003

Clinical Response	Ofloxacin (N=33)	Cortisporin® (N=44)
Eradication	33 (100%)	44 (100%)
Persistence + Recurrence	0 (100%)	0 (0%)
Ofloxacin vs. Cortisporin® for Eradication	0%, 95%CI: -2.7%, 2.7%	

Medical Officer's Comment: In summary, at Visit 3, at Visit 4, and for the Overall Microbiological Assessment by Subject, therapeutic equivalence of the treatments was shown in both the Applicant's Microbiologically Evaluable Population and the Medical Officer's Microbiologically Evaluable Population.

Overall Microbiologic Assessment by Pathogen

The distribution and response rates of the pathogens in the Applicant's Microbiologically Evaluable Population are shown in the table below.

Overall Microbiological Assessment by Pathogen for the Applicant's Microbiologically Evaluable Population

Pathogen	Ofloxacin 0.25ml b.i.d.			Cortisporin® 0.15ml q.i.d.	
	Eradication	Persistence	Total	Eradication	Total
<i>Pseudomonas aeruginosa</i> *	35	1	36	42	42
<i>Proteus mirabilis</i>	5	0	5	3	3
<i>Staphylococcus aureus</i>	3	0	3	8	8
<i>Enterobacter cloacae</i>	3	0	3	1	1
<i>Klebsiella pneumoniae</i>	2	0	2	1	1
<i>Enterococcus faecalis</i>	1	0	1	3	3
<i>A. Calcoaceticus V. Anitratus</i>	1	0	1	2	2
<i>Enterococcus casseliflavus</i>	1	0	1	1	1
<i>Enterobacter aerogenes</i>	1	0	1	0	0
<i>Enterobacter agglomerans</i>	1	0	1	0	0
<i>Haemophilus parahemolyticus</i>	1	0	1	0	0
<i>Pseudomonas fluorescens</i>	1	0	1	0	0
<i>Pseudomonas vesicularis</i>	1	0	1	0	0
<i>Sphingomonas paucimobilis</i>	1	0	1	0	0
<i>Xanthomonas maltophilia</i>	0	0	0	3	3
<i>Alcaligenes xylosoxidans</i>	0	0	0	2	2
<i>Escherichia coli</i>	0	0	0	2	2
<i>Citrobacter freundii</i>	0	0	0	1	1
<i>Pseudomonas cepacia</i>	0	0	0	1	1
<i>Serratia marcescens</i>	0	0	0	1	1
<i>Streptococcus agalactiae</i>	0	0	0	1	1
<i>Streptococcus pneumoniae</i>	0	0	0	1	1
<i>Streptococcus pyogenes</i>	0	0	0	1	1
Total			58		74

* Comparison of the two treatment groups with respect to eradication rate of *Pseudomonas aeruginosa* gave a p-value of 0.386 and a 95% C.I. of (-10.7, 5.2%).

The distribution of baseline pathogens for subjects in the Applicant's Microbiologically Evaluable Population appeared to be similar to the distribution of baseline pathogens in the Intent-to-Treat Population. The response rates, on a per pathogen basis, were 100% for all but one isolate of *Pseudomonas aeruginosa* in the ofloxacin group.

Looking at just the six pathogens which the Applicant seeks in labeling, the eradication rates in the Medical Officer's Microbiologically Evaluable Population are as shown in the table below:

Overall Pathogen Eradication Rates for the Most Common Baseline Pathogens of the Medical Officer's Microbiologically Evaluable Population		
Pathogen	Ofloxacin	Cortisporin®
<i>P. aeruginosa</i>	28/28 (100%)	35/35 (100%)
<i>P. mirabilis</i>	0/0	1/1 (100%)
<i>S. aureus</i>	1/1 (100%)	4/4 (100%)
<i>E. cloacae</i>	3/3 (100%)	0/0
<i>K. pneumoniae</i>	0/0	1/1 (100%)
<i>E. faecalis</i>	1/1 (100%)	2/2 (100%)
Ofloxacin vs. Cortisporin for Eradication of <i>P. aeruginosa</i>	0%, 95%CI: -3.2%, 3.2%	

Overall Microbiological/Clinical Assessment

The following tables outline the Overall Microbiological/Clinical Assessments for the Applicant and MO Microbiologically Evaluable Populations.

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

Assessment	Ofloxacin 0.25ml b.i.d.		Cortisporin® 0.15ml b.i.d.		P-value	95% C.I.
Success	44	(97.8%)	53	(100%)	0.386	(-8.6%, 4.1%)
Failure	1	(2.2%)	0			
Total	45		53			

Overall Microbiological/Clinical Assessment for the Medical Officer's Microbiologically Evaluable Population

Assessment	Ofloxacin (N=33)	Cortisporin® (N=44)
Success	33 (100%)	44 (100%)
Failure	0 (0%)	0 (0%)
Ofloxacin vs. Cortisporin®	0%, 95%CI: -2.7%, 2.7%	

Medical Officer's Comment: The above tables show that there is equivalence for the two treatment groups in the Applicant's and the Medical Officer's Microbiologically Evaluable Population for the Overall Microbiological/Clinical Assessment.

The following table outlines the Medical Officer's Overall Microbiological/Clinical Efficacy rates for the ofloxacin-treated subjects with respect to the six pathogens the Applicant has requested in the labeling.

