CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50675_S14

MEDICAL REVIEW

Medical Officer's Review Of An Efficacy Supplement: Short Course (5day) Vantin Po Suspension For Otitis Media

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Sponsor :	Pharmacia and Upjohn Trading Corporation

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I. Introduction To Otitis Media Studies:

1)Proposed Package Insert Regarding Dosage and Administration for Otitis Media:

The sponsor seeks approval for a 5 day dosing regimen of Vantin®for the treatment of otitis media which is a reduction in dosing from 10 days to 5 days. They would like to include the following:

Table 1. Dosing Regimen for AOM for 5 days

	Total Daily Dose	Dose Frequency
Children (1M-12Y)	10mg/kg/day max 400 mg/day	5mg/kg q 12 h max 200 mg/dose

2) Background:

Some of the following text is excerpted from the applicants submission.

Medication: Vantin oral suspension

Cefpodoxime proxetil,an orally administered, extended spectrum, semi-synthetic third generation oral cephalosporin, is a prodrug that is absorbed from the intestinal tract and de-esterified to its active metabolite, cefpodoxime. It has a broad spectrum of activity that encompassing both Gram-negative and Gram-positive bacteria. It is bactericidal, and is resistant to most β-lactamases.

The sponsor is seeking the following indication:.

Acute otitis media caused by *Streptococcus pneumoniae, Streptococcus pyogenes,Haemophilus influenzae* (including beta-lactamase-producing strains),or *Moraxella(Branhamella) catarrhalis*(including beta-lactamase-producing strains).

Vantin® is indicated for the treatment of the following infections when caused by susceptible organisms:

- upper and lower respiratory tract infections,
- AOM(10day treatment regimen)
- pharyngitis,
- community acquired pneumonia,
- skin and skin structure infections(uncomplicated),
- urinary tract infections (uncomplicated), and
- uncomplicated gonorrhea (cervical/urethral and rectal).

A. History Of This Submission:

Cefpodoxime proxetil received market approval in the United States on August 7th, 1992 for the treatment of patients with acute otitis media, tonsillitis/pharyngitis, acute bronchitis and pneumonia, urinary tract infections, and skin and skin structure infections.

Microbiologic,studies,completed during short course therapy for AOM, that were identical with respect to design, study conduct, methods, and analyses have been submitted. Protocols M/1140/0098-A, and M/1140/0098-B.

Safety data from these two studies have been integrated with pre-existing safety data for cefpodoxime proxetil to form a 2128-patient safety database.

A pharmacokinetics study is also provided in which the concentration of cefpodoxime proxetil in the middle ear effusion (MEE) of pediatric patients with acute otitis media treated with either 5 mg/kg of drug twice a day or 10 mg/kg of drug once a day was determined.

Additionally, as agreed to in discussions between representatives of Pharmacia & Upjohn Company and the US Food and Drug Administration , on 3 December 1996 – the efficacy and safety dat of a 10 day cefpodoxime regimen from three studies (Protocols M/1140/0013, M/1140/0014 , and M/1140/0060) was submitted to provide a context in which to evaluate the 5 day data.

For completeness, available safety data as of the 31 July 1997 data cutoff date for this sNDA are provided from four additional studies that investigated 10-day cefpodoxime regimens: a completed pharmacokinetics study (Protocol M/1140/0116), an ongoing Phase III study of once- versus twice-daily administration of cefpodoxime (Protocol M/1140/0119), an ongoing food-effect study of cefpodoxime in pediatric patients (Protocol P/1140/0047), and a discontinued taste-test study (Protocol M/1140/0106).

B. Regulatory Guidance Documents

Points to Consider Document:

The DAIDP Points to Consider (PTC) document suggests 2 trials one clinical and one microbiologic whose features include the following:

1) 1 statistically adequate and well-controlled multicenter trial, establishing equivalence or superiority to an approved product in which tympanocentesis need not be done, (but it is strongly encouraged and recommended for treatment failures

2) 1 open label study utilizing tympanocentesis should be done. The microbiology should include: 25 patients with *H.influenzae*, 25 with *S. pneumoniae* and 15 patients with *M. cattharalis*.

Medical Officer's Comments: The Applicant has conducted two clinical trials. Both of these trials utilized tympanocentesis. These trials were performed in the United States.

Divisional Evaluability Criteria

The divisional evaluability criteria from 2/97 stipulates the following:

- for clinically evaluable patients a clinical diagnosis of AOM is based on the following:

1) history (earpain, earache, ear fullness , fever, vomiting, fussiness, etc.),

2) physical examination (I - swollen bulging tympanic membrane which may be erythematous -because hyperemia may be present in a febrile or crying child, a red tympanic membrane alone is not adequate for the diagnosis of otitis media; II - loss of the light reflex,

3) pneumatic otoscopy (abnormal tympanic membrane mobility on pneumatic otoscopy due to the presence of pus or fluid behind the membrane and edema of the membrane), and

4) tympanometry.

- To be microbiologically evaluable the patient requires a microbiological diagnosis of AOM obtained by tympanocentesis. Also, typically the test-of-cure visit should occur approximately 1 to 2 weeks after the completion of therapy.

C. Clinical Background:

i. Overview of disease characteristics

Otitis media is a very common disease with high morbidity but low mortality, primarily affecting infants and young children. The median age of otitis patients is 3.2 years; although the peak (mode) age-specific incidence is between the ages of 6 and 18 months. Acute otitis media is the most common reason for which children were taken to the physician's office, accounting for 24.5 million visits in 1990. Approximately three-fourths of all children will have had at least one episode of acute otitis media before the age of 3, and more than a third of all children will have suffered from recurrent infections, ie, three or more episodes. Children have 6 to 10 episodes of upper respiratory infections per year, and up to 33% of children have effusion at any given time.

Acute otitis media is defined by the presence of fluid in the middle ear, accompanied by signs and symptoms of acute infection. The patient may have signs specific to ear disease including pain, otorrhea and hearing loss, as well as systemic signs such as fever, irritability, headache, lethargy, anorexia or vomiting. The abnormal tympanic membrane may be retracted or bulging, red and immobile; these findings suggest an acute inflammation and a fluid-filled space .

The pathophysiology of an acute episode of otitis media usually involves the following sequence of events: The patient has a condition, such as a viral infection or allergic reaction, that results in congestion of the upper respiratory tract mucosa. Congestion of the mucosa in the auditory tube results in obstruction of the eustachian tube at its isthmus. Serous fluid accumulates in the middle ear. The serous exudate is a potential medium for the multiplication of bacterial pathogens which have spread to the middle ear from the nasopharynx. The result is suppurative infection.

A bacterial pathogen can be isolated from the middle ear fluid of two-thirds of children with acute otitis media as shown in the table below[1]

Pathogen	Proportion of Cases
Streptococcus pneumoniae	25-50%
Haemophilus influenzae	15-30%
Moraxella catarrhalis	3-20%
Group A Streptococcus	2-3%
Staphylococcus aureus	2-3%

ii. Current therapeutic approaches:

The effective management of acute otitis media is dependent upon the selection of an appropriate antimicrobial agent for the treatment of the acute infection. Standard therapy is a 10-day course (2 to 3 doses per day) of an oral antibiotic such as amoxicillin, amoxicillin plus clavulanate potassium (Augmentin), cefaclor, trimethoprim-sulfamethoxazole (TMP-SMZ) or erythromycin-sulfisoxazole.

Currently all anti-infective agents approved for AOM are oral therapies except single dose Ceftriaxone. Although the majority of agents are approved for 10 days, there is one oral agent (Azithromycin) that is labeled for 5 day treatment of acute otitis media.

The American Academy of Pediatrics/Red Book guidelines from 1997 for Otitis media states the following: For acute otitis media, most experts recommend treatment with oral amoxicillin. Duration of therapy is for 5 to 10 days. In uncomplicated cases, 5-7 days is preferred in order to minimize the emergence of resistant bacteria in the community. Effective alternative drugs, especially for ampicillin-resistant strains *of H. influenzae*, and or penicillin-resistant strains of *Streptococcus pneumoniae*, include, pediazole,augmentin,extended-spectrum oral cephalosporins and clarithromycin. Narrow-spectrum drugs, when appropriate, are recommended.

iii. Emergence of resistance

The increase in antimicrobial resistance has complicated the management of acute otitis media (AOM). The three most common pathogens causing this childhood illness are *S. pneumoniae*, *H. influenzae* and *M catarrhalis*. Penicillin-resistance among *S. pneumoniae* isolates from middle-ear fluid or nasopharynx of children with AOM in the United States has been reported to be as high as 30%. Rates of β-lactamase production in *H. influenzae* isolates range from 15% to 30%. Beta-lactamase production occurs in the majority of *M. catarrhalis* isolates, and up to 90% of the strains are resistant to ampicillin.[2]

D. Rationale For The Study:

In the sponsor's view, cefpodoxime is an effective and safe oral therapy. The emergence of penicillin-resistant strains in the United States presents a challenge to find alternative therapies. Newer antibiotics, such as the third generation cephalosporins, show efficacy. Cefpodoxime has an MIC against *S. pneumoniae* that is 4-8x that of cefixime. [3]Cefpodoxime has a pharmacokinetic/pharmacologic profile (i.e. high plasma concentrations, long half-life, low plasma protein binding, rapid penetration into middle ear effusion, in vitro activity against the common pathogens of otitis media that suggests that a shorter duration of treatment might be as effective as the 10 day treatment regimens.[4]

The sponsor also mentions improved compliance and cost with a shorter duration of therapy.

3) Studies:

A. Overview Of Investigations

i. Current Studies

Two Phase III, prospective, randomized, evaluator-blind studies that were identical with respect to design, study conduct, methods, and analyses. Cefpodoxime was administered in these studies at a dose of 5 mg/kg every 12 hours for 5 days to 481 pediatric patients with acute otitis media. Cefixime, the active comparator in these studies, was administered at a dose of 8 mg/kg every 24 hours for 10 days to 488 pediatric patients with acute otitis media (Protocols M/1140/0098-A and M/1140/0098-B). The results of the primary efficacy analyses and medical-event data from these studies (Protocols 0098-A and 0098-B) provide the primary evidence of the safety and efficacy of the 5-day, twice-daily cefpodoxime regimen.

ii. Studies of a 10 day Regimen

The efficacy and safety profile of the 5-day cefpodoxime regimen, as determined from integrated data from Protocols 0098-A and 0098-B, was retrospectively compared with that of a 10-day cefpodoxime regimen. The 10-day data for this comparison were obtained from three studies (Protocols M/1140/0013, M/1140/0014, and M/1140/0060) in which pediatric patients with otitis media were treated with either cefpodoxime at a dose of 5 mg/kg every 12 hours for 10 days or amoxicillin/clavulanate potassium at a dose of 13.3 mg/kg every 8 hours for 10 days.

