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APPLICATION NUMBER:

50-739

50-749

MEDICAL AND STATISTICAL REVIEW(S)

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTRODUCTION**

**MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW :
CEFDINIR ORAL SUSPENSION AND CAPSULE FOR PHARYNGITIS
/ TONSILLITIS**

Date of Submission: September 3, 1996
Date Received: September 4, 1996
Date Assigned: September 3, 1996
45 Day Meeting Date: November 14, 1996
User Fee Date: September 4, 1997
Date Review Completed: 5/30/97
Date Review Edited: 12/17/98
Material Reviewed: Volume 233-289 and 326 (clinical data sections)
 Volume 290 (case report forms)
 Volume 1.1 (archival)

I. Introduction to Pharyngitis Studies

1) Proposed Package Insert Regarding Dosage and Administration for Pharyngitis and/ or Tonsillopharyngitis:

The sponsor seeks approval for 5 and 10 day courses and would like to include the following:

	Total Daily Dose	Dose Frequency	Duration
Adults (age 13 and older ¹)	600 mg	300 mg q 12h	5 to 10 days
		or	
		600 mg q 24 h	10 days
Children (age 6 months through 12 years):	14mg/kg/day 600 mg maximum	7mg/kg/dose q12h	5 to 10 days
		or	
		14 mg/kg/day q24 h	10 days

¹The current Paediatric final Labeling Rule became effective December, 1994, and states that those 16 and under be considered paediatric. Prior to this rule, the agency recognized paediatric patients as anyone up to age 13. These protocols were designed and undertaken prior to the new rule.

PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTRODUCTION

2) Background:

The following is excerpted from the applicants submission:

Cefdinir (CI-983, PD 134393, FK 482) is a semisynthetic, extended-spectrum cephalosporin antibiotic intended for use in the treatment of mild to moderate bacterial infections.⁽¹⁾ The bactericidal action of cefdinir results from inhibition of cell-wall synthesis. Cefdinir is highly stable in the presence of β -lactamase enzymes. As a result, many β -lactamase-producing organisms that confer resistance to penicillins and to some cephalosporins are susceptible to cefdinir.^(2,3)

Streptococcus pyogenes (Group A β -hemolytic streptococcus, GABHS) is the major cause of bacterial pharyngitis in both children and adults.⁽⁴⁾ It has been estimated that pharyngitis occurs in 10% of people per year.⁽⁵⁾ Although antibiotic therapy may relieve symptoms of acute pharyngitis and shorten the course of the disease, its primary goal is to reduce the risk of nonsuppurative complications, particularly rheumatic fever.⁽⁶⁻¹¹⁾ Since it was first introduced in the 1940s, penicillin has been the treatment of choice for bacterial pharyngitis and for many years effected a consistent microbiologic eradication rate of over 90%.⁽¹²⁾ However, in the 1980s a number of studies suggested that the percentage of penicillin treatment failures was rising, perhaps to as much as 30%.^(13,14) Although *S. pyogenes* isolates remain virtually 100% susceptible to penicillin in vitro, it is possible that the presence of β -lactamase-producing commensal organisms in the pharynx may be destroying the β -lactamase-sensitive penicillin before it can eradicate the streptococci.⁽¹⁵⁻¹⁷⁾

First- and second-generation oral cephalosporins have been studied for their effectiveness in treating streptococcal pharyngitis and have compared favorably with penicillin.^(13,18) This study was designed to compare the efficacy and safety of cefdinir, a third-generation oral cephalosporin, with penicillin in the treatment of GABHS pharyngitis.

Cefdinir capsules (adult/adolescent indications) have been approved for use in Japan since October, 1991, and a fine granule formulation for pediatric use was approved in April, 1993. Cefdinir was approved for use in the Philippines in 1994.

Parke-Davis Pharmaceutical Research licensed cefdinir from Fujisawa and has developed the drug independent of the Japanese program.

IND for cefdinir capsules and suspension was submitted on May 2, 1990. During the development of cefdinir, Parke-Davis held 4 formal meetings with the FDA to discuss the clinical plan and NDA.

Cefdinir was developed during a transitional period in the FDA's expectations for appropriate indications and studies for anti-infective products. Development began prior to October 1991 when the Divisional Points to Consider (PTC) were issued, and continued after the second version in 1992 (PTC2). Accordingly, the development plan underwent some changes with time, as reflected in the FDA discussions.

The Points-to-Consider document states that in order for a drug to receive approval for streptococcal pharyngitis, the applicant ought to submit "one statistically adequate and well-controlled multicentre trial establishing equivalence or superiority to any approved product." (page 41) Two adequate and well

PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTRODUCTION

controlled studies are needed however because this application reduces the dosing duration. In such a circumstance the following guidelines applies: "applications for treatment of infections with dosing regimen durations less than generally approved for that infections should ordinarily contain two statistically adequate and well-controlled trials, despite the subsequent individual infection suggestions in this document." (Section XIII, Issues About Specific Infections, P. 28). This application has completed this guideline. There are four studies in the treatment of patients with pharyngitis or tonsillitis. Two studies are of five days duration and two studies are of ten days duration. With adults, capsules are used. While in children a suspension is used. In adults, there is one five day study and one ten day study. In children, there is one five day study and one ten day study. All four studies are pivotal, i.e., premiere studies to garner the indication. All four studies were done in the U.S. and Canada.

The following Table briefly outlines pertinent features of the reviewed studies.

TABLE 49. List of Studies
Pharyngitis

Study	Design	Patients Enrolled		Pts enrolled without site 14 and 5	Patients patients Microb micro iologic eval. ally Without Evalua site 14 ble and 5		Regimen
983-7	R, C, DB, 2T	919	305		210		Cefdinir 600 mg QD × 10d
			304		217		Cefdinir 300 mg BID × 10d
			310		217		PenV 250 mg QID × 10d
983-58	R, C, IB, 2T	558	278		218		Cefdinir 300 mg BID × 5d
			280		214		PenV 250 mg QID × 10d
983-51	R, C, IB, 2T	869	289	792 (lost 264	252	228	Cefdinir 14 mg/kg QD × 10d
			290	77) 264	250	227	Cefdinir 7 mg/kg BID × 10d
			290	264	250	227	PenV 10 mg/kg QID × 10d
983-56	R, C, IB, 2T	482	240	425 (lost 211	224	196	Cefdinir 7 mg/kg BID × 5d
			242	57) 214	216	193	PenV 10 mg/kg QID × 10d

R = Randomized; C = Controlled; IB = Investigator-blind; DB = Double-blind; PenV = Penicillin V-K; 2T = Two-tailed equivalence testing.

PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES



INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES:

1. Introduction:

Primary efficacy endpoints were the rate of eradication of baseline pathogens summarized by pathogen and by patient, and rate of clinical cure based on resolution of clinical signs and symptoms. Four active-controlled studies in pharyngitis, (2 adult, 2 pediatric) showed that cefdinir given for 5 or 10 days was superior to penicillin microbiologically, and equivalent or superior to penicillin clinically. Differences in response rates to QD versus BID dosing regimens were few and generally not of statistical or clinical significance. A summary of eradication and clinical cure rates for pivotal studies is shown below.

Indication	Study Number	Pathogen Eradication Rates (%) ^a			Clinical Cure Rates (%) ^b		
		Cefdinir QD	Cefdinir BID	Control Drug(s)	Cefdinir QD	Cefdinir BID	Control Drug(s)
Pharyngitis	983-7	91	92	83	95	96	89
	983-58	—	89	82	—	89	85
	983-51	93	95	71	98	96	87
	983-51	94	94	70	97	96	86
	excluding Irivani						
	983-56	—	90	72	—	92	91
	983-56 excluding Irivani		90	70		91	90

^a Microbiologically evaluable patients.

^b Microbiologically evaluable patients, except for otitis media and sinusitis studies, in which rates for clinically evaluable patients are used.

TABLE 1. List of Pivotal and Supportive Clinical Studies for Efficacy
Cefdinir Capsules

Study Number	Indication	Location	Regimens	Number of Patients Enrolled
983-7	Pharyngitis	NA	Cefdinir 600 mg QD × 10d Cefdinir 300 mg BID × 10d PenV 250 mg QID × 10d	919
983-58	Pharyngitis	US	Cefdinir 300 mg BID × 5d PenV 250 mg QID × 10d	558

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

**TABLE 2. List of Pivotal and Supportive Clinical Studies
Cefdinir Suspension**

Study No.	Indication	Location	Regimens	Number of Patients Enrolled	Patients enrolled excluding site 14 and 5
983-51	Pharyngitis	NA	Cefdinir 14 mg/kg QD × 10d Cefdinir 7 mg/kg BID × 10d Pen V 10 mg/kg QID × 10d	869	792
983-56	Pharyngitis	US	Cefdinir 7 mg/kg BID × 5d Pen V 10 mg/kg QID × 10d	482	425

NA = North America; US = United States; Pen V = penicillin V-K.

In Vitro Susceptibility Surveys

Medical Officer's Note: Please refer to the microbiologist's review.

Human Pharmacokinetics

Medical Officer's Note:

It is important to note, that overall exposure to study medication, as demonstrated by AUC values, is similar in adults and children. Thus, pediatric and adult efficacy data was used together to support an indication where the disease state is not expected to differ between children and adults; i.e., pharyngitis clinical programs were designed with this in mind. Please refer to the pharmacologist's review for further details.

Study Methods:

Medical Officer's Note: Data for the 10-day and 5-day regimens were collected in different pharyngitis studies.

Consequently, regimen effects are confounded with study effects, and statistical inference as to whether 10- vs 5-day rate differences are due to regimen differences, study differences, or other effects is not possible.

However the difference in cure rates was calculated using 2 tailed 95% CIs. Clinical cure rates and microbiologic eradication rates in the microbiologically evaluable population were examined.

2. COMPARISON AND ANALYSIS OF RESULTS OF PIVOTAL AND SUPPORTIVE CLINICAL STUDIES

Pharyngitis/Tonsillitis

List of Studies

Five randomized, controlled studies were initiated to evaluate cefdinir for the treatment of pharyngitis/tonsillitis caused by Group A β -hemolytic streptococci (*S. pyogenes*, GABHS). One European pediatric study, 983-36, was discontinued early because of poor enrollment (9 patients) and will not be summarized.

Two North American studies evaluated conventional 10-day (QD and BID)^(25,26) courses of cefdinir. Two other studies, conducted only in the US, used 5-day BID regimens of cefdinir.^(27,28) One pediatric suspension study and one adult capsule study ~~was~~^{were} conducted for each regimen. For all studies, pharyngitis was diagnosed on the basis of

PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES

clinical signs and symptoms and the presence of GABHS. All patients were required to have pain and erythema of the pharyngeal cavity. All studies compared cefdinir with penicillin V-K. The studies are listed in Table 49.