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Eradi) of the Six Requested Pathogens Medical Officer's Microbiologically Evaluable <u>Ofloxacin Treated Subjects (N=33)</u> PRT-003 Pediatric Otitis Externa		
<u>Baseline Pathogen Requested</u>	<u>Pathogens Eradicated</u>	<u>Clinical Cure + Pathogen Eradication</u>
<i>Enterococcus faecalis</i>	1/1	1/1 (100%)
<i>Staphylococcus aureus</i>	1/1	1/1 (100%)
<i>Enterobacter cloacae</i>	3/3	3/3 (100%)
<i>Klebsiella pneumoniae</i>	0/0	0/0 (100%)
<i>Proteus mirabilis</i>	0/0	0/0 (100%)
<i>Pseudomonas aeruginosa</i>	28/28	28/28 (100%)

Medical Officer's Comment: *The overall clinical response rates among the clinically evaluable adults were generally lower than those seen in pediatric subjects for both treatments. The cure rates for adults were 76.8% for the ofloxacin-treated subjects and 80.6% for the Cortisporin®-treated subjects, versus the respective rates of 96.3% and 92.3% seen in pediatric subjects.*

The Medical Officer looked for possible explanations for this difference in clinical efficacy rates between adults and children. The MO questioned if there was a difference between the groups with respect to the baseline disease characteristics, compliance with therapy, use of debridement or other cleaning methods, or the baseline microbiology.

Of the baseline disease characteristics, there were a few differences between the groups. A greater proportion of adults (75%) were felt to have exacerbating otitis externa at baseline than pediatric subjects (64%). And the mean duration of otitis externa prior to enrollment was longer in adults (~5 days) than pediatric subjects (~3 days). Additionally, though not otherwise specified, a greater percentage of the adults (13%) than pediatric subjects (3%) had a history of endocrine or metabolic conditions.

The compliance with therapy was similar between adults and children. Wicks for medication application were provided to be used at the discretion of the investigator, and the MO questioned if perhaps there was greater use of these, which might have enhanced the medication delivery to the treatment area, in children than adults. Unfortunately, data on the use of wicks were not collected.

Cleaning procedures were done fairly infrequently in both studies, but somewhat more commonly in adults than in children. Overall, 8% of the adults and 5% of the children in the studies had a cleaning procedure or debridement performed. With respect to these procedures, there was no significant difference between the two treatment arms in either study.

Comparing the baseline microbiology, a greater proportion of adults than children had a baseline pathogen. In fact, more adults than children had multiple pathogens at baseline. The MIC-values of the baseline pathogens of microbiologically evaluable subjects were similar between the adult and pediatric subjects.

Looking a bit more closely at the adult population, the clinical cure rates for male subjects was only 68% for ofloxacin-treated subjects and 74% for Cortisporin®-treated males, while the respective rates of 88% and 87% for adult females more closely approached those seen in the pediatric subjects. The Medical Officer thought perhaps there was less penetration of the medication in the ear canals of adults, particularly men, due to more hair and cerumen. It was also thought that the medication may have been administered more effectively when given by a caregiver to the pediatric subjects than when self-administered by an adult. Both of these thoughts are speculative. No definitive reason for the difference in cure rates between adults and children was identifiable.

The 95% confidence interval, by the Weighted Mantel-Haenszel Method, for the clinical cure rates in the adult study was (-14.4%, 6.6%). The 95% confidence interval, by the Weighted Mantel-Haenszel Method, for the clinical cure rates in the pediatric study was (-2.4%, 9.3%). In the opinion of the Medical Officer, ofloxacin otic 0.3% solution demonstrated therapeutic equivalence to Cortisporin® otic solution in the treatment of otitis externa in both adults and pediatric subjects greater than one year of age.

SAFETY ANALYSIS-PRT003

Safety Analyses will be presented for 2 populations:

- All enrolled (ITT)
- Modified ITT (excludes centers 59, 72, and 73)

All Adverse Events

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

Adverse Events During the Study in the Intent-to-Treat Population as Presented in the NDA-PRT003

Parameter	Ofloxacin 0.25ml b.i.d.		Cortisporin® 0.15ml q.i.d.		P-value
Number of Subjects	143		144		
Subjects with any AE	50	(35.0%)	37	(32.7%)	0.096
Subjects with Treatment-related AEs	4	(2.8%)	5	(3.5%)	1.000
Subjects with Severe or Life-threatening AEs ¹	1	(0.7%)	0	(0%)	0.498
Subjects with Serious AEs ²	2	(1.4%)	0	(0%)	0.247
Subjects Discontinued due to AEs	2	(1.4%)	5	(3.5%)	0.445

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.

As shown in the above table, the Applicant noted that the two treatment groups in the Intent-to-Treat Population presented in the NDA had similar incidence profiles of adverse events (P=.096).

The following table shows these same parameters for the Modified Intent-to-Treat Population (after the exclusion of Centers 59, 72, and 73.)

Adverse Events During the Study in the Modified Intent-to-Treat Population-PRT003 (Excludes Centers 59, 72, 73)

Parameter	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.		P-value
Number of Subjects	100		102		
Subjects with any AE	41	(41.0%)	32	(31.4%)	0.188
Subjects with Treatment-related AEs	3	(3.0%)	4	(3.9%)	1.000
Subjects with Severe or Life-threatening AEs ¹	0	(0%)	0	(0%)	NA
Subjects with Serious AEs ²	2	(2.0%)	0	(0%)	0.244
Subjects Discontinued due to AEs	2	(2.0%)	5	(4.9%)	0.445

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.