All three studies were prospectively randomized and evaluator-blinded. Protocols 0013 and 0060 were multicenter studies conducted at 13 and 4 sites, respectively, while Protocol 0014 was conducted at a single site. The randomization scheme was such that the ratio of cefpodoxime-treated patients to amoxicillin/clavulanate-treated patients was 2:1 in Protocols 0013 and 0014 and 1:1 in Protocol 0060.

These studies were previously reviewed by Dr. Susan Alpert.

iii. Pharmacokinetics study :

In another study, the concentration of cefpodoxime proxetil in the middle ear effusion (MEE) of pediatric patients with acute otitis media treated with either 5 mg/kg of drug twice a day or 10 mg/kg of drug once a day was determined.

The tables of all the studies are subsequently shown:

Table E-1. Completed Phase III Efficacy and Safety Studies of Cefpodoxime Proxetil (5-Day Regimen) Versus Cefixime (10-Day Regimen) in Pediatric Patients With Otitis Media

Protocol No. Investigator(s) Study Dates (mo/d/y)	Study Design	Study Drug & Regimen	Patients				Location of Documents (Vol, page)			
			No. Enrolled [Evaluable]*	No. Completed	Age (y) Range [Mean]	No.M/F† W/B/O‡	Synopsis	Study Report	CRF§ Tabulations	CRFs¶
M/1140/0098-A Multicenter** 11/10/93-08/01/96	Phase III, prospective, randomized, evaluator-blind, parallel-group, multicenter (12 centers)	Cefpodoxime: 5 mg/kg q 12 h x 5 d (Total dosage/d: 10 mg/kg) (Maximum dose/d: 400 mg)	225 [124]	88	0.2-11.3 [3.3]	121/104 109/17/99	Vol 4, 8/1/43	Vol 11, 8/8/1	Vol 13, 8/10/1	Vol 33, 12/1/1
		Cefixime: 8 mg/kg q 24 h x 10 d (Total dosage/d: 8 mg/kg) (Maximum dose/d: 400 mg)	230 [132]	93	0.2-12.9 [3.2]	135/95 111/22/97				
M/1140/0098-B Multicenter** 10/25/93-07/30/96	Phase III, prospective, randomized, evaluator-blind, parallel-group, multicenter (19 centers)	Cefpodoxime: 5 mg/kg q 12 h x 5 d (Total dosage/d: 10 mg/kg) (Maximum dose/d: 400 mg)	256 [136]	107	0.2-14.6 [3.5]	136/120 188/41/27	Vol 4, 8/1/47	Vol 15, 8/12/1	Vol 18, 8/15/1	Vol 35, 12/3/1
		Cefixime: 8 mg/kg q 24 h x 10 d (Total dosage/d: 8 mg/kg) (Maximum dose/d: 400 mg)	258 [140]	111	0.2-12.9 [3.3]	148/110 192/42/24				

* For efficacy
†No. of males/females
‡No. of patients by race: white/black/other
§Case report forms
¶For patients who discontinued treatment due to medical events
** A complete list of investigators is included in the study report

Table E-2. Historical Studies of Cefpodoxime Proxetil (10-Day Regimen) Versus Amoxicillin/Clavulanate Potassium (10-Day Regimen) in Pediatric Patients With Otitis Media

Protocol No. Investigators Study Dates (mo/d/y)	Study Design	Study Drug & Regimen	Patients				Location of Documents (Vol, page)	
			No. Enrolled [Evaluable]*	No. Completed	Age (y) Range [Mean]	M/F† W/B/O‡	Synopsis	Study Report
M/1140/0013 Multicenter** 10/26/89-06/26/90	Phase III, prospective, randomized, evaluator-blind, parallel-group, multicenter (13 centers) microbiologic	Cefpodoxime: 5 mg/kg q 12 h x 10 d (Total dosage/d: 10 mg/kg) (Maximum dose/d: 400 mg)	153 [95]	98	0.4-13.6 [3.4]	83/70 108/24/21	Vol 4, 8/1/56	Vol 20, 8/17/1
		A/C††: 13.3 mg/kg q 8 h x 10 d (Total dosage/d: 40 mg/kg) (Maximum dose/d: 1500 mg)	76 [48]	52	0.3-12.8 [3.4]	40/36 57/10/9		
M/1140/0014 Howie 10/17/89-01/07/91	Phase III, prospective, randomized, evaluator-blind, parallel-group, single-center microbiologic	Cefpodoxime: 5 mg/kg q 12 h x 10 d (Total dosage/d: 10 mg/kg) (Maximum dose/d: 400 mg)	120 [56]	54	0.2-6.9 [2.0]	67/53 50/43/21	Vol 4, 8/1/62	Vol 23, 8/19/1
		A/C††: 13.3 mg/kg q 8 h x 10 d (Total dosage/d: 40 mg/kg) (Maximum dose/d: 1500 mg)	60 [37]	33	0.3-7.5 [1.8]	35/25 22/18/20		

Table continued

M/1140/0060 Hellerstedt, Martin, Meissner, & Netoskie 2/26/92-6/15/94	Phase III, prospective, randomized, evaluator-blind, parallel-group, multicenter (4 centers)	Cefpodoxime: 5 mg/kg q12h x 10 d (Total dosage/d: 10 mg/kg) (Maximum dose/d: 400 mg)	59 [54]	52	0-14.0 [4.6]	34/20 33/8/13	Vol 4, 8/1/68	Vol 26, 8/22/1
		A/C**: 13.3 mg/kg q8h x 10 d (Total dosage/d: 40 mg/kg) (Maximum dose/d: 1500 mg)	59 [56]	56	0-16.0 [5.2]	31/25 35/1[illegible] 1		

* For efficacy
†No. of males/females
‡No. of patients by race: white/black/other
§Case report forms
¶For patients who discontinued treatment due to medical events
** A complete list of investigators is included in the study report.
††Amoxicillin/clavulanate potassium; doses are based on amoxicillin component.

Table B-3. Completed Pharmacokinetic Study of Cefpodoxime Proxetil in Pediatric Patients With Otitis Media

Protocol No. Investigator(s) Study Dates (mo/d/y)	Study Design	Study Drug & Regimen	Patients				Location of Documents (Vol, page)		
			No. Enrolled	No. Completed	Age (y) Range (Mean)	M/F* W/B/O†	Synopsis	Study Report	CRFs‡
M/1140/0116 Schwartz McCormick 10/22/95- 01/13/97	Randomized, open-label, parallel-group, two-center	Cefpodoxime: 5 mg/kg q 12 h x 10 d (Total dose/d: 10 mg/kg) (Maximum dose/d: 400 mg)	25	23	0.5-10.2 (2.3)	15/10 14/8/3	N/A	N/A	Vol 36, 12/4/25
		Cefpodoxime: 10 mg/kg q 24 x 10 d (Total dose/d: 10 mg/kg) (Maximum dose/d: 400 mg)	25	23	0.5-10.2 (2.1)	15/10 13/11/1			

N/A = Not Available
* No. of males/females
†No. of patients by race: white/black/other
‡Case report forms for patients who discontinued treatment due to medical events

Table E-4. Other Studies of Cefpodoxime Proxetil in Pediatric Patients With Otitis Media

Protocol No. Investigator(s)	Study Design	Study Status*	Study Drug & Regimen	No. of Pts*	Location of CRFs† (Vol, page)
P/1140/0047 Kearns	Open-label, two-way crossover study of the effect of food on the extent and rate of absorption of cefpodoxime in pediatric patients	Complete in clinic; report in progress	Cefpodoxime: 10 mg/kg with and without food	27	§
M/1140/0119 Multicenter	Phase III, prospective, randomized, investigator-blind, parallel-group, multicenter, efficacy and safety study	Ongoing	Cefpodoxime: 5 mg/kg q 12 h x 10 d	306	Vol 36, 12/4/35
			Cefpodoxime: 10 mg/kg q 24 h x 10 d		
M/1140/0106 Multicenter	Phase III, prospective, randomized, investigator-blind, parallel-group, multicenter study of the acceptability of currently marketed cefpodoxime proxetil formulation versus a flavor-modified formulation and cefprozil	Discontinued‡	Marketed cefpodoxime formulation: 5 mg/kg q 12 h x 10 d	122	Vol 36, 12/4/1
			Flavor-modified cefpodoxime formulation: 5 mg/kg q 12 h x 10 d		
			Cefprozil: 7.5 mg/kg q 12 h x 10 d (pharyngitis/tonsillitis)		
			Cefprozil: 15 mg/kg q 12 h x 10 d (all other infections)		

* As of 31 July 1997 (data cutoff date for sNDA submission)
†Case report forms for patients who discontinued treatment due to medical events
‡Discontinued after 122 of the planned 210 patients had been enrolled
§Not applicable; no patients discontinued due to medical events

II. Current Studies: Protocols M/1140/0098-A, M/1140/0098-B

1) Methods pertaining to efficacy evaluations

The two pivotal, controlled studies (Protocols 0098-A and 0098-B) included in this application to show efficacy and safety of a twice daily 5-day regimen of VANTIN Oral Suspension for the treatment of otitis media were evaluator-blind, multicenter studies conducted at 12 and 19 sites, respectively. The chart below (Table E-5) shows the schedule of activities that were pertinent to the efficacy evaluations.

Medical Officer's Note: Of note, the comparator Cefixime is not currently approved for S. pneumoniae in AOM. Given that the commonest organism cause for AOM is by S.pneumoniae, this is not an optimal active control. Please see subsequent discussion.

Table E-5. Schedule of Activities Pertinent to Efficacy in Pivotal Studies (Protocols M/1140/0098-A and M/1140/0098-B)

Activity	Pretreatment	Second Visit (Day 7-10)	Third Visit (Day 12-15)	Final Visit (Day 25-38)
Informed Consent	X			
Medical History	X			
Physical Examination	X			
Pneumatic Otoscopy	X	X	X	X
Microbiology Culture & Sensitivity Testing	X	X†	X†	X†
Clinical Observations	X	X	X	X
Record Concomitant Therapy	X	X	X	X
Drug Compliance			X	

† If clinically indicated because of failure to respond.

Medical Officer's Note: Ideally, a tympanogram should have been performed to correlate with the clinical and bacteriologic findings.