TABLE 49. List of Studies
Pharyngitis

Pharyngitis									
Study	Design	Pts Enrolled	Pts enrolled without site 14 and 5			Micro. Eval.	Micro. eval. Sans site 14 and 5	Regimen	
983-7	R, C, DB, 2T	919	305			210		Cefdinir 600 mg QD × 10d	
			304			217		Cefdinir 300 mg BID × 10d	
			310			217		PenV 250 mg QID × 10d	
983-58	R, C, IB, 2T	558	278			218		Cefdinir 300 mg BID × 5d	
			280			214		PenV 250 mg QID × 10d	
983-51	R, C, IB, 2T	869	289	792(lost 77)	264	252	228	Cefdinir 14 mg/kg QD × 10d	
			290		264	250	227	Cefdinir 7 mg/kg BID × 10d	
			290		264	250	227	PenV 10 mg/kg QID × 10d	
983-56	R, C, IB, 2T	482	240	425(lost 57)	211	224	196	Cefdinir 7 mg/kg BID × 5d	
			242		214	216	193	PenV 10 mg/kg QID × 10d	

R = Randomized; C = Controlled; IB = Investigator-blind; DB = Double-blind; PenV = Penicillin V-K; 2T = Two-tailed equivalence testing.

In Vitro Susceptibility Data

In vitro susceptibility data for *S. pyogenes* obtained from the pharyngitis studies are summarized in Table 50.

TABLE 50. Distribution of Baseline *S. pyogenes* by Susceptibility to Study Medications
Pharyngitis Studies
(Number of Pathogens)

Study	Cefdinir				Penicillin			
	S	I	R	U	S	I	R	U
983-7	725	0	0	0	725	0	0	0
983-58	484	0	0	0	484	0	0	0
983-51	832	0	0	0	830	0	0	2
983-56	472	0	0	0	472	0	0	0
Total	2513	0	0	0	2511	0	0	2

S = Susceptible; I = Intermediate; R = Resistant; U = Unknown.

As expected, *S. pyogenes* was very susceptible to both cefdinir and penicillin. All 2513 isolates were susceptible to cefdinir. Two isolates had unknown susceptibility to penicillin and the remaining 2511 isolates were susceptible to penicillin.

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

Tonsil Tissue Pharmacokinetic Data

Twelve patients undergoing elective tonsillectomy participated in a single-dose, nonblind, randomized study to evaluate the penetration of cefdinir into tonsil tissue.⁽²⁹⁾ Plasma and tonsil tissue samples collected 4 hours following administration of single oral 300 or 600 mg cefdinir doses (6 subjects/dose group) were analyzed for cefdinir using a microbiological assay. Ratios of tissue to plasma concentrations were also determined for each dose (Table 51).

TABLE 51. Mean (Range) Tonsil Tissue and Plasma Cefdinir Concentrations and Tissue/Plasma Concentration Ratios
Study 983-24

Dose (mg)	Concentration ($\mu\text{g/mL}$)		
	Tonsil Tissue	Plasma	Ratio
300	0.28 (0.22-0.46)	1.13 (0.6-2.0)	0.27 (0.16-0.43)
600	0.44 (0.22-0.80)	2.17 (1.1-3.4)	0.21 (0.14-0.29)

The plasma and tonsil tissue concentrations of cefdinir increased proportionately with increasing cefdinir dose. Tonsil tissue/plasma cefdinir concentration ratios were similar following both doses, with an overall mean ratio of 0.24.

Study 983-7, Capsule Study Versus Penicillin V⁽²⁵⁾

This was a multicenter, randomized, well-controlled, statistically adequate (2-tailed testing), double-blind study comparing:

- Cefdinir 600 mg QD,
- Cefdinir 300 mg BID, and
- Penicillin 250 mg QID

for the treatment of patients at least 13 years of age with clinical signs and symptoms of pharyngitis and a positive screening test for GABHS. All regimens were given for 10 days. Patients were evaluated 5 to 9 days after completion of therapy (the TOC visit), and assessed for recurrence at a LTFU visit 18 to 24 days after therapy. Clinical signs and symptoms and a throat culture were collected at each visit. Clinical outcome was determined by the investigator's assessment.

Twenty-four investigators enrolled 919 patients into the study, 305 on QD cefdinir, 304 on BID cefdinir, and 310 on penicillin. Of these, 644 (70.1%) were microbiologically evaluable, 210 in the cefdinir QD group, 217 in the cefdinir BID, and 217 in the penicillin group. The 3 groups were comparable: 60% to 68% of the patients enrolled were women, 84% to 86% were white, and the median ages were 25 to 28 years.

Microbiologic eradication rates for *S. pyogenes* and clinical cure rates for microbiologically evaluable patients at the TOC visit are shown in Table 52.

PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES

TABLE 52. Microbiologic and Clinical Outcomes - Microbiologically Evaluable Patients
Pharyngitis Study 983-7

Parameter	Cefdinir QD		Cefdinir BID		Penicillin	
	n/N	%	n/N	%	n/N	%
<i>S. pyogenes</i> Eradication	192/210	91.4	199/217	91.7	181/217	83.4
Clinical Cure	199/210	94.8	209/217	96.3	193/217	88.9

n/N = Number of patients with eradication or clinically cured/total number of patients.

TABLE 14. Summary of Efficacy Analyses at TOC-per applicant (pharyngitis study 983- 7)

Pairwise Comparison	Population	Rates (%)	95% CI	Interpretation
Microbiologic Eradication				
QD vs Penicillin	Evaluable*	91 vs 83	1.8, 14.3	QD Superior
	MITT	91 vs 84	1.5, 13.3	QD Superior
	ITT	70 vs 64	-2.1, 12.7	Equivalent
BID vs Penicillin	Evaluable*	92 vs 83	2.1, 14.5	BID Superior
	MITT	92 vs 84	2.1, 13.8	BID Superior
	ITT	71 vs 64	-0.9, 13.9	Equivalent
QD vs BID	Evaluable	91 vs 92	-5.5, 5.0	Equivalent
	MITT	91 vs 92	-5.5, 4.5	Equivalent
	ITT	70 vs 71	-8.5, 6.1	Equivalent
Clinical Response				
QD vs Penicillin	Evaluable	95 vs 89	0.7, 11.0	QD Superior
	Clinically Evaluable	91 vs 85	0.1, 11.3	QD Superior
	ITT	90 vs 85	-0.2, 10.2	QD at Least Equivalent
BID vs Penicillin	Evaluable	96 vs 89	2.5, 12.2	BID Superior
	Clinically Evaluable	93 vs 85	2.8, 13.5	BID Superior
	ITT	92 vs 85	1.6, 11.6	BID Superior
QD vs BID	Evaluable	95 vs 96	-5.5, 2.4	Equivalent
	Clinically Evaluable	91 vs 93	-7.1, 2.3	Equivalent
	ITT	90 vs 92	-6.2, 2.9	Equivalent

* Primary efficacy analysis

Statistical Reviewer's Note: The Sponsor did not incorporate Yates' Continuity correction in the calculation of the 95% confidence interval in Table 14. Based on the underlying sample sizes, this is not expected to change the results to a considerable extent.

The following is excerpted from the Sponsor's submission:

The differences in eradication rates and clinical cure rates between the 2 cefdinir groups were not statistically significant. For eradication rates, the 95% CIs were (1.8%, 14.3%) for cefdinir QD-penicillin and (2.1%, 14.5%) for cefdinir BID-penicillin. The exploratory CMH test showed that the eradication rates for both the cefdinir QD

**PHARYNGITIS/TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

group and cefdinir BID group were significantly higher than the penicillin group ($p = 0.02$ for QD versus penicillin and $p = 0.01$ for BID versus penicillin). The 95% CIs for clinical cure rates were (0.7%, 11.0%) for cefdinir QD-penicillin and (2.5%, 12.2%) for cefdinir BID-penicillin. The exploratory CMH test showed that the clinical response rates for both cefdinir treatment groups were significantly higher than the penicillin group ($p = 0.02$ for QD versus penicillin and $p < 0.01$ for BID versus penicillin). Therefore, eradication rates and clinical cure rates in both cefdinir groups were statistically significantly higher than those in the penicillin group.

Of the qualified patients who had *S. pyogenes* eradicated at the TOC visit, 94.9% (166/175) in the cefdinir QD group, 96.1% (174/181) in the cefdinir BID group, and 92.3% (144/156) in the penicillin group also had microbiologic eradication at the LTFU visit. In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 95.6% (175/183) for the cefdinir QD group, 98.4% (188/191) for the cefdinir BID group, and 92.8% (154/166) for the penicillin group.

This study demonstrated that a 10-day course of cefdinir, 600 mg/day, given either QD or BID was more effective than penicillin 250 mg QID in eradication of *S. pyogenes* from the pharynx in adult patients, and in providing symptomatic relief in streptococcal pharyngitis.

Study 983-58, Capsule Study Versus Penicillin V, 5-Day⁽²⁷⁾

This was a multicenter, randomized, well-controlled, statistically adequate (2-tailed testing), investigator-blind study comparing:

- Cefdinir 300 mg BID $\times$ 5 days, and
- Penicillin 250 mg QID $\times$ 10 days

in the treatment of patients at least 13 years of age with signs and symptoms of pharyngitis and a positive screening test for GABHS. Patients were evaluated 5 to 10 days after completion of therapy at the TOC visit, and assessed for recurrence 25 to 31 days after completion of therapy at the LTFU visit. Clinical signs and symptoms and a throat culture were collected at each visit. Clinical outcome was determined by the investigator's assessment.

Twenty-one investigators enrolled 558 patients into the study, 278 into the cefdinir group and 280 into the penicillin group. Of these, 432 (77.4%) of the patients were microbiologically evaluable, 218 in the cefdinir group and 214 in the penicillin group. The 2 study arms were comparable demographically. Fifty-seven percent of the cefdinir group and 63% of the penicillin group were women. Eighty-six percent of the cefdinir group were white, as were 89% of the penicillin group. The median age in the cefdinir group was 26 years, versus 25 years in the penicillin group. Microbiologic eradication rates for *S. pyogenes* and clinical cure rates for microbiologically evaluable patients at the TOC visit are summarized in Table 53.

**TABLE 53. Microbiologic and Clinical Outcomes - Microbiologically Evaluable Patients
Pharyngitis Study 983-58**

Parameter	Cefdinir		Penicillin		95%CI
	n/N	%	n/N	%	
<i>S. pyogenes</i> Eradication	193/218	88.5	176/214	82.2	-0.4% 12.9%

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

Clinical Cure	194/218	89.0	181/214	84.6	-2%—10.8%

The eradication rates of cefdinir and penicillin were equivalent, although CMH testing showed a marginally significant difference ($p = 0.053$) in favor of cefdinir. The 95% CI about the difference between eradication rates for cefdinir-penicillin was (-0.4%, 12.9%). The clinical cure rates were also equivalent. The 95% CI about the difference between clinical cure rates for cefdinir-penicillin was (-2.0%, 10.8%).

Recurrences with *S. pyogenes* (baseline strain) between the TOC visit and the LTFU visit was uncommon. Of the qualified cefdinir patients who had *S. pyogenes* eradicated at TOC, 94.0% (156/166) had negative cultures at LTFU. The corresponding rate for penicillin patients was 96.8% (152/157). In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 94.0% (158/168) for the cefdinir group and 95.6% (152/159) for the penicillin group.