Medical Officer's Comment: After the Medical Officer excluded Centers 59, 72, and 73, there were no significant differences between the two treatment groups in the Modified Intent-to-Treat Population with respect to the following safety parameters: the rates of subjects experiencing at

least one adverse event, at least one treatment-related adverse event, a severe adverse event, a serious adverse event, or discontinuation due to an adverse event. While there was no statistically significant difference between the two groups, the percentages of the population affected did rise somewhat due to the smaller size of the respective populations and the observation that the excluded investigators recorded relatively few AEs.

Deaths and Other Serious AEs

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.

Two ofloxacin-treated subjects experienced adverse events that were considered to be serious:

- Subject developed a 2x3 cm. rash on the neck on Day 2 and the medication was discontinued. The rash resolved off therapy on Day 4. The Investigator deemed this rash to be unexpected, of mild intensity, serious in nature, and remotely related to the study drug. The Applicant considered that the rash was possibly related to the study drug.
- Subject developed a follicular rash bilaterally on her thighs on Study Day 4. The study medication was discontinued until what would have been Study Day 8 when she resumed use until Day 11. The rash resolved on Day 15. In the opinion of the Investigator, the rash was possibly related to the study drug.

No Cortisporin®-treated subject experienced an adverse event considered serious.

Severe Adverse Events

Subject experienced non-treatment-related severe otitis media. This subject was excluded by the MO. There were no other subjects who had adverse events that were severe in intensity.

Discontinuations due to Adverse Events

Two ofloxacin-treated subjects and 5 Cortisporin®-treated subjects were discontinued due to adverse events. None of these 7 subjects were among those excluded from analyses by the Medical Officer. Therefore, the following table is a summary of the adverse events that led to subject discontinuation from treatment in both the ITT Population and the Modified ITT Population.

**Adverse Events that Caused Discontinuation from Treatment
 Same Events for the ITT Population in the NDA and for the Modified ITT Population (Relative percentage of Respective Population)**

<u>Adverse Event</u>	<u>Ofloxacin 0.25ml b.i.d.</u>		<u>Cortisporin® 0.15ml q.i.d.</u>	
<u>Hearing and Vestibular Disorders</u>				
Earache	1	(0.7% NDA 1.0% MO)	1	(0.7% NDA 1.0% MO)
<u>Skin and Appendages Disorders</u>				
Rash	1	(0.7% NDA 1.0% MO)	0	
<u>Respiratory System Disorders</u>				
Pharyngitis	0		2	(1.4% NDA 2.0% MO)
<u>Application Site Disorders</u>				
Tympanic Membrane Perforation	0		1	(0.7% NDA 1.0% MO)
Application Site Reaction	0		1	(0.7% NDA 1.0% MO)

The 2 subjects in the ofloxacin group were:

- Subject earache (not treatment-related)
- Subject rash described as serious (see above section for details)

The 5 subjects in the Cortisporin® group were:

- Subject earache (not treatment-related)
- Subject pharyngitis (not treatment-related)
- Subject -pharyngitis (not treatment-related)
- Subject withdrawn due to tympanic membrane perforation diagnosed at Visit 2; also had ear pain (possibly tx-related) and taste of medication in throat (probably study medication-related)
- Subject -application site reaction ("stinging" in ear immediately after dosing possibly related to study drug)

The Medical Officer reviewed the capsule summaries of all 7 of these subjects and concurred with the assessments reported by the Applicant.

Severe Adverse Events

Subject experienced non-treatment-related severe otitis media. This subject was excluded by the MO. There were no subjects who had adverse events that were severe in intensity.

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Subjects with Adverse Events who were excluded by the Medical Officer

Of the 85 total subjects excluded by the Medical Officer, only 9 ofloxacin-treated subjects and 5 Cortisporin®-treated subjects had adverse events reported. These subjects and their respective reported adverse events are listed below:

9 Ofloxacin-treated subjects

<u>Subject</u>	<u>Adverse Event</u>	<u>Severity</u>	<u>Relationship to Study Drug</u>
Subject	Fever	Mild	Not related
Subject	Earache (burning)	Mild	Probably related
Subject	Otitis Media	Severe	Not related
Subject	Bronchitis Earache	Mild Mild	Not related Not related
Subject	Otitis Media	Moderate	Not related
Subject	Skin Depigmentation	Mild	Not Related
Subject	Upper Respiratory Tract Infection	Moderate	Not Related
Subject	Upper Respiratory Tract Infection	Mild	Not Related
Subject	Coughing	Mild	Not Related

5 Cortisporin®-treated subjects

Subject	Pharyngitis	Moderate	Not Related
Subject	Earache	Mild	Probably Related
Subject	Otitis Media	Mild	Not Related
Subject	Pruritus Bronchospasm Coughing	Mild Mild Mild	Not related Not related Not-related
Subject	Pruritus	Mild	Not Related

Most of these adverse events were mild and not-related to the study drug. There were only two that were probably treatment-related: one event of an earache in an ofloxacin-treated subject and one event of an earache in a Cortisporin®-treated subject. The case of otitis media in ofloxacin-treated subject was considered to be severe in intensity, but not treatment-related. None of these subjects was reported to have experienced a serious adverse event.