Identification of Primary and Secondary Efficacy Measures

Four primary efficacy measures were selected by the Sponsor for Protocols 0098-A and 0098-B: percentage of patients with clinical success at an end of therapy evaluation and at a "Test of Cure" visit and percentage of patients with bacteriologic cure at End of Therapy and "Test of Cure" evaluations. The primary efficacy endpoints defined in the pivotal protocols were clinical success and bacteriologic cure at the End of Therapy, which was defined by the protocol as 2 to 5 days posttreatment. This evaluation window corresponded to Visit 2 for the cefpodoxime-treated patients and Visit 3 for the cefixime-treated patients. In an attempt to comply with current proposed guidelines for a 1-2 week follow-up analysis, a "Test of Cure" analysis was undertaken. The "Test of Cure" window was retrospectively defined as 4 to 21 days posttreatment, inclusive. A conservative approach was taken for patients with more than one follow-up visit in the 4-21 day window; ie, the worse (or worst) response was used as the "Test of Cure" response.

The secondary efficacy measures were (1) percentages of clinical success or bacteriologic cure at Visit 2, Visit 3, and Final Visit and (2) change in temperature from Pretreatment values.

Medical Officer's Note: The primary efficacy endpoint that will be used is the microbiological endpoint measured at the "test of cure visit". During a teleconference on 1/29/98 (NDA 50-

675/SNC 104) a frequency distribution of the patients visit date after end of therapy was requested at was to include means and standard deviations. This information was provided on 3/20/98(NDA 50-675/SE2-014). Please refer to this amendment for detailed information. In summary, the pooled data for Study A and B showed the following μ +/-σ respectively for Cefpodoxime and Cefixime as number of days post treatment:

- Cefpodoxime 8.7 d+/-3.3
- Cefixime 9.1 d+/-5.6.

The frequency distribution was acceptable. Therefore "the test-of-cure" window as defined above by the sponsor will be accepted.

Study Population: Inclusion/Exclusion Criteria

Patients accepted for participation in the study were required to satisfy the following criteria:

- Age 2 months through 12 years;
- Signs and symptoms of acute suppurative, unilateral or bilateral otitis media (duration of current infection ≤7 days) as demonstrated by fever, earache, and/or irritability; and evidence of abnormal discoloration of tympanic membrane or perforation with purulent drainage less than 24 hours in duration; middle ear effusion documented by pneumatic otoscopy;
- Positive bacteriologic culture from fluid obtained at tympanocentesis; and
- Signed written informed consent from parent or guardian.

Patients who met any of the following criteria were excluded from enrolling in the study:

- Menstruating females who were not on acceptable birth control methods (eg, birth control pills, condom, abstinence)
- Hypersensitivity to cephalosporins or penicillin
- Antibiotic treatment within the previous 5 days (including topical antimicrobial therapy for otitis externa)
- Significant renal, hepatic, or hematologic disease
- Immunologic or neoplastic disease, or immunosuppressive therapy
- Tympanostomy tubes, cholesteatoma or retraction pockets
- Known pre-existing sensorineural hearing loss
- Spontaneous perforation of the tympanic membrane(s) >24 hours prior to study entry
- Patients in whom tympanocentesis and pneumatic otoscopy were not possible (unless perforation of tympanic membranes occurred ≤24 hours prior to study entry)
- Patients currently enrolled in any other investigational treatment protocol or who were previously enrolled in this study

Medical Officer's Note: I concur with the Applicant's inclusion and exclusion criteria with the following additional exclusions:

- *patients with chronic otitis media ; and*
- *patients with recurrent otitis media which is defined as in infants< 1 year, 3>= episodes, and in children >1y , >=4 episodes/year over a two year period.*

These two exclusions will be placed into a subgroup analysis as this patient cohort is different from e usual group of patients with AOM.

The following patients were to be withdrawn from the study and listed as nonevaluable for efficacy:

- Those found to have a pathogen resistant to either of the drugs being used
- Those in whom no pathogenic organism (as evaluated by the investigator) was found on culture
- Those who received concomitant antimicrobial drug therapy, including topical antimicrobial therapy of otitis externa (unless this therapy was given to patients who failed on protocol therapy)
- Those in whom adequate follow-up was not possible
- Those who received less than 80% of the prescribed therapy (except failures) or missed two or more consecutive doses of study medication

Medical Officer's Note: Follow-up data was included on these patients and they wee included in the ITT analysis as failures.

Evaluations

Patients underwent the following pretreatment examinations and tests during the study to ensure study eligibility. Some of the procedures were repeated at subsequent visits.

- Medical History and Physical Examination
- Pneumatic Otoscopy
- Microbiological Culture and Sensitivity Testing

  Tympanocentesis was performed to obtain fluid from the affected middle ear(s) for microbiological culture by a certified microbiology laboratory. If perforation had occurred (≤24 hours), the pus from the external ear was cultured instead of performing tympanocentesis. This procedure was to be repeated at subsequent visits if considered necessary because of failure to respond.

  Identification of pathogen - Specimens from the external ear canal swab and middle ear fluid were cultured aerobically. The pathogens isolated were identified and the beta-lactamase activity of each pathogen was determined. Cultures that yielded the same organism (other than *S pneumoniae, H influenzae*, and/or *M catarrhalis*) from both the external ear canal and the middle ear effusion were classified as "no growth" due to the presumption that the middle ear effusion specimen was contaminated with organisms from the external ear canal. If the tympanic membrane was spontaneously perforated, a culture was to be taken only from the external ear canal.

  Susceptibility testing - Susceptibility to cefpodoxime and cefixime was determined for all pathogens isolated. Patients found to have a pathogen resistant to either antibiotic were to be withdrawn from the study. Patients discovered to have cefpodoxime- or cefixime-resistant pathogens in the middle ear effusion, at the discretion of the investigator, could be allowed to continue taking the study medication if they were showing improvement. *Medical Officer's Note: Susceptibility testing was not made available, only organism identification was made available.*

- Clinical Observations

Efficacy Evaluation Methods

e evaluations of efficacy included both clinical and bacteriologic responses at Days 7-10 (Visit 12-15 (Visit 3), 25-38 (Final Visit), and at a "Test of Cure Visit" at 4-21 days posttherapy.

Clinical Response

Progress of Infection. The progress of infection for each ear was determined by evaluating the degree of change from the previous visit. This evaluation was based only on clinical signs and symptoms and was independent of any bacteriologic culture that may have been obtained. Patients were evaluated by ear at each follow-up visit and categorized as follows:

- Clinical cure - Complete disappearance of signs and symptoms of acute otitis media: earache, fever, irritability, tympanic membrane erythema. Middle ear effusion may or may not be present.
- Clinical improvement - Clinical signs and symptoms subsided significantly compared to the previous visit, but with incomplete resolution of symptoms and signs
- Unchanged - Signs and symptoms unchanged from previous visit
- Worsened - Signs and symptoms worsened from previous visit
- Recurrence/Reinfection - Clinical evidence of infection present at Final Visit after patient had been considered clinically cured at End of Therapy evaluation

Overall Clinical Evaluation. The overall clinical evaluation was independent of any bacteriologic luation. The investigators were instructed to record the progress of infection (since the last visit) ividually.

Overall Bacteriologic Evaluation. An overall bacteriologic evaluation was obtained for each patient at each post-Pretreatment visit. If tympanocentesis was done at any of these visits and any one of the patient's pretreatment pathogens was isolated, then the overall bacteriologic response was "Bacteriologic Failure." Conversely, if none of the pretreatment pathogens was isolated from the post-Pretreatment tympanocentesis, then the patient was considered a "Bacteriologic Cure." If a pathogen was isolated at a later visit that was not present at Pretreatment, the patient was classified as having a "Superinfection" for that visit. Patients who had no pretreatment pathogen isolated were considered "Not Assessable." When tympanocentesis was not done at a post-Pretreatment visit, the overall bacteriologic response was presumed based on the overall clinical response (See Table E-6). ***Medical Officer's Note: It does not appear that the treatment failures underwent tympanocentesis, although this is strongly recommended in the FDA's "Points to Consider"***

Table E-6. Determination of Overall Bacteriologic Response in Patients w/o Tympanocentesis (Protocols M/1140/0098-A and M/1140/0098-B)

Overall Clinical Response	Overall Bacteriologic Response
Cured	Presumptive Cure
Improved	Presumptive Cure
Unchanged	Presumptive Failure
Worsened	Presumptive Failure
Recurrence (Final Visit only)	Presumptive Recurrence
Side Effect Failure	Side Effect Failure
Noninvestigational Antibiotic	Noninvestigational Antibiotic

Not Reported	Not Reported

Medical Officer's Note: The overall bacteriologic evaluation is also referred to as "outcome by infection".

By-Pathogen Bacteriologic Evaluation. The by-pathogen bacteriologic evaluations were obtained using information from both ears. If tympanocentesis was not done at a post-Pretreatment visit for patients who had one or more pretreatment pathogens isolated, the by-pathogen bacteriologic response was obtained using the patient's clinical response as indicated below in Table E-7.

Medical Officer's Note: If a patient does not have any of the four major pathogens isolated at baseline, the patient is considered non-evaluable.

Table E-7. Determination of By-Pathogen Bacteriologic Response in Patients w/o Subsequent Tympanocentesis (Protocols M/1140/0098-A and M/1140/0098-B)

Overall Clinical Response	Pathogen Response
Cure	Eradicated
Improved	Eradicated
Unchanged	Persistence
Worse	Persistence
Side Effect Failure	Persistence
Noninvestigational Antibiotic	Persistence
Recurrence (FINAL VISIT only)	Recurrence
Not Reported	Not Reported

Collapsed Efficacy Classifications:

For all possible overall bacteriologic and clinical evaluations for each follow-up study visit,for analysis purposes, each patient's response was collapsed into one of two categories – cure/success or failure .

Primary Efficacy & Secondary Efficacy Measures

Medical Officer's Note: The primary efficacy parameters used in the evaluable population analysis are "outcome by infection" at the "TOC" window. The secondary efficacy parameters used in the evaluable population analysis are"outcome by pathogen" and clinical outcomes at the "TOC" window.

2) Efficacy Results And Discussion: Pivotal Studies

The efficacy results and discussion presented in this section pertain to the integrated data from the two pivotal studies (Protocols 0098-A and 0098-B). With the exception of patient disposition (ie, reasons given for discontinuation of therapy and reasons given for nonevaluability), the results shown in this section include those patients who met all protocol entry (inclusion/exclusion) criteria and other criteria for evaluability.