This study demonstrated that a 5-day course of cefdinir 300 mg BID was as or more effective than penicillin 250 mg QID in eradication of *S. pyogenes* from the pharynx in adult patients and in accelerating symptomatic relief in streptococcal pharyngitis.

Study 983-51, Suspension Study Versus Penicillin V⁽²⁶⁾

This was a multicenter, randomized, well-controlled, statistically adequate (2-tailed testing), investigator-blind study comparing:

- Cefdinir 14 mg/kg QD,
- Cefdinir 7 mg/kg BID, and
- Penicillin 10 mg/kg QID

in the treatment of patients 6 months to 12 years of age with signs and symptoms of pharyngitis and a positive screening test for GABHS. All regimens were given for 10 days. Patients were evaluated 4 to 9 days after completion of therapy (the TOC visit), and were assessed for recurrence 17 to 24 days after completion of therapy (the LTFU visit). Clinical signs and symptoms and a throat culture were collected at each visit. Clinical outcome was determined by the investigator's assessment.

Thirteen investigators enrolled 869 patients into the study, 289 on cefdinir QD, 290 on cefdinir BID, and 290 on penicillin. Of these, 752 (86.5%) were microbiologically evaluable, 252 in the cefdinir QD group and 250 in each of the cefdinir BID and penicillin groups. The 3 treatment groups were comparable: 46% to 51% of the patients enrolled were girls, 88% to 90% were white, and median ages were 6.9 to 7.5 years.

Microbiologic eradication rates for *S. pyogenes* and clinical cure rates for microbiologically evaluable patients at the

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

TOC visit are shown in the table below:

**Microbiologic and Clinical Outcomes - Microbiologically Evaluable Patients
Pharyngitis Study 983-51**

Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Clinical Efficacy				
All sites	246/252(97.6%)	241/250(96.4%)	217/250(86.8%)	<u>Cefdinir QD vs Cefdinir BID</u> 252,250(-0.0216, 0.0459) _{97.6%, 96.4%} <u>Cefdinir QD vs Penn</u> 252,250(0.0582, 0.1582) _{97.6%, 86.8%} <u>Cefdinir BID vs Penn</u> 250,250(0.0441, 0.1479) _{96.4%, 86.8%}
Excluding Iravani(Sites14)	222/228(97.3%)	218/227(96%)	196/227(86.3%)	<u>Cefdinir QD vs Cefdinir BID</u> 228,227(-0.0238, 0.0505) _{97.3%, 96%} <u>Cefdinir QD vs Penn</u> 228,227(0.0566, 0.1639) _{96%, 86.3%} <u>Cefdinir BID vs Penn</u> 227,227(0.0411, 0.1527) _{96%, 86.3%}
Microbiologic Eradication				
All sites	233/252(92.4%)	237/250(94.8%)	177/250(70.8%)	<u>Cefdinir QD vs Cefdinir BID</u> 252,250(-0.0701, 0.0232) _{92.4%, 94.8%} <u>Cefdinir QD vs pen</u> 252,250(0.1475, 0.2857) _{92.4%, 70.8%} <u>Cefdinir BID vs Pen</u> 250,250(0.1732, 0.3067) _{94.8%, 70.8%}

Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Excluding Iravani(Site 14)	215/228(94.3%)	214/227(94.3%)	159/227(70%)	<u>Cefdinir QD vs Cefdinir BID</u> 228,227(-0.0468, 0.0473) _{94.3%, 94.3%} <u>Cefdinir QD vs Pen</u> 228,227(0.1713, 0.3137) _{94.3%, 70%} <u>Cefdinir BID vs Pen</u> 227,227(0.1711, 0.3135) _{94.3%, 70%}

According to the Sponsor, the differences in eradication and clinical cure rates between the 2 cefdinir groups were not statistically significant. The eradication rates and clinical cure rates in both the cefdinir groups were statistically significantly higher than those of the penicillin group. For microbiologic eradication, the 95% CI about the difference in rates was (15.1%, 28.2%) for cefdinir QD-penicillin and (17.7%, 30.3%) for cefdinir BID-penicillin. The exploratory CMH test showed that the the study comp eradication rates for both the cefdinir QD group and cefdinir BID group were significantly higher than the penicillin group ($p < 0.001$ for QD vs penicillin and $p < 0.001$ for BID vs penicillin). For clinical cure rates, the 95% CIs were (6.2%, 15.4%) for cefdinir QD-penicillin and (4.8%, 14.4%) for cefdinir BID-penicillin. When confidence intervals were recalculated by incorporating Yates' Continuity Correction, there were no changes in the inference.

Of the qualified patients who had their baseline pathogen eradicated at the TOC visit, 93.8% (197/210) in the cefdinir QD group, 88.8% (190/214) in the cefdinir BID group, and 89.5% (136/152) in the penicillin group also had microbiologic eradication at the LTFU visit. In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 95.4% (208/218) for cefdinir QD, 93.5% (202/216) for cefdinir BID, and 93.6% (160/171) for penicillin.

This study demonstrated that a 10-day course of cefdinir, given either 14 mg/kg QD or 7 mg/kg BID, was more effective than penicillin 10 mg/kg QID in eradication of *S. pyogenes* from the pharynx in pediatric patients, and in accelerating symptomatic relief in streptococcal pharyngitis.

Medical Officer's Note: When Dr Iravani's data was not included in the analysis for clinical and microbiologic efficacy, there was very little effect on response rates. Please see Appendix EP page 1 and 2.

Exclusion of data from Dr Iravani's site did not affect results of the cefdinir capsule studies, as his site enrolled only pediatric patients taking the suspension.

In the study comparing 10 days treatment of QD and BID cefdinir to penicillin, exclusion of data from Dr Iravani's site did not affect efficacy conclusions. Either cefdinir regimen was superior to penicillin in eradication of *S. pyogenes* from the pharynx, by both CI testing (the confidence interval did not include zero), and p-value (CMH) testing. Both of the cefdinir regimens were statistically superior to the penicillin regimen in achieving clinical cures as well.

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

Study 983-56, Suspension Study Versus Penicillin V, 5-Day

This was a multicenter, randomized, well-controlled, statistically adequate (2-tailed testing), investigator-blind study comparing:

- Cefdinir 7 mg/kg BID × 5 days, and
- Penicillin 10 mg/kg QID × 10 days

in the treatment of patients 6 months to 12 years of age with signs and symptoms of pharyngitis and a positive screening test for GABHS. Patients were evaluated 5 to 10 days after completion of therapy at the TOC visit, and assessed for recurrence 25 to 31 days after completion of therapy at the LTFU visit. Clinical signs and symptoms and a throat culture were collected at each visit. Clinical outcome was determined by the investigator's assessment.

Thirteen investigators enrolled 482 patients into the study, 240 into the cefdinir group and 242 into the penicillin group. Four hundred forty patients (91.2%) were microbiologically evaluable, 224 in the cefdinir group and 216 in the penicillin group. The patients enrolled in each group were comparable: 53% and 50% of the patients were boys, 89% and 88% were white, and the median ages were 7.4 and 7.7 years for the cefdinir and penicillin groups, respectively.

Microbiologic eradication rates for *S. pyogenes* and clinical cure rates for microbiologically evaluable patients at the TOC visit are shown in the FDA analysis with continuity correction below:

Table 55 Clinical and microbiologic outcome: Study 983-56				
Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Clinical Efficacy (all evaluable patients)				
All sites		205/224(91.5%)	196/216(90.7%)	224,216(-0.0499, 0.0655) _{91.5%, 90.7%}
Sites excluding Dr Iravani		179/196(91.3%)	173/193(89.6%)	196,193(-0.0465, 0.0804) _{91.3%, 89.6%}
Microbiologic Eradication				
All sites		201/224(89.7%)	155/216(71.7%)	224,216(0.1031, 0.2563) _{89.7%, 71.7%}
Sites excluding	176/196(89.7%)	135/193(69.9%)	196,193(0.1160, 0.274)	

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

Table 55 Clinical and microbiologic outcome: Study 983-56				
Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Clinical Efficacy (clinically evaluable patients)				
All sites		209/228(91.6%)	200/220(90.9%)	228,220(-0.0491, 0.0642) _{91.6%, 90.9%}
Sites excluding Dr Iravani		182/199(91.4%)	175/195(89.7%)	199,195(-0.0455, 0.0798) _{91.4%, 89.7%}

According to the sponsor, the eradication rate in the cefdinir group was significantly higher than in the penicillin group. The 95% CI about the difference between eradication rate for cefdinir BID versus penicillin was (10.8%, 25.2%). The exploratory CMH test showed that the eradication rate for cefdinir was significantly higher ($p < 0.001$) than that for penicillin. The clinical cure rates for cefdinir and penicillin were equivalent. The 95% CI about the difference between clinical cure rates for cefdinir versus penicillin was (-4.5%, 6.1%). The exploratory CMH tests showed no significant difference between the clinical cure rate for cefdinir and penicillin ($p = 0.80$). There were no changes in inferences when the confidence intervals were recalculated by incorporating Yates' Continuity Correction.

Microbiologic responses were durable in both treatment groups at the LTFU visit. Among qualified patients with *S. pyogenes* eradication at TOC 95.9% (164/171) of those in the cefdinir group and 97.7% (127/130) of those in the penicillin group remained culture-negative for this pathogen. In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 94.9% (166/175) for the cefdinir group and 96.5% (138/143) for the penicillin group.

This study demonstrated that cefdinir 7 mg/kg BID, given for 5 days, was more effective than a 10-day course of penicillin 10 mg/kg QID in eradicating *S. pyogenes* from the pharynx of pediatric patients, and equivalent to penicillin in providing symptomatic relief in streptococcal pharyngitis.

*Medical Officer's Note: When Dr. Irivani's data was not included in the analysis for clinical and microbiologic efficacy, there was very little effect on response rates. Please see appendix EP pages 3 and 4. In comparing 5 days treatment of BID cefdinir to 10 days treatment with penicillin, cefdinir was superior to penicillin in eradication of *S. pyogenes* from the pharynx, by both CI and CMH testing. Clinical response for the 2 regimens was equivalent by CI testing.*

Discussion

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

Antimicrobial treatment of streptococcal pharyngitis may benefit the patient by shortening the duration of symptoms and by preventing suppurative complications. The primary reason to treat streptococcal pharyngitis, however, is to reduce the risk of nonsuppurative complications, ie, rheumatic fever. Studies performed in the early 1950s showed a good correlation between eradication of GABHS and a lowered incidence of rheumatic fever.^{6,7} Presumably, elimination of the organism prevents the persistent antigenic stimulation which sets off an autoimmune response.

Parenteral benzathine penicillin has been best documented to reduce the risk of rheumatic fever. However, in practice, oral agents such as penicillin V have been used more often and are generally accepted as effective because GABHS are reliably eradicated. The primary objective of therapy of streptococcal pharyngitis is eradication of *S. pyogenes* from the pharynx, in order to decrease the risk of complications such as rheumatic fever. The studies included in the cefdinir NDA, with or without data from Dr Iravani's site, demonstrate that cefdinir effectively eradicates streptococci from the pharynx, and does so more reliably than penicillin.