Most Common Adverse Events

Shown in the table below are the adverse events that were seen in five or more subjects of the Intent-to-Treat Population submitted in the NDA:

Adverse Events that Occurred in Five¹ or More Subjects of the Intent-to-Treat Population as presented in the NDA-PRT003

<u>Adverse Event by Body System</u>	<u>Ofloxacin 0.25ml b.i.d. (N=143)</u>		<u>Cortisporin® 0.15ml q.i.d. (N=144)</u>		<u>P-value³</u>
	<u>Subjects (%)</u>	<u>Events²</u>	<u>Subjects (%)</u>	<u>Events²</u>	
<u>Respiratory System Disorders</u>					
Rhinitis	9 (6.3%)	10	8 (5.6%)	9	0.808
Coughing	6 (4.2%)	6	7 (4.9%)	7	1.000
Pharyngitis	4 (2.8%)	4	6 (4.2%)	7	0.750
Upper Resp Tract Infection	5 (3.5%)	5	0	0	
<u>Hearing and Vestibular Disorders</u>					
Earache	11 (7.7%)	13	5 (3.5%)	5	0.132
<u>Resistance Mechanism Disorders</u>					
Otitis Media	11 (7.7%)	13	6 (4.2%)	6	0.223
<u>Body as a Whole - Gen Disorders</u>					
Fever	8 (5.6%)	8	9 (6.3%)	9	1.000
<u>Centr & Periph Ner Sys Disorders</u>					
Headache	2 (1.4%)	2	4 (2.8%)	4	0.684

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.

³ Treatment comparison of the number of subjects with the AE. P-values were not computed when the number of subjects was less than 2 in either arm.

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The following table shows how the number of these events was changed by the Medical Officer's exclusion of three investigative centers. Those events that changed in actual subject numbers, not just relative percentage of the population, are shown in bold print.

Adverse Events that Occurred in Five¹ of More Subjects of the Modified Intent-to-Treat Population-PRT003 (excludes centers 59, 72, 73)					
	Ofloxacin 0.25ml b.i.d. (N=100)		Cortisporin[®] 0.15ml q.i.d. (N=102)		
Adverse Event by Body System	Subjects (%)	Events²	Subjects (%)	Events²	P-value³
<u>Respiratory System Disorders</u>					
Rhinitis	9 (9.0%)	10	8 (7.8%)	9	0.805
Coughing	5 (5.0%)	5	6 (5.9%)	6	1.000
Pharyngitis	4 (4.0%)	4	5 (4.9%)	6	1.000
Upper Resp Tract Infection	5 (5.0%)	5	0	0	0.028
<u>Hearing and Vestibular Disorders</u>					
Earache	9 (9.0%)	11	4 (3.9%)	4	0.162
<u>Resistance Mechanism Disorders</u>					
Otitis Media	9 (9.0%)	11	5 (4.9%)	5	0.281
<u>Body as a Whole-Gen. Disorders</u>					
Fever	7 (7.0%)	7	9 (8.8%)	9	0.796
<u>Central and Peripheral Nervous System Disorders</u>					
Headache	2 (2.0%)	2	4 (3.9%)	4	0.683

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.

³ Treatment comparison of the number of subjects with the AE. P-values were computed by the Fisher's Exact Test.

In the Modified Intent-to-Treat Population, the percentage of the population who experienced the respective adverse events listed above increased in each case due to the smaller populations. However, there was an actual decrease in the number of subjects who had an experience of coughing, pharyngitis, earache, otitis media, or fever.

The only significant difference in the rates of these adverse events was that 5.0% of the ofloxacin-treated subjects experienced an upper respiratory tract infection versus none (0%) of the Cortisporin[®]-treated subjects (P-value=0.028). The Medical Officer notes that this does not necessarily reflect treatment attribution.

Treatment-Related Adverse Events

In the following table, the Applicant summarized the Treatment-Related Adverse Events seen in the Intent-to-Treat Population as submitted in the NDA.

Treatment-Related Adverse Events in the Intent-to-Treat Population Presented in the NDA-PRT003

<u>Adverse Event by Body System</u>	<u>Ofloxacin 0.25ml b.i.d. (N=143)</u>			<u>Cortisporin® 0.15ml q.i.d. (N=144)</u>			<u>P-value²</u>
	<u>Subjects</u>	<u>(%)</u>	<u>Events¹</u>	<u>Subjects</u>	<u>(%)</u>	<u>Events¹</u>	
<u>Skin and Appendages Disorders</u>							
Eczema	1	(0.7%)	1	0	(0.0%)	0	Not Done
Pruritus	0	(0.0%)	0	1	(0.7%)	1	Not Done
Rash Follicular	1	(0.7%)	1	0	(0.0%)	0	Not Done
<u>Centr & Periph Nerv Sys Disorders</u>							
Dizziness	1	(0.7%)	1	0	(0.0%)	0	Not Done
<u>Hearing and Vestibular Disorders</u>							
Earache	1	(0.7%)	1	1	(0.7%)	1	Not Done
<u>Special Senses Other Disorders</u>							
Taste Perversion	0	(0.0%)	0	1 ^a	(0.7%)	1	Not Done
<u>Application Site Disorders</u>							
Application Site Reaction	0	(0.0%)	0	3	(2.1%)	3	Not Done

^a Subject had two AEs: Taste Perversion and an Application Site Reaction

¹ No subject had more than one treatment-related adverse event.

² Treatment comparison of the number of subjects with the AE. P-values were not computed when the number of subjects was less than 2 in either arm.

The Applicant noted that the number of subjects with treatment-related adverse events, 4/143 (2.8%) of the ofloxacin-treated subjects and 5/144 (3.5%) of the Cortisporin®-treated subjects, was similar (p=1.000) for the two treatment groups.

All of these adverse events were of either mild or moderate severity. The only adverse event that was considered to be serious in nature was the single case of follicular rash in the ofloxacin group. This event was of mild intensity.

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The following table shows how the numbers of Treatment-Related Adverse Events were changed by the Medical Officer's exclusion of three investigative sites.