Medical Officer's Note: The combined results are reported since the studies were comparable with respect to inclusion/exclusion criteria, endpoints measured and methods pertaining to study design. Individual study results were consistent with the combined results.

Patient Population

Disposition of Patients

Discontinuation of Therapy

Table E-10 summarizes the reasons given by the investigators for patients discontinuing participation in the combined studies. The most frequent reasons given for early discontinuation – ineligibility for the study followed by lack of efficacy – were comparable in both treatment groups.

Table E-10.-Summary of Investigator's Assessment of Primary Reasons for Patient Discontinuation from the Study (All Patients)[a] (Protocols 0098-A & 0098-B)

Reasons for Discontinuation		Cefpodoxime N=451	Cefixime N=488
Completed Planned Study		195 (41%)	204 (42%)
Early Termination of Treatment		286 (59%)	284 (58%)
Reasons for Early Termination	Ineligible for Protocol	191 (40%)	193 (40%)
	Lack of Efficacy	50 (10%)	48 (10%)
	Noncompliance with Dosage Regimen	17 (4%)	13 (3%)
	Noncompliance with Protocol	–	1 (<1%)
	Lost to Follow-up	17 (4%)	14 (3%)
	Medical Event (Nonserious)	11 (2%)	13 (3%)
	Medical Event (Serious)	–	1 (<1%)
	Personal Request	–	1 (<1%)

Medical Officer's Note: All not evaluable patients were considered failures in the ITT analysis

Evaluability Status

Table E-11 shows the number and percentage of patients who were considered by the investigator to be evaluable or nonevaluable for the efficacy analyses. The primary reasons for nonevaluability in each treatment group were no isolated pathogen or resistant pathogens at pretreatment.

Table E-11. Summary of Investigator's Assessment of Patient Evaluability Status (All Patients) (Protocols 0098-A & 0098-B)

Status		CFD N=451	CFX N=488
Evaluable		260 (54%)	272 (56%)
Not Evaluable		221 (46%)	216 (44%)
Reasons for Nonevaluability	No Pathogen Isolated at Pretreatment	152 (32%)	152 (31%)
	Resistant Pathogen at Pretreatment	33 (7%)	41 (8%)
	Failure to Follow Protocol	13 (3%)	8 (2%)
	Lost to Follow-Up	10 (2%)	6 (1%)
	Failure to Meet Entry Criteria	3 (1%)	3 (1%)
	Received Additional Antibiotic Therapy	6 (1%)	2 (<1%)
	Noncompliance with the Dosage Regimen	4 (1%)	2 (<1%)
	Missed Two Follow-up Visits	–	1 (<1%)
	Other (Patient's mother declined participation in study)	–	1 (<1%)

CFD = cefpodoxime proxetil
CFX = cefixime

Subgroup analysis populations:

The following patients in Study A with recurrent otitis media, "frequent" otitis media and chronic otitis media were placed into a subgroup analysis:

3183-495	15862-1261
15862-1269	15862-1287
14421-252	14421-254
14521-295	14521-296
15421-789	14521-791
14521-815	14521-1431
14521-1436	12182-74
12182-74	12182-78
12182-366	12182-383
12182-385	14531-404
3183-496	15862-1263
15862-1268	15862-1283
15862-1285	14421-880
14521-315	14521-810
14521-1433	14521-1445
11701-538	
12182-51	12182-71
12182-400	12182-549

The only patient change made in study A, based on the case definition of AOM was the following patient:

14521-315

The following patients in Study B with recurrent otitis media, "frequent" otitis media and chronic otitis media were placed into a subgroup analysis:

13762-1145	13033-121
12228-223	12270-3
12270-8	12270-9
12270-10	12270-14
12270-21	12270-30
12270-31	12270-321
12270-332	12270-342
12270-356	12270-667
12270-673	14757-621
15390-1032	15390-1042
15390-1049	13033-141
12228-212	12228-221
15134-744	12270-6
12270-11	12270-345
12270-353	12270-358
12270-359	12270-661
12270-663	12270-669
15390-1039	15390-1046
15390-1050	

There were no patient changes made in study B, based on the case definition of AOM.

Medical Officer's Note: Analysis was done of the patients in the Subgroup, and this was compared to the patients in the Applicant's evaluable population. Both in demographics and in

efficacy, there were no demonstrable differences either at TOC or LTFU. Additionally, given the strenghth of the sponsor's inclusion criteria and that only one patient change was made, the Applicant's evaluable population was accepted. What follows are ITT, Evaluable and Subgroup analysis of demographics and efficacy.

B. Demographics At Pretreatment

Medical Officer's Note: Table E-12 summarizes the pretreatment demographic characteristics for evaluable patients in the two studies. The treatment groups were comparable in age, sex and race distribution, and weight before treatment.

Table E-12. Summary of Demographic Characteristics of Evaluable Patients (Protocols 0098-A & 0098-B)

Variable	CFD N=260	CFX N=272
Age (y):		
Mean	3.3	3.1
Median	2.6	2.1
Range	0.4-12.1	0.2-12.9
Sex:		
Male	144 (55%)	156 (57%)
Female	116 (45%)	116 (43%)
Race (No. & %):		
White	176 (68%)	186 (68%)
Black	26 (10%)	23 (8%)
Oriental/Asian	2 (1%)	2 (1%)
Hispanic	53 (20%)	58 (21%)
Other	3 (1%)*	3 (1%)†
Weight (kg):		
Mean	15.5§	15.2
Median	13.6§	13.6
Range	5.9-57.0§	5.0-120.1

* Other = 1 each Biracial, Arabic, and Pakistani
† Other = Black/White (2) and White/Oriental (1)
§ N=259
Reference: ISE Appendix Table 2.1

Medical Officer's Note: There were no notable treatment differences with respect to the percentage of subjects included in each analysis group in Study A. Demographic data for the intent-to-treat, the evaluable, and the Medical Officer sub-population showed no statistically significant differences in these pretreatment characteristics of the two treatment groups.Please refer to the Statistical review for all tables. The one shown below are all subjects for protocol A:

TABLE 1: STUDY 0098A: SUBJECTS POPULATIONS		
Treatment Group for Clinical Response	Subjects Included	
	Cefpodoxime (N=225)	Cefixime (N=230)
Intent-to-Treat	225 (100%)	230 (100%)
Evaluable	124 (55.1%)	132 (57.4%)

MO Sub-Population	125 (55.6%)	128 (55.7%)

TABLE 2.5: STUDY PRT-0098A: SUMMARY OF DEMOGRAPHIC DATA FOR THE MO SUB-POPULATION SUBJECTS

Number of Subjects	Cefpodoxime (N=125)	Cefixime (N=128)	P-value
Age (yrs.)	3.1 ± 2.3	2.9 ± 2.4	*0.542
< 2 yrs.	54 (43.2%)	64 (50.0%)	0.314
≥ 2 yrs.	71 (56.8%)	64 (50.0%)	
Gender			
Male	64 (51.2%)	69 (53.9%)	0.706
Female	61 (48.8%)	59 (46.1%)	
Race			
White	70 (56.0%)	71 (55.5%)	0.413
Black	10 (8.0%)	10 (7.8%)	
Hispanic	40 (32.0%)	46 (35.9%)	
Other	5 (4.0%)	1 (0.8%)	

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

TABLE 2: STUDY PRT-0098A: SUMMARY OF PNEUMATIC OTOSCOPY AND/OR TYMPANOMETRY DATA AT PRETREATMENT FOR THE ITT SUBJECTS

Number of Subjects	Cefpodoxime (N=225)	Cefixime (N=230)	P-value
Tympanic Membrane abnormal	225 (100%)	230 (100%)	NA
Hyperemic			
yes	217 (96.4%)	216 (93.9%)	0.275
Opaque			
yes	221 (98.2%)	225 (97.8%)	1.000
Bulging			
yes	191 (84.9%)	197 (85.7%)	0.895
Light Reflex Absent			
yes	224 (99.6%)	226 (98.3%)	0.372
Impaired Mobility			
yes	224 (99.6%)	227 (98.7%)	0.623
Perforation			
yes	45 (20.0%)	55 (23.9%)	0.365

TABLE 3: STUDY PRT-0098A: SUMMARY OF PNEUMATIC OTOSCOPY AND/OR TYMPANOMETRY DATA AT PRETREATMENT FOR THE EVALUABLE SUBJECTS			
Number of Subjects	Cefpodoxime (N=124)	Cefixime (N=132)	P-value
Tympanic Membrane abnormal	124 (100%)	132 (100%)	NA
Hyperemic yes	117 (94.4%)	122 (92.4%)	0.620
Opaque yes	123 (99.2%)	130 (98.5%)	1.000
Bulging yes	105 (84.7%)	116 (87.9%)	0.473
Light Reflex Absent yes	124 (100%)	131 (99.2%)	1.000
Impaired Mobility yes	124 (100%)	131 (99.2%)	1.000
Perforation yes	22 (17.7%)	27 (20.5%)	0.635

TABLE 2.6: STUDY PRT-0098A: SUMMARY OF PNEUMATIC OTOSCOPY AND/OR TYMPANOMETRY DATA AT PRETREATMENT FOR THE MO SUB-POPULATION SUBJECTS			
Number of Subjects	Cefpodoxime (N=125)	Cefixime (N=128)	P-value
Tympanic Membrane abnormal	118 (94.4%)	124 (96.9%)	0.372
Hyperemic yes	112 (89.6%)	114 (89.1%)	1.000
Opaque yes	117 (93.6%)	123 (96.1%)	0.407
Bulging yes	99 (79.2%)	111 (86.7%)	0.133
Light Reflex Absent yes	118 (94.4%)	124 (96.9%)	0.372
Impaired Mobility yes	118 (94.4%)	124 (96.9%)	0.372
Perforation yes	21 (16.8%)	25 (19.5%)	0.627

There were no notable treatment differences with respect to the percentage of subjects included in each analysis group. Demographic data for the intent-to-treat, the evaluable, and the Medical Officer sub-population subjects show no statistically significant differences in these pretreatment characteristics of the two treatment groups. A summary of the MO sub-population is shown below:

TABLE 4: STUDY 0098B: SUBJECTS POPULATIONS		
Treatment Group for Clinical Response	Subjects Included	
	Cefpodoxime (N=256)	Cefixime (N=258)
Intent-to-Treat	256 (100%)	258 (100%)
Applicant Evaluable	136 (53.1%)	140 (54.3%)
MO Evaluable	126 (49.2%)	130 (50.4%)