Eradication rates of *S. pyogenes* for the 4 major studies in the cefdinir program are shown in Table 56, by study regimen.

TABLE 56. Summary of Microbiologic Eradication Rates

Study	Population	Pharyngitis Studies								Penicillin	
		Cefdinir								10d QID	
		10d QD		10d BID		10d QD + BID		5d BID		n/N	%
		n/N	%	n/N	%	n/N	%	n/N	%		
983-7	Adult	192/210	91.4	199/217	91.7	391/427	91.6	—	—	181/217	83.4
983-58	Adult	—	—	—	—	—	—	193/218	88.5	176/214	82.2
983-51	Pediatric	233/252	92.5	237/250	94.8	470/502	93.6	—	—	177/250	70.8
983-56	Pediatric	—	—	—	—	—	—	201/224	89.7	155/216	71.8

n/N = Number of patients with eradication/total number of patients.

The reasons for the higher eradication rates for cefdinir are not immediately obvious. It is not due to increased penicillin resistance in *S. pyogenes*. In vitro testing showed no isolates resistant to penicillin, and others have not found evidence of increased penicillin resistance in North America.

Clinical cure rates for these studies are summarized in Table 57.

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

TABLE 57. Summary of Clinical Cure Rates

Study	Population	Pharyngitis Studies							
		Cefdinir						Penicillin	
		10d QD		10d BID		10d QD + BID		5d BID	
		n/N	%	n/N	%	n/N	%	n/N	%
983-7	Adult	199/210	94.8	209/217	96.3	408/427	95.6	—	—
983-58	Adult	—	—	—	—	—	—	194/218	89.0
983-51	Pediatric	246/252	97.6	241/250	96.4	487/502	97.0	—	—
983-56	Pediatric	—	—	—	—	—	—	205/224	91.5
								193/217	88.9
								181/214	84.6
								217/250	86.8
								196/216	90.7

n/N = Number of patients clinically cured/total number of patients.

Ten days' treatment with cefdinir, as 600 mg QD (capsules), 14 mg/kg QD (suspension), 300 mg BID (capsules), or 7 mg/kg BID (suspension), were statistically superior to 10 days of penicillin in eradicating *S. pyogenes* and providing symptomatic relief. In the 5-day capsule study, cefdinir 300 mg BID and penicillin were equivalent in their eradication and clinical cure rates, although eradication rates were marginally significant ($p = 0.053$) in favor of cefdinir. In the suspension study, 5-day treatment with cefdinir 7 mg/kg BID was statistically superior to penicillin in *S. pyogenes* eradication and equivalent to penicillin in clinical cure rate.

One 7-year-old girl in Study 983-56 who was treated with a 5-day course of cefdinir developed symptoms which were consistent with rheumatic fever. Several atypical aspects of this case make it difficult to ascribe it to cefdinir failure. The onset of symptoms was unusually short, 8 days after pharyngitis appeared. The patient's isolate was eradicated after cefdinir therapy. The patient's isolate of GABHS was typed, and was nonrheumatogenic. In summary, if the patient did in fact develop rheumatic fever, it would appear more likely that it was related to another asymptomatic episode of GABHS pharyngitis which preceded the infection under study.

Eradication rates in patients treated with penicillin V are usually lower than those in patients given therapy with cephalosporins or the newer macrolide agents. This apparent inferiority of penicillin has been described by Pichichero.⁽¹¹⁾ It may be due to β -lactamases released into the extracellular fluid, resulting in destruction of the penicillin molecule before it can reach its target binding protein in the still-susceptible streptococci.

Consistent with this explanation is the lower efficacy of penicillin seen in the 2 cefdinir pediatric studies. Increased β -lactam exposure in children, such as for episodes of otitis media, would select for a pharyngeal flora enriched in β -lactamase producers. An alternative explanation for the age effect could be a greater contribution of a more mature immune system in older patients.

Whatever the mechanism, however, it is clear that penicillin is not as effective as a number of other agents in the eradication of *S. pyogenes* in children or adults. For cefdinir, the present studies document differences in eradication rates on the order of 10% to 20%. This was true of both the 5-day and 10-day cefdinir regimens, although it must be noted that, while a study to compare the 2 regimens was not performed, the 5-day regimen appears to give somewhat lower eradication rates than the 10-day regimen.

Eradication of *S. pyogenes* is the primary reason for the treatment of streptococcal pharyngitis, to decrease the risk of subsequent rheumatic fever. Recently, an increased incidence of rheumatic fever, severe streptococcal infections, and a new entity, streptococcal toxic-shock-like syndrome, have been described[12-15]. Eradication of the

PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES

pathogen in patients with pharyngitis would also decrease its transmission throughout the population, and theoretically lessen the incidence of these complications as well. Two of the streptococcal pharyngitis studies were conducted in adolescents/adults, and 2 in children. As the pathophysiology of the infection in children and adults is similar, the pathogen identical, and the pharmacokinetics of cefdinir in the populations very similar, study results in adolescents/adults and children can be used interchangeably to evaluate the effectiveness of a treatment in either population. The studies included in the cefdinir NDA thus support the use of this compound for the treatment of streptococcal pharyngitis in both children and adults with a treatment duration of 5 or 10 days.

Medical Officer's Conclusions:

- *GABHS are susceptible to cefdinir.*
- *Cefdinir, given as either a 5-day (BID) or 10-day (QD or BID) regimen, is as effective than penicillin in the eradication of GABHS from the throats of patients with streptococcal pharyngitis.*
- *Cefdinir, given as either a 5-day (BID) or 10-day (QD or BID) regimen, is equivalent to penicillin in symptomatic relief in streptococcal pharyngitis.*
- *The 5-day regimen appears to give somewhat lower eradication rates than the 10-day regimen.*
- *Cefdinir has not been studied for effectiveness in the prevention of rheumatic fever.*

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PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES

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NDA 50-739 (CEFDINIR)

600 MG QD OR 300 MG BID X 10 D VS.

PEN VK 250 MG QID X10 DAYS

PHARYNGITIS /TONSILLITIS-ADULTS

MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW

PROTOCOL 983-7

**PROTOCOL 983-7: COMPARISON OF THREE ANTIBIOTIC REGIMENS FOR THE TREATMENT OF
ACUTE PHARYNGOTONSILLITIS IN PATIENTS DUE TO GROUP A BETA HEMOLYTIC
STREPTOCOCCUS**

1) OBJECTIVES:

The objectives of this study were to evaluate the efficacy and safety of two 10-day dosage regimens of cefdinir (600 mg QD or 300 mg BID) versus a 10-day regimen of penicillin V-K (250 mg QID) in the treatment of patients with Group A β -hemolytic streptococcal (GABHS) pharyngitis/tonsillitis infections.

2) STUDY MANAGEMENT

Twenty-five centers in the United States and Canada participated in the study (table 1), which was monitored by Parke-Davis Pharmaceutical Research. The final protocol, dated July 23, 1992, was approved by the Institutional Review board or Ethical Committee for each site prior to enrollment of patients.

Amendment 1 to the protocol instructed patients to withhold antacid therapy for 2 hours before and after dosing to avoid cefdinir interaction with aluminum or magnesium in the antacid.

Addendum A described pharmacokinetic sampling to further characterize the pharmacokinetics of cefdinir in patients with pharyngitis. These results are summarized in RR 764-02336.

Addendum B made additions to the selection and exclusion criteria and to the precautions section to comply with Canadian Health Protection Bureau regulations. (Amendments apply to all study sites, whereas addenda apply only to specific sites.)

All study participants supplied written informed consent before they were enrolled. An investigator's meeting was held on September 19, 1992, to familiarize investigators with the protocol. On-site investigator's meetings were held separately for Sites 8 (February 23, 1993) and 18 (May 20, 1993). This study was conducted according to Good Clinical Practice Guidelines. Clinical laboratory and microbiological data were measured by a central laboratory. The first patient received the first dose of medication on September 30, 1992, and the last patient had the last follow-up visit on February 14, 1994.

The treatment code was broken by investigators for 2 patients. Patient 4 (983-7-16) was receiving cefdinir 600 mg QD when he experienced pneumonia. The investigator broke the blind in order to determine appropriate treatment. Patient 6 (983-7-24) was receiving cefdinir 300 mg QID when she experienced an allergic reaction. The investigator broke the blind to inform the patient which medication she had been taking. For all other patients, the blind was broken on December 21, 1994.

TABLE 1. List of Investigators

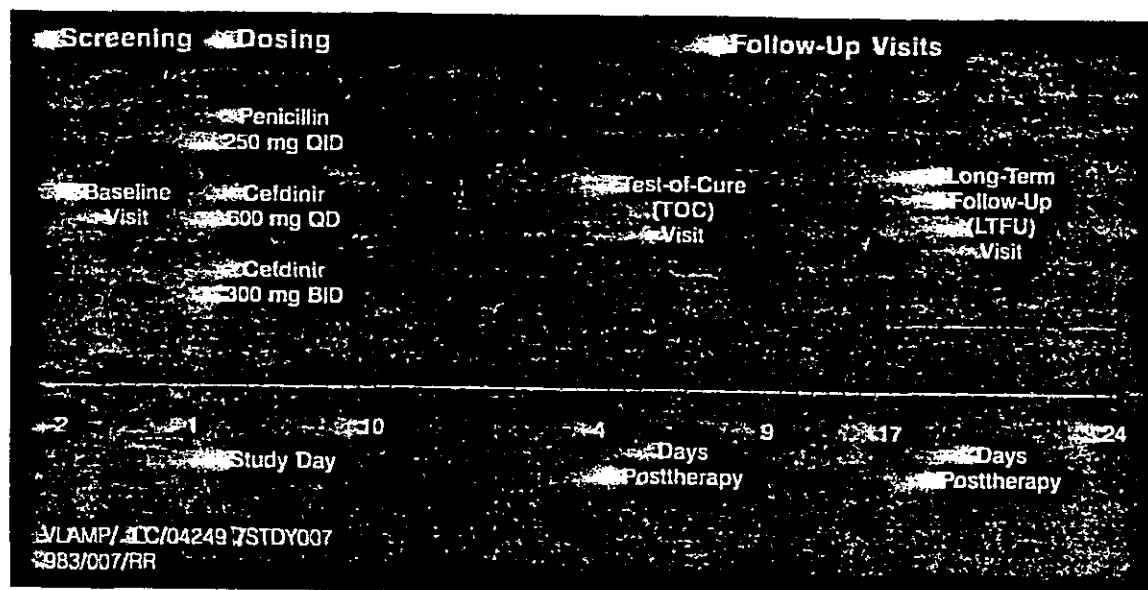
Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable
1	J. Adelglass	45	35	35
2	R. Chiulli	17	12	11
3	H. Collins	32	27	24
4	V. Elinoff	35	30	24
5	W. Gooch	108	87	78
6	D. Henry	90	79	73
7	J. Hedrick	45	44	43
8	E. Dattani	9	7	6
9	R. Knight	12	8	6
10	J. McCarty	108	99	86
11	S. McLinn	7	7	2
12	B. Cochran	23	22	13
	J. McCarty			
13	Z. Munk*	0	0	0
14	T. Littlejohn	72	62	37
15	R. Paster	38	32	29
16	A. Puopolo	51	41	39
17	J. Scott	25	18	7
18	F. Boucher	3	2	2
19	E. Rothstein	1	0	0
20	J. Salisbury	72	57	44
21	R. Simon	46	34	22
22	J. Finnegan	22	18	17
23	M. Sperling	45	40	38
24	G. Stein	6	4	2
25	S. Weakley	7	7	6
Total		919	772	644

* This site received drug but did not enroll any patients.