Treatment-Related Adverse Events in the Modified Intent-to-Treat Population-PRT003 (excludes centers 59, 72, 73)					
	Ofloxacin 0.25ml b.i.d. (N=100)		Cortisporin® 0.15ml q.i.d. (N=102)		
Adverse Event by Body System	Subjects (%)	Events¹	Subjects (%)	Events¹	P-value²
<u>Skin and Appendages Disorders</u>					
Eczema	1 (1.0%)	1	0 (0%)	0	Not Done
Pruritus	0 (0%)	0	1 (1.0%)	1	Not Done
Follicular Rash	1 (1.0%)	1	0 (0%)	0	Not Done
<u>Central and Peripheral Nervous System Disorders</u>					
Dizziness	1 (1.0%)	1	0	0	Not Done
<u>Hearing and Vestibular Disorders</u>					
Earache	0 (0%)	0	0 (0%)	0	Not Done
<u>Special Senses & Other Disorders</u>					
Taste Perversion	0 (0%)	0	1 ^a (1.0%)	1	Not Done
<u>Application Site Disorders</u>					
Application Site Reaction	0 (0%)	0	3 (2.9%)	3	Not Done

^a Subject had two AEs: Taste Perversion and an Application Site Reaction

¹ No subject had more than one treatment-related adverse event.

² Treatment comparison of the number of subjects with the AE. P-values were not computed when the number of subjects was less than 2 in either arm.

In the Modified Intent-to-Treat Population there was one subject less in each treatment arm compared to the ITT Population. Both of the excluded subjects had been reported to have had the adverse event of a mild earache. When these two subjects were removed, there were no subjects who had a treatment-related adverse event of an earache.

Subgroup Analysis for Adverse Events

The Applicant looked at the adverse events by the subgroups of age (<1, 1, 2-11, and >11 years), race (Caucasian, African American, Hispanic, and other), and gender (female, male). The number of subjects experiencing treatment-related adverse events were similar for all body systems and individual adverse events in all subgroups analyzed. As shown above, when looking at treatment-related adverse events, the Medical Officer's changes equally affected both treatment groups (each lost one subject who had the adverse event of earache.) Therefore, the treatment related adverse events reported in the Modified Intent-to-Treat population were similar for these subgroups also.

Summary of Safety-PRT003

The safety analyses were performed on the Intent-to-Treat Population as submitted in the NDA and as revised by the Medical Officer, after the exclusion of 3 centers. Except for a small difference in age, the two treatment groups were similar with respect to all demographic and baseline characteristics. In both the Applicant's and the Medical Officer's assessments, the groups were similar with respect to the safety parameters of: the number of subjects experiencing any adverse events, treatment-related adverse events, severe adverse events, serious adverse events, or discontinuation from the study due to adverse events. There were no life-threatening adverse events seen during this study. There were no deaths during treatment or within 30 days of the last dose of study medication.

Overall, most of the adverse events were of mild to moderate severity, there were very few treatment-related adverse events, and very infrequently was discontinuation of therapy required.

Medical Officer's Summary-Comments and Conclusions-Protocol 003

This study was of analogous design to Protocol 002 with appropriate adjustments made for pediatric subjects. Like Protocol 002, the only complicating factor in reviewing the data was the need to exclude three investigative centers. Otherwise, the Medical Officer made very few changes in the evaluability status or outcome assessments.

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

Overall Clinical Response MO Clinically Evaluable Population PRT-003 (after the Exclusion of Three Centers)		
<u>Clinical Response</u>	<u>Ofloxacin (N=81)</u>	<u>Cortisporin® (N=78)</u>
Cure	78 (96.3%)	72 (92.3%)
Failure	3 (3.7%)	6 (7.7%)
Ofloxacin vs. Cortisporin® by cure	4.0%, 95%CI: -4.5%, 12.4%	

The Overall Microbiological Assessment by Subject for the MO's Microbiologically Evaluable Population is shown in the table below:

Overall Microbiological Assessment by Subject for the Medical Officer's Microbiologically Evaluable Population-PRT003		
<u>Clinical Response</u>	<u>Ofloxacin (N=33)</u>	<u>Cortisporin® (N=44)</u>
Eradication	33 (100%)	44 (100%)
Persistence + Recurrence	0 (100%)	0 (0%)
Ofloxacin vs. Cortisporin® for Eradication	0%, 95%CI: -2.7%, 2.7%	

The Medical Officer's Overall Microbiological/Clinical Efficacy rates for the six pathogens requested in the labeling are shown in the table below:

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erاد) of the Six Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects (N=33) PRT-003 Pediatric Otitis Externa		
<u>Baseline Pathogen Requested</u>	<u>Pathogens Eradicated</u>	<u>Clinical Cure + Pathogen Eradication</u>
<i>Enterococcus faecalis</i>	1/1	1/1 (100%)
<i>Staphylococcus aureus</i>	1/1	1/1 (100%)
<i>Enterobacter cloacae</i>	3/3	3/3 (100%)
<i>Klebsiella pneumoniae</i>	0/0	0/0 (100%)
<i>Proteus mirabilis</i>	0/0	0/0 (100%)
<i>Pseudomonas aeruginosa</i>	28/28	28/28 (100%)

The safety analyses showed ofloxacin otic to be generally well-tolerated. Most of the adverse events were of mild to moderate severity. The most common adverse events in both treatment arms were: rhinitis, coughing, pharyngitis, earache, otitis media, fever, and headache. Both groups were similar with respect to these adverse events. There were only three ofloxacin-treated subjects who experienced adverse events that were felt to be treatment-related. There was one case each of eczema, follicular rash, and dizziness. All of these were of mild intensity.