TABLE 5: STUDY 0098B: SUMMARY OF DEMOGRAPHIC DATA FOR THE ITT SUBJECTS

Number of Subjects	Cefpodoxime (N=256)	Cefixime (N=258)	P-value
Age (yrs.)	3.5 ± 3.1	3.3 ± 2.6	*0.353
< 2 yrs.	107 (41.8%)	104 (40.3%)	0.788
≥ 2 yrs.	149 (58.2%)	154 (59.7%)	
Gender			
Male	136 (53.1%)	148 (57.4%)	0.375
Female	120 (46.9%)	110 (42.6%)	
Race			
White	188 (73.4%)	192 (74.4%)	0.374
Black	41 (16.0%)	42 (16.3%)	
Hispanic	25 (9.8%)	18 (7.0%)	
Other	2 (0.8%)	6 (2.3%)	

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

TABLE 6: STUDY 0098B: SUMMARY OF DEMOGRAPHIC DATA FOR THE EVALUABLE SUBJECTS

Number of Subjects	Cefpodoxime (N=136)	Cefixime (N=140)	P-value
Age (yrs.)	3.4 ± 2.9	3.4 ± 2.7	*0.816
< 2 yrs.	57 (41.9%)	58 (41.4%)	1.000
≥ 2 yrs.	79 (58.1%)	82 (58.6%)	
Gender			
Male	80 (58.8%)	84 (60.0%)	0.903
Female	56 (41.2%)	56 (40.0%)	
Race			
White	110 (80.9%)	114 (81.4%)	0.262
Black	16 (11.8%)	14 (10.0%)	
Hispanic	10 (7.4%)	8 (5.7%)	
Other	0 (0%)	4 (2.9%)	

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

TABLE 3.4: STUDY 0098B: SUMMARY OF DEMOGRAPHIC DATA FOR THE MO SUB-POPULATION

Number of Subjects	Cefpodoxime (N=126)	Cefiximef (N=130)	P-value
Age (yrs.)	3.4 ± 2.9	3.2 ± 2.7	*0.763
< 2 yrs.	54 (42.9%)	56 (43.1%)	1.000
≥ 2 yrs.	72 (57.1%)	74 (56.9%)	
Gender			
Male	74 (58.7%)	78 (60.0%)	0.899
Female	52 (41.3%)	52 (40.0%)	
Race			
White	100 (79.4%)	105 (80.8%)	0.391
Black	15 (11.9%)	14 (10.8%)	
Hispanic	11 (8.7%)	8 (6.2%)	
Other	0 (0%)	3 (2.3%)	

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

TABLE 3.5: STUDY PRT-0098B: SUMMARY OF PNEUMATIC OTOSCOPY AND/OR TYMPANOMETRY DATA AT PRETREATMENT FOR THE MO SUB-POPULATION

Number of Subjects	Cefpodoxime (N=126)	Cefixime (N=130)	P-value
Tympanic Membrane abnormal	125 (99.2%)	128 (98.5%)	1.000
Hyperemic yes	115 (91.3%)	115 (88.5%)	0.537
Opaque yes	113 (89.7%)	118 (90.8%)	0.835
Bulging yes	111 (88.1%)	117 (90.0%)	0.691
Light Reflex Absent yes	118 (93.7%)	123 (94.6%)	0.795
Impaired Mobility yes	116 (92.1%)	123 (94.6%)	0.460
Perforation yes	20 (15.9%)	16 (12.3%)	0.474

TABLE 7: STUDY PRT-0098B: SUMMARY OF PNEUMATIC OTOSCOPY AND/OR TYMPANOMETRY DATA AT PRETREATMENT FOR THE ITT SUBJECTS			
Number of Subjects	Cefpodoxime (N=256)	Cefixime (N=258)	P-value
Tympanic Membrane abnormal	256 (100%)	256 (99.2%)	0.499
Hyperemic yes	235 (91.8%)	231 (89.5%)	0.449
Opaque yes	232 (90.6%)	227 (88.0%)	0.392
Bulging yes	223 (87.1%)	218 (84.5%)	0.449
Light Reflex Absent yes	244 (95.3%)	243 (94.2%)	0.693
Impaired Mobility yes	245 (95.7%)	243 (94.2%)	0.547
Perforation yes	48 (18.8%)	47 (18.2%)	0.910

TABLE 8: STUDY PRT-0098B: SUMMARY OF PNEUMATIC OTOSCOPY AND/OR TYMPANOMETRY DATA AT PRETREATMENT FOR THE EVALUABLE SUBJECTS			
Number of Subjects	Cefpodoxime (N=136)	Cefixime (N=140)	P-value
Tympanic Membrane abnormal	136 (100%)	138 (98.6%)	0.498
Hyperemic yes	125 (91.9%)	123 (87.9%)	0.321
Opaque yes	124 (91.2%)	128 (91.4%)	1.000
Bulging yes	122 (89.7%)	126 (90.0%)	1.000
Light Reflex Absent yes	128 (94.1%)	133 (95.0%)	0.796
Impaired Mobility yes	127 (93.3%)	133 (95.0%)	0.614
Perforation yes	21 (15.4%)	19 (13.6%)	0.733

C. Efficacy Results (Pivotal Studies)

Medical Officer's Note: *All efficacy analyses were conducted for the Intent-to-treat, the evaluable, and the Medical Officer sub-population subjects, and the evaluable was considered primary for the analysis of efficacy data.*

The efficacy analysis was the comparison of the treatment groups with respect to the bacteriologic cure rate at Test of Cure in the Medical Officer evaluable population for the purpose establishing the equivalence of the two treatments. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the

atment groups were considered equally effective is judged by the draft DAIDP "Points to nsider" document pertaining to results of confidence intervals.

The additional efficacy measures included overall bacteriologic evaluations, by pathogen bacteriologic evaluations, and overall clinical evaluations at End of Therapy, Visit 2, Visit 3, and Final Visit, which were analyzed using the same methods as were used to evaluate the primary efficacy measures.

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

Current FDA draft guidelines (17 February 1997) for evaluating antimicrobial agents for the treatment of acute otitis media indicate that a posttherapy (ie, "Test of Cure") visit should be made approximately 1-2 weeks after completion of therapy. The purpose of this visit is to evaluate the patients for all presenting signs and symptoms of acute otitis media and to document the emergence of any new signs and symptoms. Since these protocols did not have a visit scheduled specifically for 1-2 weeks posttherapy, data were summarized for all evaluable patients who had a clinic visit at any time during a 4-21 day posttherapy window. In cases where a patient had two or more visits within this window, the visit included in the summary is the one with the worst outcome. All of the patients considered evaluable for some of the other efficacy analyses did not have data available for the "Test of Cure" evaluation. Consequently, all failures that occurred prior to this window were carried forward; the outcomes of cured or improved, however, had to be assessed within the ndow.

"Test of Cure" Overall Bacteriologic Evaluation

Table E-19 summarizes the results of the "Test of Cure" overall bacteriologic evaluation. The overall bacteriologic cure rates (which comprise both culture-proven bacteriologic cures and presumptive bacteriologic cures) for cefpodoxime (67%) and cefixime (64%) were not significantly different; ie, the 95% CI for difference in cure rates is -5.49% to 11.74%.

Table E-19. Summary of "Test of Cure" Overall Bacteriologic Evaluation* at 4-21 Days Posttherapy (Protocols 009E-A & 009E-B)

Evaluation	Results	Cefpodoxime N=254†	Cefixime N=257†
Cure	Bacteriologic Cure	–	–
	Presumptive Cure	171 (67%)	165 (64%)
	Total Cures	171 (67%)	165 (64%)
Failure	Bacteriologic Failure	3 (1%)	11 (4%)
	Presumptive Failure	67 (26%)	59 (23%)
	Superinfection	6 (2%)	5 (2%)
	Side Effect Failure	5 (2%)	6 (2%)
	Antibiotic Noninvestigational Medication	2 (1%)	11 (4%)
	Total Failures	83 (33%)	92 (36%)

* Because of rounding, percentages may not total 100

† N= 254 and 257 in the cefpodoxime and cefixime treatment groups, respectively, because 21 patients considered evaluable for efficacy (6 in the cefpodoxime group and 15 in the cefixime group) had no data available in the 4-21 day window.

† *Medical Officer's Note: These patients were considered failures in the ITT analysis.*

Reference: ISE Appendix Tables 4.9-4.10

Medical Officer's Note:

- *The subjects who were presumptive failures were those who were clinical failures.They did not show clinical response.*
  The overall bacteriologic responses at Test of Cure as per the intent-to-treat, the evaluable, and the Medical Officer sub-population are presented in Tables 2.6, 2.7, and 2.8, respectively for Study A. Comparisons (95% confidence intervals) of the difference between the two treatment groups show that cefpodoxime was therapeutically equivalent to cefixime with respect to overall bacteriologic outcomes.

- *Subset analyses by gender, age, and race for the overall bacteriologic cure rates in the Medical Officer evaluable subjects are shown in Table 2.9. Results are consistent across all three demographic aspects.*

TABLE 2.6: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE ITT SUBJECTS AT TEST OF CURE		
Bacteriological Response	Cefpodoxime (N=225)	Cefixime (N=230)
Cure Failure	89 (39.6%) 136 (60.4%)	80 (34.8%) 150 (65.2%)
Cefpodoxime vs Cefixime by Cure	4.8%, 95% C.I.: -4.5%, 14.1%	

dical Officer's Note: The primary reason patients were considered failures in the ITT analysis s no pathogen at baseline.

TABLE 2.7: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE EVALUABLE SUBJECTS AT TEST OF CURE		
Bacteriological Response	Cefpodoxime (N=124)	Cefixime (N=132)
Cure Failure	77 (62.1%) 47 (37.9%)	75 (56.8%) 57 (43.2%)
Cefpodoxime vs Cefiximeby Cure	5.3%, 95% C.I.: -7.5%, 18.1%	

Medical Officer's Note: The patients who were were failures at test- of- cure were true clinical failures.