3) MATERIALS AND METHODS

3.1. Study Design

This was a double-blind, randomized, comparative, multicentre study with 3 parallel treatment groups (Figure 1). Patients with GABHS pharyngitis were randomly assigned to receive either cefdinir QD, cefdinir BID, or penicillin QID for 10 days. The protocol and Case Report Forms (CRFs) specified that efficacy assessments were to be performed once during the 5- to 9-day posttherapy interval (test-of-cure visit; TOC) and once during the 18- to 24-day posttherapy interval (long-term follow-up visit; LTFU). However, in some cases the TOC visit occurred on Day 15 and the LTFU visit on Day 28. These were actually Days 4 and 17 posttherapy, respectively, for patients who began BID or QID treatments midday on Day 1, and therefore did not finish treatment until Day 11. For purposes of analysis, the TOC window was widened to 4 to 9 days posttherapy and the LTFU window to 17 to 24 days posttherapy to include these patients.



3.1.1. Treatment

3.1.1.1. Materials

All study medications were provided by Parke-Davis Pharmaceutical Research and packaged individually for each patient. Cefdinir and penicillin capsules were identical, but were packaged differently, so to maintain blinding, placebo capsules were also packaged in 2 different ways to match both active medications.

3.1.1.2. Drug Administration

Patients were assigned randomly to receive 10 days of treatment with cefdinir QD, cefdinir BID, or penicillin QID (Table 3). Study medications were taken without regard to meals.

TABLE 3. Dosing Schedule

Treatment Group	Dose (Number of Capsules)			
	Morning	Noon	Afternoon	Evening
Cefdinir QD	2 × 300 mg cefdinir 1 × placebo	3 × placebo	3 × placebo	3 × placebo
Cefdinir BID	1 × 300 mg cefdinir 2 × placebo	3 × placebo	3 × placebo	1 × 300 mg cefdinir 2 × placebo
Penicillin QID	1 × 250 mg penicillin 2 × placebo	1 × 250 mg penicillin 2 × placebo	1 × 250 mg penicillin 2 × placebo	1 × 250 mg penicillin 2 × placebo

3.1.1.3. Methods of Assigning Patients to Treatment

An independent randomization schedule was prepared for each study center. The planned treatment group ratio at each site was 1:1:1 for cefdinir (600 mg QD and 300 mg BID) and penicillin (250 mg QID). A block size of 6 patients was used with 2 treatment replicates per block.

Study medication for each center was prelabeled with sequential patient numbers according to the randomization schedule. At each center, patients who met the entry criteria at screening were given the next consecutive patient number and dispensed the corresponding prelabeled study medication.

3.2. Patient Selection

3.2.1. Inclusion Criteria

Eligible patients were diagnosed with GABHS pharyngitis, were at least 13 years of age, and included males and nonpregnant, nonlactating females who were unable or unlikely to become pregnant during treatment (postmenopausal, surgically sterilized, sexually inactive, or using an effective method of birth control). A baseline rapid screening test had to be positive for streptococcus Group A antigen (CARDS® O.S.™ Strep A Direct Antigen Test,¹ Pain and erythema of the pharyngeal cavity were required symptoms for inclusion.

3.2.2. Exclusion Criteria

Patients were excluded from the study if they had:

- A history of rheumatic fever or rheumatic heart disease;
- Peritonsillar abscesses or other locally invasive disease;
- An illness thought to be terminal, or any condition that would preclude evaluation of the response to study medication;
- Hepatic disease, obstruction of the biliary tract, or bilirubin or hepatic enzyme levels >2 times the upper limit of normal;
- Serum creatinine >2 times the upper limit of normal or creatinine clearance <30 mL/min;
- Hypersensitivity to β -lactam drugs;
- A baseline pathogen known to be resistant to either study medication prior to randomization;
- A concomitant infection requiring systemic antimicrobial therapy;
- Receipt of any other investigational drug within the 4 weeks prior to this study;
- Receipt of cefdinir at any previous time; or
- Receipt of another systemic antibiotic within 3 days prior to receiving the first dose of study medication, or received a systemic antibacterial for which <5 half-lives had elapsed, whichever is longer.

3.2.3. Prohibited Medications or Precautions

Concurrent treatment with other systemic antibiotics or probenecid was not allowed during the study. Probenecid has been reported to inhibit renal tubular secretion of concomitantly administered cefdinir, resulting in a 50% increase in the elimination half-life.⁽¹⁹⁾

Concurrent dietary iron supplements, including iron-containing multivitamins, were also not allowed. This was because of concerns that the bioavailability of cefdinir may be decreased following the formation of a nonabsorbable cefdinir-iron complex in the gastrointestinal tract.⁽²⁰⁾

3.2.4. Guidelines for Patient Withdrawal

Treatment could be discontinued early because of lack of efficacy, an adverse event, a laboratory abnormality, lack of cooperation, resistant baseline pathogen, or negative baseline culture. Patients could also be withdrawn from the study after completing treatment but before the LTFU visit due to an adverse event. All patients who received therapy were to have a complete physical examination, clinical assessment of signs and symptoms, overall assessment of clinical efficacy, clinical laboratory tests, and a microbiologic assessment at the time of treatment discontinuation or withdrawal. Patients who received at least 9 days of study medication were also evaluated at the TOC and LTFU visits, provided they had received no additional antibacterial therapy in the interim.

3.3. Criteria for Evaluation

3.3.1. Efficacy

The primary efficacy parameters were the microbiologic and clinical response rates at the TOC visit. The microbiologic response rate was the percentage of patients in whom *S. pyogenes* was eradicated and the clinical response rate was the percentage of patients cured of specific signs and symptoms. Microbiologic and clinical response rates were also calculated for the LTFU visit, mainly to provide information on incidence of recurrence.

3.3.1.1. Microbiologic Response

At the TOC visit, patients were classified by their overall microbiologic response relative to baseline:

- **Eradication:** *S. pyogenes* eliminated,
- **Persistence:** *S. pyogenes* present, or
- **Not Assessable:** No *S. pyogenes* at baseline or no follow-up data.

At the LTFU visit, patients were classified by their overall microbiologic response relative to baseline and the TOC visit:

- **No Relapse:** Eradication of *S. pyogenes* at TOC and continued eradication at LTFU,
- **Relapse:** Eradication of *S. pyogenes* at TOC and reappearance at LTFU,
- **Persistence:** Persistence of *S. pyogenes* at TOC (these patients were automatically classified as having persistence at LTFU), or
- **Not Assessable:** No *S. pyogenes* at baseline or no follow-up data.

The microbiologic eradication rate was the percentage of patients with eradication of *S. pyogenes*. Each patient provided only 1 observation. Rates were calculated separately for the TOC and LTFU visits.

Microbiologic cultures and Susceptibility Testing:

Throat cultures for *S. pyogenes* at TOC and LTFU visit. Identification of *S. pyogenes* was confirmed by beta-hemolysis on sheep blood agar and sensitivity to bacitracin, or by antigen identification assay. A positive

culture was defined as 10 or more colonies on the isolation plate. Susceptibility testing was performed using 5 mcg cefdinir disks and 10 unit penicillin disk. Susceptibility was defined on the basis of zone diameter inhibition as follows

Diameter of Zones of Inhibition

Discs	Disc Content	Resistant	Moderately Susceptible	Susceptible
cefdinir	5 mcg disc	<=16mm MICequivalent<=4mcg/ml	17-19mm MICequivalent<=2 mcg/ml	>=20mm MICequivalent<=1mcg/ml
penicillin	10 unit disc	<=19 mm	20-27 mm	>=28 mm

Disc susceptibility testing followed the National Committee for Clinical Laboratory Standards (NCCLS) criteria defined in NCCLS document Vol.10, No. 7 M2-A4.

3.3.1.2. Clinical Response

Assessments of clinical response were performed by both the investigator and the sponsor. Different definitions of response were used for investigator and sponsor assessments but both were based on the following signs and symptoms: pharyngeal pain, pharyngeal erythema, exudate, swelling, fever, cervical lymph node tenderness, and dysphagia.

Investigator Assessment of Clinical Response at TOC:

- **Cure:** Absence or satisfactory remission of all signs and symptoms *and* no further antibacterial therapy required,
- **Failure:** No significant remission of signs and symptoms *and* further antibacterial therapy required, or
- **Not Assessable:** Unable to assess patient (no data).

Investigator Assessment of Clinical Response at LTFU:

- **Cure:** Absence or satisfactory remission of all signs and symptoms *and* no further antibacterial therapy required,
- **Failure/Recurrence:** Worsening or no significant remission of signs and symptoms *and* further antibacterial therapy required,
- **Not Assessable:** Unable to assess patient (no data).

The protocol specified that both investigator and sponsor assessments of patient clinical response would be made Based on the investigator's follow-up assessments of the clinical signs and symptoms (but before unblinding), the sponsor used a scoring algorithm to calculate an assessment of clinical efficacy. Thus, the recorded clinical signs and symptoms, or their calculated total score, provided the basis for all assessments of patient clinical response (see below).

NDA 50-739 (CEFDINIR)

PHARYNGITIS/TONSILLITIS-ADULTS

600 MG QD OR 300 MG BID X 10 D VS. MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW

PEN VK 250 MG QID X10 DAYS

PROTOCOL 983-7

The sponsor's clinical assessments, based on a quantitative evaluation of the total clinical score, were defined as follows: *(see next page.)*

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DETERMINATION OF CLINICAL SCORE

Form	Sum of (Symptom Weight) x (Symptom Score) for All Symptoms
Symptom Status	Symptom Score
Absent	0
Mild/Present	1
Moderate	2
Severe	3
Symptom	Symptom Weight
Pain	2
Erythema	2
Exudate	2
Swelling	2
Fever ^a	2
Cervical Lymph Node Tenderness	2
Dysphagia	2

^a Oral body temperature $\geq 101.4^{\circ}\text{F}$ or 38.5°C

Parko-Davis Pharmaceutical Research's determination of clinical outcome was based on the percent change in total clinical score from baseline.

The total clinical score was calculated for each observation based on the sign/symptoms using the following values for severity: Absent = 0, Mild = 1, Moderate = 2, and Severe = 3. The formula used was:

$$\text{Total Score} = (2) (\text{Pain}) + (2) (\text{Erythema}) + (2) (\text{Exudate}) + (2) (\text{Swelling}) + (2) (\text{Fever}) + (2) (\text{Cervical Lymph Node Tenderness}) + (2) (\text{Dysphagia})$$

The percent change from baseline was then calculated for each nonbaseline observation using the following:

$$\% \text{ Change} = 100 \times (\text{Observation Score} - \text{Baseline Score}) \div (\text{Baseline Score})$$

Symptoms with missing data either at baseline or a subsequent follow-up visit were not used in calculating the percent change from baseline at that particular visit.