In summary, by DAIDP guidelines, ofloxacin otic 0.3% solution demonstrated clinical efficacy equivalent to Cortisporin® otic solution in treating otitis externa in pediatric subjects under the age of twelve years. The safety profile of ofloxacin in this study was similar to that of Cortisporin® otic solution.

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INDICATION CONCLUSION-Otitis Externa

Summary of Clinical Efficacy in Otitis Externa

The Applicant conducted two adequate and well-controlled studies, one in adults and one in pediatric subjects, comparing ofloxacin otic 0.3% solution to Cortisporin® otic solution in the treatment of acute otitis externa.

Summary of Adult Otitis Externa Study (PRT002)

Overall Clinical Response MO Clinically Evaluable Subjects-PRT002 (after the Exclusion of Two Centers)		
<u>Clinical Response</u>	Ofloxacin (N=99)	Cortisporin® (N=98)
Cure	76 (76.8%)	79 (80.6%)
Failure	23 (23.2%)	19 (19.4%)
Ofloxacin vs. Cortisporin® by cure	-3.8%, 95%CI; -16.3%, 8.6%	

**Overall Microbiological Assessment by Subject
 Medical Officer's Microbiologically Evaluable Population-PRT002**

Assessment	Ofloxacin 0.5ml b.i.d.		Cortisporin® 0.2ml q.i.d.	
Eradication	44	(97.8%)	46	(97.9%)
Persistence	0		1	(2.1%)
Recurrence	1	(2.2%)	0	
Total	45		47	

Ofloxacin vs. Cortisporin® by Eradication -0.1%, 95%: -8.2%, 8.0%

Summary of Pediatric Otitis Externa Study (PRT003)

Overall Clinical Response MO Clinically Evaluable Population PRT-003 (after the Exclusion of Three Centers)		
<u>Clinical Response</u>	Ofloxacin (N=81)	Cortisporin® (N=78)
Cure	78 (96.3%)	72 (92.3%)
Failure	3 (3.7%)	6 (7.7%)
Ofloxacin vs. Cortisporin® by cure	4.0%, 95%CI; -4.5%, 12.4%	

**Overall Microbiological Assessment by Subject for the
 Medical Officer's Microbiologically Evaluable Population-PRT003**

Clinical Response	Ofloxacin (N=33)	Cortisporin® (N=44)
Eradication	33 (100%)	44 (100%)
Persistence + Recurrence	0 (100%)	0 (0%)
Ofloxacin vs. Cortisporin® for Eradication	0%, 95%CI: -2.7%, 2.7%	

Summary of Microbiological Efficacy in Otitis Externa

Pathogen Eradication Rates and Overall Clinical/Micro Success Rates (Cure+Erad) of the Six Requested Pathogens Medical Officer's Microbiologically Evaluable Ofloxacin Treated Subjects Otitis Externa: Combined Protocols PRT-002 and PRT-003 (N=78)						
Pathogen	Pathogen Eradication Rates			Clinical Cure + Pathogen Eradication		
	PRT-002	PRT-003	Total	PRT-002	PRT-003	Total
<i>Enterococcus faecalis</i>	5/5	1/1	6/6	4/5 (80.0%)	1/1 (100%)	5/6 (83%)
<i>Staphylococcus aureus</i>	6/6	1/1	7/7	6/6 (100%)	1/1 (100%)	7/7 (100%)
<i>Enterobacter cloacae</i>	3/3	3/3	6/6	1/3 (33.3%)	3/3 (100%)	4/6 (67%)
<i>Klebsiella pneumoniae</i>	5/5	0/0	5/5	4/5 (80.0%)	0/0 (100%)	4/5 (80%)
<i>Proteus mirabilis</i>	3/3	0/0	3/3	2/3 (66.7%)	0/0 (100%)	2/3 (67%)
<i>Pseudomonas aeruginosa</i>	32/32	28/28	60/60	28/32 (87.5%)	28/28 (100%)	56/60 (93%)

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Summary of Safety in Otitis Externa

In general, ofloxacin otic 0.3% solution was well-tolerated in both adults and pediatric subjects. The following table summarizes the treatment-related adverse events seen in each otitis externa study.

All Treatment-Related Adverse Events Seen in The Ofloxacin-Treated Subjects in the Modified Intent-to-Treat Populations Otitis Externa Protocols PRT-002 and PRT-003			
Body System Specific Adverse Event	Ofloxacin Subjects PRT-002 (Adults) (N=129) (% of 129)	Ofloxacin Subjects PRT-003 (Pediatric) (N=100) (% of 100)	Overall Total (N=229) (% of 229)
<u>Application Site Disorders</u>			
Application Site Reaction	6 (4.7%)	0 (0)	6 (2.6%)
<u>Skin and Appendages Disorders</u>			
Dermatitis	1 (0.8%)	0	1 (0.4%)
Eczema	0	1 (1.0%)	1 (0.4%)
Rash, Erythematous	1 (0.8%)	0	1 (0.4%)
Rash, Follicular	0	1 (1.0%)	1 (0.4%)
Rash, NOS	1 (0.8%)	0	1 (0.4%)
Pruritus	10 (7.8%)	0	10 (4.4%)
<u>Central and Peripheral Nervous System</u>			
Dizziness	1 (0.8%)	1 (1.0%)	2 (1.0%)
Hypoaesthesia	1 (0.8%)	0	1 (0.4%)
Vertigo	2 (1.6%)	0	2 (1.0%)
<u>Hearing and Vestibular System Disorders</u>			
Earache	2 (1.6%)	0	2 (1.0%)
Otorrhagia	1 (0.8%)	0	1 (0.4%)
Tinnitus	1 (0.8%)	0	1 (0.4%)
<u>Gastrointestinal System Disorders</u>			
Dyspepsia	1 (0.8%)	0	1 (0.4%)
<u>Special Senses</u>			
Taste Perversion	0	0	0
<u>Body as a Whole-General Disorders</u>			
Hot Flashes	1 (0.8%)	0	1 (0.4%)
<u>Vascular (Extracardiac) Disorders</u>			
Flushing	1 (0.8%)	0	1 (0.4%)