TABLE 2.8: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUBPOPULATION AT TEST OF CURE		
Bacteriological Response	Cefpodoxime (N=125)	Cefixime (N=128)
Cure Failure	75 (60.0%) 50 (40.0%)	72 (56.3%) 56 (43.7%)
Cefpodoxime vs Cefixime by Cure	3.8%, 95% C.I.: -9.2%, 16.7%	

TABLE 2.9: STUDY 0098A: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL BACTERIOLOGICAL CURE RATES OF THE MO SUB-POPULATION				
Subset	Cefpodoxime (N=125)	Cefixime (N=128)	95% C.I.	P-value Breslow-Day's
Male	38/64 (59.4%)	42/69 (60.9%)	(-19.7%, 16.7%)	0.367
Female	37/61 (60.7%)	30/59 (50.8%)	(-9.6%, 29.2%)	
< 2 yrs.	25/54 (46.3%)	30/64 (46.9%)	(-20.4%, 19.2%)	0.641
≥ 2 yrs.	50/71 (70.4%)	42/64 (65.6%)	(-12.4%, 22.0%)	
White	41/70 (58.6%)	41/71 (57.7%)	(-16.9%, 18.5%)	0.501
Black	8/10 (80.0%)	5/10 (50.0%)	NA	
Hispanic	23/40 (57.5%)	25/46 (54.3%)	(-20.2%, 26.5%)	
Other	3/5 (60.0%)	1/1 (100%)	NA	

: The overall bacteriologic responses at Test of Cure as per the intent-to-treat, the evaluable, and the Medical Officer sub-populations are presented in Tables 3.5, 3.6, and 3.7, respectively for Study B. Comparisons (95% confidence intervals) of the difference between the two treatment groups show that cefpodoxime was therapeutically equivalent to cefixime with respect to overall bacteriologic outcomes.

Subset analyses by gender, age, and race for the overall bacteriologic cure rates in the Medical Officer's subpopulation are shown in Table 3.8. Significant heterogeneity of treatment effects was detected among the race subgroup, and the treatment effect favored cefpodoxime in Black and Hispanic subjects. Results are consistent across gender and age subgroups.

TABLE 3.5: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE ITT SUBJECTS AT TEST OF CURE		
Bacteriological Response	Cefpodoxime (N=256)	Cefixime (N=258)
Cure	109 (42.6%)	101 (39.2%)
Failure	147 (57.4%)	157 (60.8%)
Cefpodoxime vs Cefixime by Cure	3.4%, 95% C.I.: -5.5%, 12.3%	

TABLE 3.6: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE EVALUABLE SUBJECTS AT TEST OF CURE		
Bacteriological Response	Cefpodoxime (N=136)	Cefixime (N=140)
Cure	94 (69.1%)	90 (64.3%)
Failure	42 (30.9%)	50 (35.7%)
Cefpodoxime vs Cefixime by Cure	4.8%, 95% C.I.: -7.0%, 16.7%	

TABLE 3.7: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT TEST OF CURE

Bacteriological Response	Cefpodoxime (N=126)	Cefixime (N=130)
Cure	89 (70.6%)	85 (65.4%)
Failure	37 (29.4%)	45 (34.6%)
Cefpodoxime vs Cefixime by Cure	5.3%, 95% C.I.: -6.9%, 17.4%	

TABLE 3.8: STUDY 0098B: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL BACTERIOLOGICAL CURE RATES OF THE MO SUB-POPULATION

Subset	Cefpodoxime (N=126)	Cefiximef (N=130)	95% C.I.	P-value Breslow-Day's
Male	56/74 (75.7%)	53/78 (67.9%)	(-7.8%, 23.3%)	0.580
Female	33/52 (63.5%)	32/52 (61.5%)	(-18.6%, 22.5%)	
< 2 yrs.	35/54 (64.8%)	32/56 (57.1%)	(-12.3%, 27.7%)	0.782
≥ 2 yrs.	54/72 (75.0%)	53/74 (71.6%)	(-12.3%, 19.1%)	
White	68/100 (68.0%)	72/105 (68.6%)	(-14.3%, 13.1%)	0.088
Black	11/15 (73.3%)	7/14 (50.0%)	(-18.0%, 64.7%)	
Hispanic	10/11 (90.9%)	4/8 (50.0%)	(-8.5%, 90.3%)	
Other	0/0 (NA)	2/3 (66.7%)	NA	

Additional Efficacy Results (Pivotal Studies)

"Test of Cure" By-Pathogen Bacteriologic Evaluation

ISE Appendix Table 4.11 lists the "Test of Cure" by-pathogen eradication rates of all the pathogens isolated at Pretreatment. Table E-20 summarizes the eradication rates for *H influenzae, M catarrhalis, S pneumoniae,* and *S pyogenes* isolates. Cefpodoxime had higher eradication rates than did cefixime for *S pneumoniae* (72% versus 58%) and *S pyogenes* (80% versus 57%), comparable rates for *H influenzae* (66% and 75%, respectively) and *M catarrhalis* (56% in both treatment groups).

The pathogen eradication rates for the most common isolated baseline pathogens at Test of Cure are summarized for, the Applicant evaluable, below for Study A and B:

Table E-20. Summary of "Test of Cure" Eradication Rates (by Pathogen) at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)

Pathogen	Cefpodoxime		Cefixime	
	n/N	%	n/N	%
Haemophilus influenzae	1/1	100	6/9	67
Haemophilus influenzae (β-lactamase negative)	27/41	66	30/37	81
Haemophilus influenzae (β-lactamase positive)	22/34	65	25/35	71
Moraxella catarrhalis	2/4	50	4/7	57
Moraxella catarrhalis (β-lactamase negative)	¾	75	2/3	67
Moraxella catarrhalis (β-lactamase positive)	17/31	55	17/31	55
Streptococcus pneumoniae	88/122	72	72/124	58
Streptococcus pyogenes	20/25	80	13/23	57

n No. patients with pathogen eradicated

N No. of patients with assessable pathogen response at Pretreatment

Reference: ISE Appendix Table 4.11

dical Officer's Note: The pathogen eradication rates for the most common isolated baseline ogens at Test of Cure are summarized for the intent-to-treat, the evaluable, and the Medical Officer sub-population in Table 2.10, 2.11, and 2.12, &Table 2.10A, 2.11A, and 2.12A, respectively for Study A.

TABLE 2.10: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	30/50 (60.0%)	34/46 (73.9%)	-13.9%, 95% C.I.: -34.6%, 6.8%
M. catarrhalis	11/20 (55.0%)	13/28 (46.4%)	8.6%, 95% C.I.: -24.3%, 41.4%
S. pneumoniae	42/64 (65.6%)	31/63 (49.2%)	16.4%, 95% C.I.: -2.1%, 35.0%
S. pyogenes	10/12 (83.3%)	7/13 (53.8%)	29.5%, 95% C.I.: -12.9%, 71.8%

TABLE 2.11: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	30/44 (68.2%)	33/45 (73.3%)	-5.2%, 95% C.I.: -26.3%, 16.0%
M. catarrhalis	11/19 (57.9%)	12/25 (48.0%)	9.9%, 95% C.I.: -24.3%, 44.1%
S. pneumoniae	35/54 (64.8%)	29/57 (50.9%)	13.9%, 95% C.I.: -6.0%, 33.9%
S. pyogenes	9/11 (81.2%)	6/12 (50.0%)	31.8%, 95% C.I.: -13.2%, 76.9%

TABLE 2.12: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	28/42 (66.7%)	31/42 (73.8%)	-7.1%, 95% C.I.: -29.0%, 14.7%
M. catarrhalis	9/17 (52.9%)	12/24 (50.0%)	2.9%, 95% C.I.: -33.1%, 39.0%
S. pneumoniae	36/55 (65.5%)	29/55 (52.7%)	12.7%, 95% C.I.: -7.3%, 32.8%
S. pyogenes	10/12 (83.3%)	5/11 (45.5%)	37.9%, 95% C.I.: -7.0%, 82.8%

TABLE 2.10A: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	0/0 (NA)	2/3 (66.7%)	NA
H. influenzae (β-l. -)	19/29 (65.5%)	19/24 (79.2%)	-13.6%, 95% C.I.: -41.2%, 13.9%
H. influenzae (β-l. +)	14/21 (66.7%)	13/19 (68.4%)	-1.8%, 95% C.I.: -35.8%, 32.3%
M. catarrhalis	0/1 (0%)	3/5 (50.0%)	NA
M. catarrhalis (β-l. -)	2/4 (50.0%)	2/3 (66.7%)	NA
M. catarrhalis (β-l. +)	9/15 (60.0%)	8/19 (42.1%)	17.9%, 95% C.I.: -21.3%, 57.1%
S. pneumoniae	42/64 (65.6%)	31/63 (49.2%)	16.4%, 95% C.I.: -2.1%, 35.0%
S. pyogenes	10/12 (83.3%)	7/13 (53.8%)	29.5%, 95% C.I.: -12.9%, 71.8%

TABLE 2.11A: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	0/0 (NA)	2/3 (66.7%)	NA
H. influenzae (β-l. -)	16/25 (64.0%)	18/23 (78.3%)	-14.3%, 95% C.I.: -43.7%, 15.2%
H. influenzae (β-l. +)	14/19 (73.7%)	13/19 (68.4%)	5.3%, 95% C.I.: -28.8%, 39.3%
M. catarrhalis	0/1 (0%)	3/5 (60.0%)	NA
M. catarrhalis (β-l. -)	2/3 (66.7%)	2/3 (66.7%)	NA
M. catarrhalis (β-l. +)	9/15 (60.0%)	7/17 (41.2%)	18.8%, 95% C.I.: -21.5%, 59.2%
S. pneumoniae	35/54 (64.8%)	29/57 (50.9%)	13.9%, 95% C.I.: -6.0%, 33.9%
S. pyogenes	9/11 (81.2%)	6/12 (50.0%)	31.8%, 95% C.I.: -13.2%, 76.9%

TABLE 2.12A: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	0/0 (NA)	2/3 (66.7%)	NA
H. influenzae (β-l. -)	16/25 (64.0%)	18/22 (81.8%)	-17.8%, 95% C.I.: -46.9%, 11.2%
H. influenzae (β-l. +)	12/17 (70.6%)	11/17 (64.7%)	5.9%, 95% C.I.: -31.4%, 43.2%
M. catarrhalis	0/1 (0%)	3/5 (60.0%)	NA
M. catarrhalis (β-l. -)	1/2 (50.0%)	2/3 (66.7%)	NA
M. catarrhalis (β-l. +)	8/14 (57.1%)	7/16 (43.8%)	13.4%, 95% C.I.: -28.8%, 55.6%
S. pneumoniae	36/55 (65.5%)	29/55 (52.7%)	12.7%, 95% C.I.: -7.3%, 32.8%
S. pyogenes	10/12 (83.3%)	5/11 (45.5%)	37.9%, 95% C.I.: -7.0%, 82.8%