Sponsor Assessment of Clinical Response at TOC:

- Cure: Decrease in the clinical score of $\geq 50\%$ relative to baseline,
- Failure: Decrease in the clinical score of $< 50\%$ relative to baseline,
- Not Assessable: No baseline signs/symptoms or no follow-up data.

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Sponsor Assessment of Clinical Response at LTFU:

- **Cure:** Cure at TOC and an increase in clinical score of <2 points relative to TOC *and* a decrease in clinical score of $\geq 50\%$ relative to baseline,
- **Failure/Recurrence:** Cure at TOC and an increase in clinical score of ≥ 2 points relative to TOC *or* a decrease in clinical score of $<50\%$ relative to baseline,
- **Not Assessable:** No baseline signs/symptoms or no follow-up data.

Symptoms that were not assessed at baseline or at a follow-up visit were not used in calculating percentage changes from baseline for that visit. If a patient fulfilled the criteria for a particular response, but had important or extenuating circumstances during the study (eg, very low scores at baseline), the computerized determination of clinical effectiveness could be changed by the sponsor prior to randomization code release. Further details on assessment override procedures are in Appendix D.1.

A combined investigator/sponsor clinical assessment was used as the primary measure of patient clinical response in the efficacy analyses (Table 4). If the investigator assessment at TOC was Not Assessable and quantitative clinical signs and symptoms data had been collected, the patient was reclassified according to the sponsor assessment. Investigator assessments of Cure and Failure were retained regardless of the sponsor assessment.

The combined investigator/sponsor clinical assessment at the LTFU visit depended not only on the investigator assessments at LTFU, but also on the combined investigator/sponsor clinical assessment at the TOC visit. For patients with a combined assessment of Cure at TOC, the investigator assessments of Cure and Recurrence took precedence over the sponsor assessment while investigator assessments of Not Assessable were reclassified according to the sponsor assessment. In contrast, patients with a combined investigator/sponsor assessment of Failure at TOC were considered failures in the combined investigator/sponsor clinical assessment at LTFU, regardless of investigator determination. (Patients assessed as failures by the sponsor at TOC were automatically sponsor failures at LTFU.)

TABLE 4. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU^{a,b}

Sponsor Assessment at TOC	Investigator Assessment at TOC		
	Cure	Failure	Not Assessable
Cure	Cure	Failure	Cure
Failure	Cure	Failure	Failure
Not Assessable	Cure	Failure	Not Assessable

Sponsor Assessment at LTFU	Investigator Assessment at LTFU		
	Cure	Failure/ Recurrence	Not Assessable
Cure	Cure	Recurrence	Cure
Failure	Cure	Recurrence	Failure
Recurrence	Cure	Recurrence	Recurrence
Not Assessable	Cure	Recurrence	Not Assessable

^a The combined assessments are shown in bold typeface.

^b Note: If a patient had a combined clinical assessment of Failure at the TOC visit, the patient was automatically a Failure on the combined assessment scale at the LTFU visit.

Medical officer note: I agree with the applicant's assessment scale. This scale was particularly useful when the investigator offered not assessable as an outcome. When this happened, the sponsor forced a cure or failure result based on a clinical score. The protocol was written initially with all patients including the non-assessable patients being thus scored. But subsequent to the development of the IDSA/FDA guidelines, this was changed in other pharyngitis protocols. The patients who had this scoring were not individually identified in the CANDAs except in the SAS data sets and retrievable by sequel assist).

The clinical cure rate was the percentage of patients rated as cured on the combined assessment scale. Each patient provided 1 observation. Clinical cure rates were calculated separately for the TOC and LTFU visit data.

MEDICAL OFFICER NOTE:

Subjects were selected on the basis of signs and symptoms of acute pharyngotonsillitis and a positive rapid test for Group A beta-hemolytic streptococci. Additional clinical criteria, such as a clinical score were further defined for all outcomes and were particularly useful for indeterminate outcomes. Multiple studies have been published attempting to derive a clinical algorithm for the diagnosis of pharyngitis due to Group A beta-hemolytic streptococci. Although these algorithms are of limited sensitivity, they suggest certain features more likely to associated with pharyngitis due to Group A beta-hemolytic streptococci. Further diagnostic tests such as antistreptolysin O or anti-DNAse B titers were not evaluated. While these tests are irrefutable evidence of infection due to Group A beta-hemolytic streptococci, they are also of limited utility because only a minority of patients will demonstrate significant antibody titer elevations.

Because people can be asymptomatic carriers of Group A beta-hemolytic streptococci, clinical scoring can decrease the bias in the study by potentially excluding a group of patients with pharyngitis due to other, often milder, usually viral causes who are carriers. The combination of clinical score and diagnostic serology would however have been best.

3.3.1.3. Appearance of New Pathogens

The appearance of a new pathogen was classified as:

Superinfection: Appearance of a pathogen other than the baseline strain of *S. pyogenes* in any culture up to and including TOC and <50% decrease or an increase in clinical score at the corresponding clinical assessment of signs and symptoms relative to baseline. Appearance of a new pathogen in any culture through TOC (including a different genotype of *S. pyogenes*) and a worsening of the clinical score relative to the previous visit also denoted superinfection. All superinfections were reviewed by the sponsor. If a patient had a new organism isolated in any postbaseline culture, but had no corresponding clinical assessment of signs and symptoms, the determination of pathogenicity was made by the sponsor.

- **Reinfection:** Appearance of a pathogen other than the baseline strain of *S. pyogenes* in the LTFU culture and classified clinically as Recurrence at LTFU; or
- **Not Assessable:** No follow-up data.

If a patient had a positive throat culture for *S. pyogenes* at TOC and/or LTFU, genotyping was performed to determine if the strain(s) present at TOC and LTFU was genetically identical to or different from the strain present at baseline.⁽²¹⁾ Genetically identical organisms were considered persistent from baseline. Genetically dissimilar organisms were considered superinfecting pathogens at TOC (if the clinical score increased or decreased by <50%) and reinfecting pathogens at LTFU (if the clinical classification was Recurrence).

3.3.2. Safety

The safety of cefdinir was assessed using adverse event data (occurrence, intensity, and relationship to study drug) and the results of physical examinations and clinical laboratory tests (hematology, blood chemistry, urinalysis). All patients randomized to treatment who received drug were evaluated for safety.

3.3.2.1. Adverse Events

Adverse events included any concurrent illness or symptom (except those related to pharyngitis) reported by the patient or noted by the investigator during the study. Laboratory abnormalities could be designated as adverse events at the judgement of the investigator. Adverse events were evaluated by the investigator for intensity (mild, moderate, or severe); relationship to drug treatment (definitely, probably, possibly, unlikely, definitely not, or insufficient information); frequency; duration; management of study medication; patient outcome (at last visit); and presence, frequency, and intensity relative to baseline. Clinical laboratory data were evaluated for values outside normal limits and for deviations of clinical importance (see Appendices A.6 and A.7)

MEDICAL OFFICER NOTE: This normal data was not attached in my review. It is located in the Cefdinir research report.

Each adverse event reported by a patient or noted by the investigator was recorded on a CRF. Investigator terms were converted to preferred COSTART IV dictionary terms for summary tables, but both the investigator and COSTART IV terms are included in patient listings.⁽²²⁾ All adverse events that began during the study or increased in intensity or frequency from baseline were summarized by number of patients. Adverse events that met these criteria are known as treatment-emergent signs and symptoms (TESS). Each patient who experienced a particular TESS adverse event was counted only once, regardless of how many times that patient may have experienced the same adverse event. TESS adverse events also were summarized for all patients by drug association, age, intensity, and study day of onset. Associated adverse events were those considered possibly, probably, or definitely related to study medication by the investigator. When summarized by drug association, a patient was counted once for each adverse event by the final investigator-reported relationship to study medication. When summarized by intensity, a patient was counted once for each adverse event by the maximum intensity recorded. All reports of adverse events (both TESS and non-TESS) for a patient are included in the Listing of Adverse Events.

A medical review of all adverse events that occurred during this study was conducted by Parke-Davis Pharmaceutical Research. Any experiences that suggested a significant hazard, contraindication, side effect, or precaution were categorized as serious. In accordance with FDA regulations, a serious adverse event included any experience that was fatal or immediately life-threatening; was severely or permanently disabling; required or prolonged inpatient hospitalization; or involved congenital anomaly, cancer, or overdose (intentional or accident). In addition, the following adverse events were categorized as serious events even though they did not meet the strict regulatory criteria described above:

- Anaphylaxis
- Blood dyscrasia
- Cardiac arrhythmia

- Collagen disorder (eg, LE syndrome, retroperitoneal fibrosis)
- Deafness
- Hemorrhage from any site
- Jaundice of any degree
- Myopathy
- Ophthalmic disorder (eg, blindness, cataract, keratitis, glaucoma, optic atrophy, retinal disorder)
- Pseudomembranous colitis
- Severe CNS/PNS disorder (eg, coma, seizures, dyskinesia, encephalopathy, neuropathy, paralysis)
- Severe dermatologic disorder (eg, exfoliative, desquamative, or vesiculobullous rashes, photosensitivity)
- Severe psychiatric disorder (eg, psychosis, drug dependence)
- Vasculitis

Beginning in December 1992 (approximately 3 months after study start) patients who discontinued study drug due to diarrhea were to be tested for *Clostridium difficile*.

Medical officer note. I concur with the applicants safety criteria.

3.3.2.2. Physical Examinations

The results from physical examinations performed at all visits were reviewed by the sponsor for clinically important adverse changes associated with treatment.

3.3.2.3. Clinical Laboratory Values

For each patient, baseline values for clinical laboratory parameters were determined prior to receipt of any study medication. Clinical laboratory measurements were recorded again at the TOC visit. These clinical laboratory values were assessed relative to standard normal values and the patient's baseline values. If a significantly abnormal value was noted at the TOC visit, the laboratory test was to have been repeated until the abnormality resolved or a reason for the abnormality was determined.

For each clinical laboratory parameter, the median differences between baseline and final laboratory values were determined and reviewed in both treatment groups.

Clinical laboratory values were also examined to determine if they were below, within, or above normal ranges. To identify any trend toward abnormal clinical laboratory values during the study, final laboratory values for all patients were categorized according to whether they decreased, increased, or remained within the same range (ie, above, within, or below normal values) as corresponding baseline values. For example, values changing from normal to high, from low to normal, or from low to high were all classified as Increase. This analysis of clinical laboratory values is referred to as "category shift changes" throughout this report.

All clinical laboratory results were also reviewed to identify markedly abnormal values at the patient's first posttherapy visit. Markedly abnormal is defined as a value of potential concern to a practicing physician and in need of evaluation or follow-up. Criteria used to define these values are contained in Appendix A.7.