Most of the adverse events in each study were of mild to moderate severity. There were more treatment-related adverse events in adults than in children, and the two most commonly reported adverse events in adults, application site reaction and pruritus, were not reported in children. There were only three treatment-related adverse events reported in children, a single episode each of eczema, follicular rash, and dizziness.

The following table summarizes the treatment-related adverse events reported in 1% or more of the subjects in the otitis externa studies.

<u>Adverse Events In Otitis Externa Studies</u>	<u>Frequency (N=229)</u>
Pruritus	4.4%
Application Site Reaction	2.6%
Dizziness	1.0%
Earache	1.0%
Vertigo	1.0%

The following treatment-related adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing, and otorrhagia.

In summary, in the treatment of otitis externa in subjects ages 1 year and above, the adverse events associated with ofloxacin otic 0.3% solution were generally of mild to moderate severity and infrequently necessitated discontinuation of therapy.

Medical Officer's Recommendation-Otitis Externa

In the opinion of the Medical Officer, adequate safety and efficacy data were demonstrated in Protocols 002 and 003 to support the approval of ofloxacin otic 0.3% solution for the treatment of otitis externa in pediatric subjects age 1 year and older and adults. Labeling for this indication should include *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

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Indication #2

Acute Purulent Otorrhea in Pediatric Subjects with Tympanostomy Tubes
(Acute Otitis Media)

Two studies of Acute Otitis Media in Pediatric Subjects with Tympanostomy Tubes were conducted:

8280A-PRT008- An Evaluator-Blinded Study with
Active Comparator Agent of Augmentin®

and

8280A-PRT007-An Open-Label Study with
Historical and Current Practice Group Controls

ACUTE PURULENT OTORRHEA

Trial #1

8280A-PRT008

"A Multicenter, Randomized, Parallel Group, Evaluator Blinded, Comparative Study of the Safety and Efficacy of Ofloxacin Otic Solution and Augmentin® Oral Suspension in the Treatment of Acute Purulent Otorrhea (Draining Ear) in Pediatric Subjects with Tympanostomy Tubes"

Study Rationale and Objective

Study Rationale

Medical Officer's Comment:

The Applicant did not outline a specific "study rationale," but did provide an introductory section with an overview of the disease entity to be studied and the reasoning behind the approach taken in this study. The following information was gleaned from the Introduction section. Sections taken verbatim from the Applicant's material are shown in quotation marks.

Insertion of tympanostomy tubes is the most common surgical procedure performed in the United States with insertion in over one million children per year. Tubes are inserted for a variety of reasons, most commonly for persistent middle ear effusion or for recurrent acute otitis media (AOM). The tubes remain in situ for an average of 12 months and are usually spontaneously extruded.

"When AOM occurs in children who have tympanostomy tubes in place, the signs and symptoms as well as the pathogenic bacteria differ somewhat from those seen in children with AOM and intact membranes. Otorrhea is the key symptom of AOM in children with tympanostomy tubes. Fever and other systemic signs and symptoms are uncommon, unless the child has a concomitant systemic infection, and otalgia is rare. Thus, acute otorrhea in children with tympanostomy tubes is synonymous with AOM in children with tympanostomy tubes."

Therapy of AOM in children with tympanostomy tubes is not standardized, and there is no agent approved specifically for this indication. Some physicians treat with oral antibiotics while others use a variety of topical agents, and occasionally, children are treated with intravenous antibiotics.

The pathogens commonly isolated from children with intact tympanic membranes who have AOM are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In children with tympanostomy tubes, pathogens may penetrate to the middle ear from either the external auditory canal or from the pharynx via the eustachian tube. Therefore, in addition to the above-mentioned pathogens commonly seen in AOM, pathogens such as enteric organisms, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* are commonly isolated from children with AOM with tympanostomy tubes.

"The present study was designed to compare the efficacy and safety of ofloxacin otic solution in children with AOM with tympanostomy tubes. An oral comparator was chosen because oral therapies are commonly used although none of those approved for pediatric use are effective

against *Pseudomonas aeruginosa*. Because of the anticipated high prevalence of beta-lactamase producing *Haemophilus influenzae*, *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae* in the intended study population, amoxicillin was considered an inadequate comparator. Augmentin®, a combination drug containing amoxicillin and clavulanic acid, was chosen because of its activity against beta-lactamase producing strains of *Haemophilus influenzae*, *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. In addition, like ofloxacin otic solution, Augmentin®, is known not to be ototoxic."

Study Objective

As stated by the Applicant, "The objective of this study was to compare the safety and efficacy of 0.3% ofloxacin otic solution to Augmentin® oral suspension in the treatment of acute purulent otorrhea (draining ear) in pediatric subjects with tympanostomy tubes. A Sub-group of approximately fifty qualified subjects 4 years of age and older was to have pre and post-therapy audiometric studies performed."