Medical Officer's Note:*The pathogen eradication rates for the most common isolated baseline pathogens at Test of Cure are summarized for the intent-to-treat, the evaluable, and the Medical Officer sub-population in Tables 3.09, 3.10, and 3.11, and 3.09A, 3.10A, and 3.11A for Study B respectively.*

TABLE 3.9: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	24/38 (63.2%)	32/48 (66.7%)	-3.5%, 95% C.I.: -26.2%, 19.2%
M. catarrhalis	12/23 (52.2%)	12/17 (70.6%)	-18.4%, 95% C.I.: -53.3%, 16.5%
S. pneumoniae	59/77 (76.2%)	45/72 (62.5%)	14.1%, 95% C.I.: -1.9%, 30.1%
S. pyogenes	13/16 (81.3%)	10/15 (66.7%)	14.6%, 95% C.I.: -22.5%, 51.6%

TABLE 3.10: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	21/35 (60.0%)	28/39 (71.8%)	-11.8%, 95% C.I.: -36.0%, 12.4%
M. catarrhalis	11/22 (50.0%)	11/16 (68.8%)	-18.8%, 95% C.I.: -55.0%, 17.5%
S. pneumoniae	53/70 (75.7%)	43/70 (61.4%)	14.3%, 95% C.I.: -2.3%, 30.9%
S. pyogenes	11/14 (78.6%)	10/15 (66.7%)	11.9%, 95% C.I.: -27.1%, 50.9%

TABLE 3.11: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	20/32 (62.5%)	27/37 (73.0%)	-10.5%, 95% C.I.: -35.4%, 14.5%
M. catarrhalis	11/21 (52.4%)	11/15 (73.3%)	-21.0%, 95% C.I.: -57.6%, 15.7%
S. pneumoniae	48/63 (76.2%)	39/62 (62.9%)	13.3%, 95% C.I.: -4.3%, 30.9%
S. pyogenes	12/15 (80.0%)	10/15 (66.7%)	13.3%, 95% C.I.: -24.6%, 51.3%

TABLE 3.09A: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	2/2 (100%)	4/7 (57.1%)	NA
H. influenzae (β-l. -)	11/17 (64.7%)	13/19 (68.4%)	-3.7%, 95% C.I.: -40.2%, 32.7%
H. influenzae (β-l. +)	11/19 (57.9%)	15/22 (68.2%)	-10.3%, 95% C.I.: -44.7%, 24.1%
M. catarrhalis	2/4 (50.0%)	1/2 (50.0%)	NA
M. catarrhalis (β-l. -)	1/1 (100%)	0/0 (NA)	NA
M. catarrhalis (β-l. +)	9/18 (50.0%)	11/15 (73.3%)	-23.3%, 95% C.I.: -61.6%, 14.9%
S. pneumoniae	59/77 (76.6%)	45/72 (62.5%)	14.1%, 95% C.I.: -1.9%, 30.1%
S. pyogenes	13/16 (81.3%)	10/15 (66.7%)	14.6%, 95% C.I.: -22.5%, 51.6%

TABLE 3.10A: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	1/1 (100%)	4/6 (66.7%)	NA
H. influenzae (β-l. -)	11/17 (64.7%)	12/15 (80.0%)	-15.3%, 95% C.I.: -52.0%, 21.4%
H. influenzae (β-l. +)	9/17 (52.9%)	12/18 (66.7%)	-13.7%, 95% C.I.: -51.7%, 24.2%
M. catarrhalis	2/4 (50.0%)	1/2 (50.0%)	NA
M. catarrhalis (β-l. -)	1/1 (100%)	0/0 (NA)	NA
M. catarrhalis (β-l. +)	8/17 (47.1%)	10/14 (71.4%)	-24.4%, 95% C.I.: -64.4%, 15.7%
S. pneumoniae	53/70 (75.7%)	43/70 (61.4%)	14.3%, 95% C.I.: -2.3%, 30.9%
S. pyogenes	11/14 (78.6%)	10/15 (66.7%)	11.9%, 95% C.I.: -27.1%, 50.9%

TABLE 3.11A: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT TEST OF CURE (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)			
Pathogen	Cefpodoxime	Cefixime	Cefpodoxime vs Cefixime by Eradication
H. influenzae	1/1 (100%)	4/6 (66.7%)	NA
H. influenzae (β-l. -)	11/17 (64.7%)	12/14 (85.7%)	-21.0%, 95% C.I.: -56.7%, 14.7%
H. influenzae (β-l. +)	8/14 (57.1%)	11/17 (64.7%)	-7.6%, 95% C.I.: -48.5%, 33.4%
M. catarrhalis	2/4 (50.0%)	1/2 (50.0%)	NA
M. catarrhalis (β-l. -)	1/1 (100%)	0/0 (NA)	NA
M. catarrhalis (β-l. +)	8/16 (50.0%)	10/13 (76.9%)	-26.9%, 95% C.I.: -67.4%, 13.6%
S. pneumoniae	48/63 (76.2%)	39/62 (62.9%)	13.3%, 95% C.I.: -4.3%, 30.9%
S. pyogenes	12/15 (80.0%)	10/15 (66.7%)	13.3%, 95% C.I.: -24.6%, 51.3%

"Test of Cure" Overall Clinical Evaluation

"Test of Cure"

Table E-18 shows the results of the overall clinical evaluation at the "Test of Cure" Visit. The overall clinical success rates (cured plus improved) for the two treatment groups (67% for cefpodoxime versus 64% for cefixime) were statistically equivalent (95% CI: -5.24% to 11.98%). Medical Officer's Note: Those patients who are "improved" have been defined as clinically cured with MEE.

Table E-18. Summary of "Test of Cure" Overall Clinical Evaluation* at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)

Evaluation	Results	Cefpodoxime N=254†	Cefixime N=258†
Success	Cured	111 (44%)	125 (48%)
	Improved	60 (24%)	40 (16%)
	Total Clinical Successes	171 (67%)	165 (64%)
Failure	Failure	76 (30%)	76 (29%)
	Side Effect Failure	5 (2%)	6 (2%)
	Antibiotic Noninvestigational Medication	2 (1%)	11 (4%)
	Total Clinical Failures	83 (33%)	93 (36%)

Table E-18. Summary of "Test of Cure" Overall Clinical Evaluation* at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)

Evaluation	Results	Cefpodoxime N=254†	Cefixime N=258†

* Because of rounding, percentages may not total 100

† N= 254 and 258 in the cefpodoxime and cefixime treatment groups, respectively, because 20 patients considered evaluable for efficacy (6 in the cefpodoxime group and 14 in the cefixime group) had no data available in the 4-21 day window.

Reference: ISE Appendix Tables 4.7-4.8

Medical Officer's Note: The 95% confidence intervals for the difference in success rates of the overall clinical responses at Test of Cure between cefpodoxime and cefixime groups indicate the therapeutic equivalence of the two treatment groups as per the intent-to-treat, the Applicant evaluable, and the Medical Officer evaluable subjects , which are presented in Tables 2.13, 2.14, and 2.15, respectively for Study A.

TABLE 2.13: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE ITT SUBJECTS AT TEST OF CURE		
Clinical Response	Cefpodoxime (N=225)	Cefiximef (N=230)
Success Failure	91 (40.4%) 134 (59.6%)	81 (35.2%) 149 (64.8%)
Cefpodoxime vs Cefixime by Success	5.2%, 95% C.I.: -4.1%, 14.6%	

TABLE 2.14: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE EVALUABLE SUBJECTS AT TEST OF CURE		
Clinical Response	Cefpodoxime (N=124)	Cefiximef (N=132)
Success Failure	77 (62.1%) 47 (37.9%)	75 (56.8%) 57 (43.2%)
Cefpodoxime vs Cefixime by Success	5.3%, 95% C.I.: -7.5%,18.1%	

TABLE 2.15: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT TEST OF CURE		
Clinical Response	Cefpodoxime (N=125)	Cefiximef (N=128)
Success Failure	75 (60.0%) 50 (40.0%)	73 (57.0%) 55 (43.0%)
Cefpodoxime vs Cefixime by Success	3.0%, 95% C.I.: -10.0%, 15.9%	

Medical Officer's Note: The 95% confidence intervals for the difference in success rates of the overall clinical responses at Test of Cure between cefpodoxime and cefixime groups indicate the therapeutic equivalence of the two treatment groups as per the intent-to-treat, the evaluable, and the Medical Officer sub-population , which are presented in Tables 3.12, 3.13, and 3.14, respectively for Study B.

TABLE 3.12: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE ITT SUBJECTS AT TEST OF CURE		
Clinical Response	Cefpodoxime (N=256)	Cefiximef (N=258)
Success Failure	110 (43.0%) 146 (57.0%)	102 (39.5%) 156 (60.5%)
Cefpodoxime vs Cefixime by Success	3.4%, 95% C.I.: -5.5%, 12.3%	

TABLE 3.13: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE EVALUABLE SUBJECTS AT TEST OF CURE		
Clinical Response	Cefpodoxime (N=136)	Cefiximef (N=140)
Success Failure	94 (69.1%) 42 (30.9%)	90 (64.3%) 50 (35.7%)
Cefpodoxime vs Cefixime by Success	4.8%, 95% C.I.: -7.0%, 16.7%	

TABLE 3.14: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT TEST OF CURE		
Clinical Response	Cefpodoxime (N=126)	Cefiximef (N=130)
Success Failure	89 (70.6%) 37 (29.4%)	85 (65.4%) 45 (34.6%)
Cefpodoxime vs Cefixime by Success	5.3%, 95% C.I.: -6.9%, 17.4%	

Ancillary Efficacy Outcomes:

Table E-30. Summary of Clinical Success and Bacteriologic Cure Rates (%) of Cefpodoxime Proxetil 5-Day Twice Daily Regimen in Pediatric Patients with Acute Suppurative Otitis Media (Protocols 0098-A & 0098-B)

Treatment Group	End of Therapy		"Test of Cure"		Visit 2		Visit 3		Final Visit	
	Clin.	Bacter.	Clin.	Bacter.	Clin.	Bacter.	Clin.	Bacter.	Clin.	Bacter.
CFD	87	87	67	67	87	87	74	74	65	65
CFX	79	79	64	64	87	87	79	79	65	65

CFD = Cefpodoxime; CFX = Cefixime
"Test of Cure" = 4-21 days posttherapy; End of Therapy = Days 7-10 for CFD and Days 12-15 for CFX
Visit 2 = Days 7-10; Visit 3 = Days 12-15, and Final Visit = Days 25-38
Reference: ISE Appendix Tables 4.2, 4.4, 4.8, 4.10, 5.2, 5.4, 5.8, 5.10, 5.14, 5.16

Table E-31. Comparison of By-Pathogen Eradication Rates (%) of Cefpodoxime Proxetil 5-Day Twice Daily Regimen in Pediatric Patients with Acute Suppurative Otitis Media (Protocols 0098-A & 0098-B)

Evaluation	M catarrhalis		H influenzae		S pneumoniae		S pyogenes	
	CFD	CFX	CFD	CFX	CFD	CFX	CFD	CFX
End of Therapy	70	75	91	85	88	71	88	79
"Test of Cure"	56	56	66	75	72	58	80	57
Visit 2	70	75	91	92	94	89	88	83
Visit 3	59	75	72	85	79	77	84	71
Final Visit	68	63	57	74	69	58	70	61

CFD = cefpodoxime
CFX = cefixime

Overall Bacteriologic Evaluation

Table E-30 summarizes the results of the overall bacteriologic evaluation at End of Therapy. The overall bacteriologic cure rate, which comprised both bacteriologic cures (ie, patients with culture-proven eradication) and presumptive bacteriologic cures (ie, patients judged clinically cured or improved), was driven by the clinical success rate since few repeat cultures were done. The overall bacteriologic cure rate, like the clinical success rate, was significantly higher in the cefpodoxime group than in the cefixime group: ie, 87% (226/260) versus 79% (215/272). The % CI for difference in cure rates is 1.16% to 14.59%.