3.3.3. Clinical Observations and Laboratory Measurements

The schedule of clinical observations and laboratory measurements is given below (Table 5).

TABLE 5. Clinical Observations and Laboratory Measurements

	Baseline	Day 1	Days 3-5	Day 10	Posttherapy Visits	
					Days 4-9 ^a	Days 17-24 ^b
Throat Swab for Strep Screen ^c	X					
Culture/Susceptibility Testing ^d	X		X		X	X
Medical History	X					
Physical Examination ^d	X				X	X
Clinical Assessment of Signs and Symptoms ^d	X		X		X	X
Investigator Assessment of Clinical Effectiveness ^d					X	X
Adverse Events and Concurrent Medications	X	X	X		X	X
Clinical Laboratory Tests ^{d,e}	X				X	X ^f
Dosing		X	X	X		

^a Test-of-cure (TOC) visit

^b Long-term follow-up (LTFU) visit

^c Must be positive for patients to enter study

^d Perform also after early treatment discontinuation or withdrawal (see Section 4.2.4).

^e See protocol, Section 5.2.5.

^f If abnormalities detected at the TOC visit

3.3.4. Data Acceptability and Evaluability

3.3.4.1. Method of Assigning Study Days

The first dose of study medication was taken on Day 1. Study days after Day 1 were numbered consecutively. Days before Day 1 were assigned consecutive negative numbers beginning with Day -1.

3.3.4.2. Data Acceptability

Medical Officer's Note: The appendices referred to in the subsequent pages, are in the cefdinir research report.

For purposes of data description and analysis, it was necessary to select baseline, TOC, and LTFU observations from among all available observations. Appendix D.1 describes the algorithm used to select data for display in tables and inclusion in analyses.

Occasionally during data review, patients were found who met 1 or more of the exclusion criteria (specified in the protocol for study entry) or who deviated from protocol instructions. The study manager and/or the medical monitor reviewed these cases to determine whether these patients would be excluded from efficacy analyses because of the protocol variation(s).

Specific criteria (Appendix A.8 in the Cefdinir research report) were used to determine protocol violations that affected the validity or availability of patient microbiologic or clinical assessments for analysis. Methods

used to identify data affected by protocol variations are discussed in Appendix D.1. Data from patients with 1 or more of these variations were excluded from some analyses and summary tables.

All safety data were evaluated.

3.3.4.3. Patient Populations for Analysis

Analysis populations examined in this report include evaluable (defined as patients who were microbiologically and clinically evaluable), clinically evaluable, modified intent-to-treat (MITT), and intent-to-treat (ITT). Each is described below.

Evaluable patients had no known protocol variations that might have affected the efficacy assessments at TOC (Appendix A.8). Patients who had microbiologic and/or clinical assessments done early (ie, before the follow-up visit window) or who took a concurrent antibacterial because they were early failures were not removed from the evaluable population for these reasons.

A subset of evaluable patients identified as "qualified patients" was examined at LTFU. Qualified patients were evaluable patients who did not have any additional protocol variations between the TOC and LTFU visits.

Patients in the clinically evaluable population had the correct indication and clinical evidence of infection at baseline, took study medication as prescribed, did not take nonstudy systemic antibacterial therapy for other concurrent infections, and had their clinical evaluations performed within the range of days specified in the protocol. Patients were not excluded from this data set if they had no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

Patients in the MITT population had the correct indication, received study medication, had *S. pyogenes* isolated from the pharyngeal area at baseline, and had a follow-up culture. The ITT and MITT populations at LTFU were the same as at TOC.

Patients in the ITT population were those randomized to treatment. Patients who had no baseline pathogen or no follow-up culture were considered to have microbiologic persistence in the ITT summaries and analyses. Similarly, patients who had no follow-up clinical assessment were categorized as failures in the ITT summaries and analyses.

3.3.5. Statistical Methodology

3.3.5.1. Sample Size

According to the sponsor, This double-blind, comparative study of cefdinir versus penicillin was designed with a sample size of 190 evaluable patients per randomized group for a total of 570 evaluable patients.

NDA 50-739 (CEFDINIR)

PHARYNGITIS / TONSILLITIS-ADULTS

600 MG QD OR 300 MG BID X 10 D VS.

MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW

PEN VK 250 MG QID X 10 DAYS

PROTOCOL 983-7

A microbiologic eradication rate of 90% across all randomized groups was assumed in the sample size calculations. Equivalence was to be assessed by comparing a two-tailed 95% confidence interval (CI) for the differences (cefdinir 600 mg QD minus cefdinir 300 mg BID, cefdinir 600 mg QD minus penicillin, and cefdinir 300 mg BID minus penicillin) in microbiologic eradication rates to a set of predetermined, fixed criteria for equivalence. Sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and penicillin microbiologic eradication rates at TOC, using this CI method.

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NDA 50-739 (CEFDINIR)

600 MG QD OR 300 MG BID X 10 D VS.

PEN VK 250 MG QID X10 DAYS

PHARYNGITIS /TONSILLITIS-ADULTS

MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW

PROTOCOL 983-7

3.3.5.2. Methods

Medical Officer's Note: I had sampled one hundred and twelve patients (approximately 10% of the sample size) in sequential unblinded fashion on this indication, including the evaluable and unevaluable group. The discrepancy rate was less than 1%, therefore validity of the data was accepted as submitted by the sponsor. For brevity, it is presented here and not in each individual report. The list of patients whose CFRs were examined at length, is noted below:

Random patient selection from entire database (evaluable+non-evaluable):

Study 983-7 (92 patient CFRs examined):

2 19 33 35 39 41 53 65 70 98 104 112 130 137 140 157 162 165 187
206 209 211 213 223 230 245 259 271 288 295 311 314 324 336 338 349 356 359
373 391 396 418 421 426 429 433 452 461 473 476 477 481 486 504 524 526 533
546 549 575 580 585 590 592 593 600 614 627 638 643 665 697 699 701 716 740
749 763 774 778 784 816 827 836 850 855 859 862 869 883 890 909

Study 983-58 (56 patient CFRs examined):

22 28 30 46 50 51 59 62 63 66 82 83 85 93 107 122 123 144 146
152 158 167 206 219 249 251 261 269 288 307 315 321 322 328 351 378 393 394
395 411 412 415 419 433 444 450 471 473 492 499 514 516 525 533 537 554

Study 983-51 (87 patient CFRs examined):

4 10 13 14 26 33 34 44 51 52 58 61 66 68 91 97 100 109 115
116 123 131 138 163 175 184 196 199 203 213 214 238 242 260 301 317 323 325
339 343 363 396 400 414 419 454 476 491 495 502 518 519 542 551 574 589 598
603 611 626 638 653 658 659 660 665 667 674 680 701 702 706 708 714 727 732
734 747 748 787 803 812 818 825 827 834 854

Study 983-56 (48 patient CFRs examined):

1 4 6 9 14 45 51 65 70 74 96 99 100 104 106 112 115 173 179
180 188 192 234 236 239 242 248 278 291 299 311 312 316 320 321 325 332 360
362 367 375 384 386 409 428 437 443 448

Efficacy

The efficacy objectives of this study were to estimate the microbiologic and clinical response rates of cefdinir QD, cefdinir BID, and penicillin in the treatment of patients with Group A β -hemolytic streptococcal

pharyngitis/tonsillitis infections, and to evaluate the response rates of cefdinir QD and cefdinir BID each versus penicillin based on predefined fixed criteria.

The primary outcome measures were the microbiologic eradication rate and the clinical cure rate by patient in the evaluable population at TOC. Data from the LTFU visit were summarized and presented as supporting information, but no inferential analyses were performed on LTFU data.

Descriptive statistics used in this study consisted primarily of frequency counts and response rates. Means, standard errors, minima, maxima, and medians were used where appropriate.

At baseline, the demographic data, microbiologic results, clinical signs and symptoms, and some history data were summarized to facilitate baseline treatment group comparisons.

Two methods of investigating treatment equivalence at TOC were used. One method was based on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient in the analysis, and were calculated as the total number of cures or eradications in the study population, divided by the total number of cases. The second method used a categorical modeling procedure to obtain center-adjusted estimates of the response rates and their standard errors. The model contained terms for study center, treatment group, and center-by-treatment interaction. The resulting parameter estimates were used to construct estimates of the treatment group response rates and standard errors in which each center was given equal weight.

The treatment difference was defined as cefdinir QD or BID minus penicillin. The estimated response rate differences and their standard errors were used to construct a two-tailed 95% confidence interval for the treatment difference, using a standard normal approximation. Each 95% confidence interval was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the 2 rates (pooled or center-adjusted) under comparison (Table 6). To demonstrate equivalence, each 95% confidence interval must contain 0 and its limits must fall within the indicated bounds.

TABLE 6. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Treatments are Equivalent if 95% Confidence Interval for Treatment Difference is Within Bounds
response rate > 90%	-10%, +10%
80% ≤ response rate ≤ 90%	-15%, +15%
response rate < 80%	-20%, +20%

Results of the 2 methods were compared for consistency. In this study, both methods agreed in all cases and the pooled analysis was presented as the final analysis.

An exploratory Cochran-Mantel-Haenszel (CMH) analysis adjusting for center was also performed to test treatment group differences in the microbiologic eradication and clinical cure rates. Pairwise comparisons among the treatment groups were made. Results of the Breslow-Day tests were reviewed in evaluating the consistency of the relationship between treatment and response among centers.

For each statistical procedure adjusting for center, study centers contributing 12 or fewer patients, or 2 or fewer patients in any treatment group, were pooled prior to analysis. Pooling was performed independently for each analysis population after any required data exclusions were made (Appendix D.1).

Patient microbiologic and clinical outcomes were visually inspected to confirm overall concordance of the 2 measures. The randomness of the discordant responses was evaluated using McNemar's test.⁽²⁵⁾

Statistical Reviewer's notes:

The sponsor's statistical plan is acceptable. However, unless center-to-center variations with respect to response rate is seen, 95% confidence intervals and equivalence criteria as outlined in Table 6 is taken to be the primary analysis. It is to be noted that the sponsor did not incorporate Yates' continuity correction factor in the calculation of confidence interval. Based on the sample sizes noted, it is not expected that this will impact in significant difference in the interval boundaries, so the sponsor's results have been accepted unless specified.

3.3.5.2.2. Safety

Safety data were summarized for all patients who received study medication. A CMH analysis, adjusting for center, was performed to compare each of the cefdinir treatment groups to penicillin with respect to the rates (ie, incidence) of all adverse events, drug-associated adverse events, diarrhea, and treatment discontinuations due to adverse events. The Breslow-Day test was reviewed in evaluating the consistency of the relationship between adverse events and treatment among centers.

4. PATIENT DEMOGRAPHICS, TREATMENT, AND DISPOSITION

4.1. Patient Characteristics

4.1.1. Patient Sample

RR 720-03460 contains the patient listings for this study. Listings contain all of the data collected on the CRFs and are organized by topic (eg, patient characteristics; infection history).

Approximately 1.5 to 2 times as many females than males entered this study (Table 7). Most patients were white and the median age was 27 years, with most patients in the 18 to <65 age group. There were no differences between treatment groups. Baseline characteristics of the evaluable population were similar to those of all patients.