Study Design

This was a multicenter, randomized, parallel-group, evaluator-blind study to compare the safety and efficacy of ofloxacin otic solution to Augmentin® oral suspension in the treatment of acute purulent otorrhea (draining ear) in pediatric subjects with tympanostomy tubes. Purulent otorrhea was defined as any purulent or mucopurulent secretion through a patent tympanostomy tube.

Subjects were to have tympanostomy tube(s) in place and acute purulent otorrhea, defined as a purulent or mucopurulent secretion of less than 3 weeks duration through a patent tympanostomy tube. Subjects were to receive either ofloxacin otic solution 0.25mL b.i.d. (12 hours apart) or Augmentin® 40 mg/kg/day (administered in three divided doses [13.3 mg/kg/dose] 8 hours apart) for 10 days. At selected study sites, qualified subjects ≥ 4 years of age were to have audiometry tests performed on both ears at the Pre-therapy visit (Visit 1) and at the Test-of-Cure visit (Visit 4) or upon early withdrawal. Subjects were to be evaluated at the following timepoints:

Visit	Period	Window (Day of Study)
1	Baseline (Pre-Therapy)	Day 1
2	During Therapy	Day 4-6
3	Post-Therapy	Day 11-13
4	Test-of-Cure	Day 17-20

Sites meeting specific American Speech-Language-Hearing Association (ASHA) guidelines were chosen to participate in the audiometry arm of the study. Audiometry evaluation was to be performed on 25 subjects per treatment group across selected sites based on a pre-determined randomization schedule. Audiometry was to be performed twice for each selected subject: once on the day of study entry (Visit 1, Pre-Therapy), and at 7 to 10 days after completion of treatment (Visit 4, Test-of-Cure).

Statistical Considerations

Approximately 320 subjects were to be enrolled to ensure data from 276 clinically evaluable subjects. The protocol was originally written so that at least 20 investigative centers, all in the United States, would participate in this study. And, the study was to be initiated in November, 1994 and completed approximately in December, 1995. However, due to a very mild 1994-1995 winter season, enrollment in the United States was slow. Therefore, in May, 1995, the Applicant revised the protocol to allow for the addition of some Latin American investigative centers. The revised

protocol allowed for no more than 6 Latin American centers to contribute approximately 106 of the 320 total targeted subjects, yielding approximately 92 of the 276 targeted clinically evaluable subjects. This plan was reviewed with the Agency prior to implementation, and was formally submitted on August 23, 1995 in IND Protocol Amendment Serial #044.

Because of the mild winter and slow enrollment, the actual study dates were quite different from those originally intended. The first subject was dosed on January 20, 1995 and the last subject was evaluated on June 18, 1996.

At study completion, there was a total of 39 investigative centers, including two Latin American centers as listed below:

Center PRT008-801

Basim Asmar, M.D.
Children's Hospital of Michigan
Division of Infectious Diseases
3901 Beaubien Blvd.
Detroit, MI 48201

Center PRT008-802

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

Center PRT008-804

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

Center PRT008-805

Earl Harley, M.D.
Georgetown University Hospital
Department of Otolaryngology
3800 Reservoir Road, NW
Washington, DC 20007

Center PRT008-806

Robert Jordan, M.D.
Carolina Clinical Research, Inc.
2990 Bethesda Place, Suite 606B
Winston-Salem, NC 27103

Center PRT008-807

William Lumry, M.D.
Allergy & Asthma Research Associates
5499 Glenn Lakes Dr., Suite 250
Dallas, TX 75231

Center PRT008-808

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

Center PRT008-809

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

Center PRT008-810

Pat McClean, M.D.
11820 Northup Way, Suite 108
Bellevue, WA 98005

Center PRT008-811

Keith Reisinger, M.D.
Pittsburgh Pediatric Research
1580 McLaughlin Run Road
Pittsburgh, PA 15241

Center PRT008-812

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

Center PRT008-813

Harry Rosenthal, M.D.
Research for Health, Inc.
902 Frostwood, Suite 315
Houston, TX 77024

Center PRT008-814

José Luis Ibarra, M.D.
Future Healthcare Research Center
California Medical Research Group
3636 N. First Street, Suite 120
Fresno, CA 93726

Center PRT008-816

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

Center PRT008-818

David Ralph Silvers, M.D.
Drug Research Services, Inc. (DRS)
4720 S. I-10 Service Road, Suite 501
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Center PRT008-840

Jeffrey M. Adelglass, M.D.
Dallas Clinical Research
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9 Medical Parkway, #202
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Center PRT008-842

C. Andrew DeAbate, M.D.
Medical Research Center
1020 Gravier Street, Suite 100
New Orleans, LA 70112

Center PRT008-844

Margaret Dreihobl, M.D.
Centre for Health Care Medical Assoc.
17190 Bernardo Center Drive
San Diego, CA 92127

Center PRT008-846

Stephen M. Fries, M.D.
Boulder Medical Center
2750 Broadway
Boulder, CO 80304

Center PRT008-849

Karen R. Westberry, M.D.
Doctors' Clinic
2300 Fifth Avenue
Vero Beach, FL 32960

Center PRT008-815

Thomas Terry Jefferson, M.D.
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Center PRT008-817

Murray Hal Rosenthal, D.O.
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Center PRT008-819

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Center PRT008-841

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Center PRT008-843

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Center PRT008-845

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Center PRT008-848

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Center PRT008-851

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