Medical Officer's Note: Please Refer to the appendix to the current studies for detailed discussion of secondary efficacy parameters which include end of therapy, visit 2, visit 3 and final visit.

Medical Officer's Note: The Tables below show a subgroup analysis of patients with recurrent and chronic OM. The arms are balanced. Please also note the lower cure rates which is to be expected in this population.

TABLE 9: STUDY 0098 A&B: OVERALL BACTERIOLOGIC RESPONSE OF THE RECURRENT & CHRONIC OM SUBJECTS AT TEST OF CURE		
Bacteriological Response	Cefpodoxime (N=40)	Cefixime (N=31)
Cure	13 (32.5%)	8 (25.8%)
Failure	27 (67.5%)	23 (74.2%)
Cefpodoxime vs Cefixime by Cure	6.7%, 95% C.I.: -17.3%, 30.7%	

TABLE 10: STUDY 0098 A&B: OVERALL CLINICAL RESPONSE OF THE RECURRENT & CHRONIC OM SUBJECTS AT TEST OF CURE		
Clinical Response	Cefpodoxime (N=40)	Cefixime (N=31)
Success	14 (35.0%)	8 (25.8%)
Failure	26 (65.0%)	45 (74.2%)
Cefpodoxime vs Cefixime by Success	9.2%, 95% C.I.: -15.0%, 33.4%	

TABLE 11: STUDY 0098 A&B: OVERALL BACTERIOLOGIC RESPONSE OF THE RECURRENT & CHRONIC OM SUBJECTS AT END OF THERAPY		
Bacteriological Response	Cefpodoxime (N=40)	Cefixime (N=31)
Cure	20 (50.0%)	16 (51.6%)
Failure	20 (50.0%)	15 (48.4%)
Cefpodoxime vs Cefixime by Cure	-1.6%, 95% C.I.: -27.9%, 24.7%	

TABLE 12: STUDY 0098 A&B: OVERALL CLINICAL RESPONSE OF THE RECURRENT & CHRONIC OM SUBJECTS AT END OF THERAPY		
Clinical Response	Cefpodoxime (N=40)	Cefixime (N=31)
Success	21 (52.5%)	16 (51.6%)
Failure	19 (47.5%)	15 (48.4%)
Cefpodoxime vs Cefixime by Success	0.9%, 95% C.I.: -25.4%, 27.2%	

TABLE 13: STUDY 0098 A&B: OVERALL BACTERIOLOGIC RESPONSE OF THE RECURRENT & CHRONIC OM SUBJECTS AT FINAL VISIT		
Bacteriological Response	Cefpodoxime (N=40)	Cefixime (N=31)
Cure	14 (35.0%)	14 (45.2%)
Failure	26 (65.0%)	17 (54.8%)
Cefpodoxime vs Cefixime by Cure	-10.2%, 95% C.I.: -35.9%, 15.6%	

TABLE 14: STUDY 0098 A&B: OVERALL CLINICAL RESPONSE OF THE RECURRENT & CHRONIC OM SUBJECTS AT FINAL VISIT		
Clinical Response	Cefpodoxime (N=40)	Cefixime (N=31)
Success	15 (37.5%)	14 (45.2%)
Failure	25 (62.5%)	17 (54.8%)
Cefpodoxime vs Cefixime by Success	-7.7%, 95% C.I.: -33.6%, 18.3%	

3) Efficacy Summary and Conclusions (Pivotal Studies)

- The two treatment groups in the pivotal studies were comparable for the following: number of patients enrolled, percentage of patients who completed the planned study, percentage of patients considered by the investigator to be evaluable for efficacy, pretreatment demographics (ie, age; weight; and distribution by sex, race, and severity of infection), and the percentage of patients who took 9-11 doses of study medication in 5-6 days (cefpodoxime) or 9-11 days (cefixime).

- The two treatments were equivalent at the "Test of Cure" evaluations and at all other evaluation

times for overall clinical success and overall bacteriological cure. Analysis was done of the patients in the Subgroup(those with recurrent OM and chronic OM) and this was compared to the patients in the Applicant's evaluable population. Both in demographics and in efficacy, there were no demonstrable differences either at TOC or LTFU. Additionally, given the strenghth of the sponsor's inclusion criteria and that only one patient change was made, the Applicant's evaluable population was accepted.

- The by-pathogen eradication rate of cefpodoxime at the end of therapy was superior to that of cefixime for *S pneumoniae*; however, the rates for the two treatments were equivalent for the remainder of the major pathogens: ie, *M catarrhalis, H influenzae,* and *S pyogenes.* At the "Test of Cure" evaluation, cefpodoxime was superior to cefixime with regard to eradication of *S pneumoniae* and *S pyogenes* and was equivalent to cefixime with regard to eradication of *M catarrhalis* and *H influenzae.*

- Thus, this shorter dosage regimen of cefpodoxime is effective for the treatment of acute suppurative otitis media caused by the following susceptible pathogens: *Streptococcus pneumoniae, Streptococcus pyogenes,* and beta-lactamase positive and negative strains of both *Haemophilus influenzae and Moraxella catarrhalis.*

III. 10 day Otitis Media Studies

tudy Design (Historical Studies)

All three studies were prospectively randomized and evaluator-blinded. Protocols 0013 and 0060 were multicenter studies conducted at 13 and 4 sites, respectively, while Protocol 0014 was conducted at a single site(Dr. Virgil Howie). The randomization scheme was such that the ratio of cefpodoxime-treated patients to amoxicillin/clavulanate-treated patients was 2:1 in Protocols 0013 and 0014 and 1:1 in Protocol-0060.

Medical Officer's Note: Please refer to the MO review(Dr. Susan Alpert) completed of this efficacy supplement for further details of the following sections in these trials:

- the schedule of activities that were pertinent to efficacy.
- Identification of Primary and Secondary Efficacy Measures
- Study Population: Inclusion/Exclusion Criteria

Classification of Clinical and Bacteriologic Responses

2) Results (Historical Studies)

Results are shown in this section for the three previously submitted safety/efficacy studies (Protocols 0013, 0014, and 0060) that compared 10-day regimens of cefpodoxime proxetil (5 mg/kg administered every 12 hours) and amoxicillin/clavulanate (13.3 mg/kg administered every 8 hours).

A. Patient Population (Historical Studies)

Disposition of Patients

Discontinuation of Therapy

The most frequent reasons given for early discontinuation – ineligibility for the study followed by lack of efficacy – were comparable in both treatment groups.

Evaluability Status

The primary reason for nonevaluability in each treatment group in Protocols 0013 and 0014 was ineligibility for protocol (including no isolated pathogen or resistant pathogens at pretreatment), while the primary reason in Protocol 0060 was failure to follow protocol (ie, visit outside the acceptable window).

B. Demographics At Pretreatment

The pretreatment demographic characteristics of the evaluable patients in Protocols 0013, 0014, and 0060were comparable in age, sex and race distribution, and weight before treatment.

C. Primary Efficacy Results (Historical Studies)

Table E-37 summarizes the primary efficacy results for the evaluable patients in Protocols)13, 0014, and 0060.

The individual statistical analyses of these three studies showed no significant differences between treatment groups in either study for any of the primary efficacy variables. Note that statistical significance was not reported for *S pyogenes* in Protocols 0013 and 0014; the numbers of patients

with this pathogen were so small that it is unlikely that the differences seen are clinically important.

Table E-37. Primary Efficacy Results (Clinical Success and Bacteriologic Cure at End of Therapy*) in the Evaluable Patient Populations in Protocols 0013, 0014, and 0060

Protocol No.	Treatment Group [No. Pts]	Clinical Success† (%)	Bacteriologic Cure (%)					
			By Patient†	By Ear† [‡]	By Pathogen †,§			
					S pneu	*S pyog*	*H infl*††	*M cat*††
0013	CFD¶ [N=95]	91	93	56 [93]	94	100§§	92	94
	AMC/CA•• [N=48]	88	88	51 [89]	91	75§§	90	67
0014	CFD¶ [N=56]	64	79	57 [82]	87	–	96	65
	AMC/CA•• [N=37]	62	84	65 [86]	100	100§§	71	93
0060	CFD¶ [N=54]	78	Not done					
	AMC/CA•• [N=56]	84						

* End of Therapy = Days 10-14 in Protocols 0013 & 0014 and Days 8-22 in Protocol 0060

† There were no statistically significant differences between treatment groups for percent clinical success or percent bacteriologic eradication by patient, by ear, or by pathogen (with the exception of *S pyogenes* for which statistical significance was not reported)

‡ Excludes nonassessable patients

§ *S pneu* = *Streptococcus pneumoniae*, *S pyog* = *Streptococcus pyogenes*, *H infl* = *Haemophilus influenzae*, *M cat* = *Moraxella catarrhalis*

¶ CFD = cefpodoxime 5 mg/kg twice daily x 10 d

•• AMC/CA = amoxicillin/clavulanate 13.3 mg/kg thrice daily x 10 d

†† Includes beta lactamase-negative and -positive strains

§§ Protocol 0013: 100% = 7/7 patients and 75% = 3/4 patients; Protocol 0014: 100% = 1/1 patient

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