TABLE 8. Patient Characteristics - Evaluable^a Patients
[Number (%) of Patients] as per applicant

Variable	Cefdinir				Penicillin		Total	
	QD N = 210		BID N = 217		N = 217		N = 644	
Sex								
Male	73	(34.8)	69	(31.8)	87	(40.1)	229	(35.6)
Female	137	(65.2)	148	(68.2)	130	(59.9)	415	(64.4)
CMH p-value	Cefdinir QD vs Penicillin = 0.256; Cefdinir BID vs Penicillin = 0.072							
Race								
White	181	(86.2)	182	(83.9)	186	(85.7)	549	(85.2)
Hispanic	16	(7.6)	21	(9.7)	19	(8.8)	56	(8.7)
Black	4	(1.9)	11	(5.1)	6	(2.8)	21	(3.3)
Asian	4	(1.9)	1	(0.5)	4	(1.8)	9	(1.4)
Other ^a	5	(2.4)	2	(0.9)	2	(0.9)	9	(1.4)
CMH p-value	Cefdinir QD vs Penicillin = 0.658; Cefdinir BID vs Penicillin = 0.829							
Age, yr								
Median	27.0		27.0		25.0		26.0	
Range	12-65		12-72		12-63		12-72	
Distribution								
6 to <13	1	(0.5)	1	(0.5)	2	(0.9)	4	(0.6)
13 to <18	46	(21.9)	45	(20.7)	55	(25.3)	146	(22.7)
18 to <65	162	(77.1)	170	(78.3)	160	(73.7)	492	(76.4)
≥65	1	(0.5)	1	(0.5)	0	(0)	2	(0.3)
CMH p-value	Cefdinir QD vs Penicillin = 0.274; Cefdinir BID vs Penicillin = 0.165							

^a Microbiologically and clinically

^b American Indian, East Indian, Hispanic/Caucasian, Laotian, Mexican, Portuguese, Samoan, Saudi Arabian

Statistical Reviewer's Notes:

Three treatment arms are balanced with respect to sex, race and age. There is a marginal imbalance in sex between Cefdinir Bid and Penicillin (p-value = 0.072), but that was not considered to be significant enough to warrant further analyses.

4.1.2. Confirmed Microbiologic Diagnosis and Baseline Susceptibility

At the baseline visit, *S. pyogenes* was isolated from throat swabs from 725 of 919 (79%) patients randomized to treatment. All *S. pyogenes* isolates were susceptible to both cefdinir and penicillin.

4.1.3. Clinical Signs and Symptoms

One patient in each treatment group did not have pharyngeal erythema at baseline. Otherwise, all patients who entered the study had both pain and erythema of the pharyngeal cavity, as required by the protocol. Most patients also had exudate, tonsillar swelling, dysphagia, and cervical lymph node tenderness. Approximately 16% of patients presented with fever. There were no apparent differences in baseline signs and symptoms between treatment groups, or between the ITT and evaluable patient populations.

4.1.4. Medical History and Secondary Diagnoses

There were no differences in prior or concurrent medical conditions between treatment groups. Approximately equal percentages of patients in each group had a history of pharyngitis in the 12 months preceding the study: 20% in the cefdinir QD group, 17% in the cefdinir BID group, and 19% in the penicillin group. Most patients had had only 1 prior episode in the 12 months preceding the study. No patients in the cefdinir QD group, 2 patients in the cefdinir BID group, and 6 patients in the penicillin group had had 3 or more episodes in the 12 months preceding the study.

4.1.5. Prior Medications for Pharyngitis

Three to 5% of patients in each treatment group had received other anti-infective medications for pharyngitis or tonsillitis within 30 days prior to the study. The most frequently used were penicillin and amoxicillin.

4.1.6. Concurrent Medications, Nondrug Therapies, Elective Surgeries/Procedures

Concurrent medications taken by at least 5% of patients included acetaminophen (26%), ibuprofen (21%), penicillin (5%), aspirin (5%), and Ortho-Novum (5% [norethindrone/ethinyl estradiol]).

No clinically relevant concurrent nondrug therapies, elective surgeries, or elective procedures were used or performed during this study.

4.2. Patient Treatment

The median number of days on study medication was 11 days in all treatment groups (Table 9). Patients in the cefdinir BID group and penicillin group who took their first dose in the afternoon or evening of Day 1 would have completed their course of treatment on Day 11. Other patients who missed doses during the 10-day course of treatment and took them at the end of the course also contributed to the patients whose exposure to study medication was greater than 10 days. Over 80% of patients in all treatment groups completed treatment in 10 or 11 days.

TABLE 9. Patient Exposure to Study Medication - All Patients
(Number of Patients)

Days of Study Medication	Cefdinir		Penicillin N = 310
	QD N = 305	BID N = 304	
1	1	3	0
2	4	1	2
3	7	5	6
4	6	6	10
5	7	6	2
6	4	4	6
7	8	9	7
8	4	2	2
9	4	3	4
10	88	91	88
11	160	163	170
12	7	4	3
13	1	0	2
14	2	0	0
16	1	0	0
Median	11	11	11
Unknown	1	7	8

4.3. Patient Disposition

Of the 919 patients who entered the study, 772 (84%) completed the treatment phase, 756 (82%) completed the TOC visit, and 632 (69%) completed the LTFU visit (Table 10).

TABLE 10. Patient Disposition - All Patients
[Number (%) of Patients]

Disposition	Cefdinir				Penicillin		Total	
	QD		BID					
Randomized to Treatment	305		304		310		919	
Withdrawn Prior to End of Treatment								
No Baseline Pathogen	28	(9.2)	23	(7.6)	26	(8.4)	77	(8.4)
Adverse Event ^a	9	(3.0)	13	(4.3)	4	(1.3)	26	(2.8)
Lack of Compliance	3	(1.0)	7	(2.3)	6	(1.9)	16	(1.7)
Failure at End of Therapy	2	(0.7)	1	(0.3)	5	(1.6)	8	(0.9)
Other/Administrative ^b	6	(2.0)	7	(2.3)	7	(2.3)	20	(2.2)
Completed Treatment ^c	25	(84.3)	253	(83.2)	26	(84.5)	772	(84.0)
	7				2			
Completed Follow-Up Visits ^c								
TOC	25	(82.3)	252	(82.9)	25	(81.6)	756	(82.3)
	1				3			
LTFU	21	(70.2)	219	(72.0)	19	(64.2)	632	(68.8)
	4				9			

^a Twelve other patients were withdrawn due to an adverse event after treatment but before the LTFU visit.

^b Reasons include medication errors or missed doses (5 patients), lost to follow-up (3), abnormal baseline laboratory values (5), patient decision (2), lost data (2), exclusionary medical history (1), previous enrollment on study (1), and site dropped (1).

^c Based on the investigator assessment of patient status at the end of treatment (CRF 10).

5. RESULTS

5.1. Protocol Variations

Protocol variations that did not exclude patients from the evaluable analyses included being <13 years old (4 patients were 12 years old), having a history of rheumatic fever (1 patient), entering the study out of numerical order (10 patients), having throat pain but not erythema at baseline (3 patients), and having baseline clinical laboratory values above the limit specified in the protocol (30 patients).

5.1.1. Efficacy Evaluations

Medical Officer's Note: Please note that the outcomes of the patients seen below have been changed :

Outcomes Changed by Medical officer

Patient No.	Applicant	FDA	REASON
70	MICRO: TOC/LTFU (Not Asse/Not Asse	MICRO: TOC/LTFU (Erad/Eradication	S. pyogenes was isolated at baseline with a non pathogen and was not considered
336	Clin: TOC/LTFU cure/cure	Clin: TOC/LTFU not asses/not ass	This patient cannot be assessed as a clinical cure when he was on amoxil concurrently
486	MICRO: TOC/LTFU (Not Asse/Not Asse	MICRO: TOC/LTFU Persis/Persi	S. pyogenes was isolated at baseline with a non pathogen(Candida) and was not considered
504	MICRO: TOC/LTFU (Not Asse/Not Asse	MICRO: TOC/LTFU Persis/Persi	S. pyogenes was isolated at baseline with a non pathogen(S. aureus) and was not considered
869	MICRO: TOC/LTFU (Not Asse/Not Asse	MICRO: TOC/LTFU Erad/Erad	S. pyogenes was isol with Serratia pathogen(S. aureus) and was not considered with

Patients were most often considered not evaluable because *S. pyogenes* was not isolated at baseline (Table 11). Other common reasons for exclusion from the evaluable analyses were that the clinical assessment of signs and symptoms at baseline or TOC was outside the range of days specified in the protocol (clinical assessment out of range), the culture at baseline or TOC was performed outside the range of days specified in the protocol (culture out of range), or the medication was not taken as prescribed. Evaluable patients were most frequently disqualified from LTFU because they missed the LTFU culture or their clinical assessment of signs and symptoms.

Patients excluded from analyses at either TOC or LTFU are summarized next.

	Cefdinir		Penicillin
	600 mg QD	300 mg BID	
Reasons For Exclusion From Evaluable Analyses at TOC			
Clinical Assessment Missed	1	9	8
Clinical Assessment Out of Range	38	33	39
Concurrent Antibacterial	6	5	7
Medication Not as Prescribed	32	30	28
No Baseline Signs or Symptoms	0	0	1
Prior Antibacterial	0	1	0
Randomization Violation	2	2	1
Culture Out of Range	34	30	33
Culture Missed	9	20	20
No Proven Pathogen	71	59	64
Total Not Evaluable	95	87	93
Reasons For Disqualification From Qualified Analyses at LTFU			
Clinical Assessment Missed	17	16	32
Clinical Assessment Out of Range	5	5	8
Concurrent Antibacterial	2	2	8
Culture Out of Range	5	5	9
Culture Missed	18	19	35
Total Disqualified	27	26	51

TABLE 12. Patients Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir		Penicillin
	600 mg QD	300 mg BID	
Intent-to-Treat (ITT)	305 (100.0)	304 (100.0)	310 (100.0)
Modified Intent-to-Treat (MITT)	232 (76.1)	234 (77.0)	237 (76.4)
Clinically Evaluable	252 (82.6)	253 (83.2)	256 (82.6)
Evaluable	210 (68.9)	217 (71.4)	217 (70.0)
Qualified	183 (60.0)	191 (62.8)	166 (53.5)

5.1.2. Safety Evaluations

All patients randomized to treatment received study medication and were included in the safety evaluations.

5.2. Efficacy

5.2.1. Overview

The response rates and confidence intervals presented in the efficacy results sections are estimates obtained from pooled analyses. Center-adjusted analyses were also performed and results are consistent between the 2 methods. A side-by-side comparison of all results from the 2 analysis methods can be found in Appendix D.1.

Cefdinir-treated patients had significantly higher microbiologic and clinical response rates than patients treated with penicillin except in the ITT population, in which cefdinir QD and BID had microbiologic eradication rates that were equivalent to penicillin. Cefdinir QD clinical cure rates were at least equivalent to penicillin while the cefdinir BID clinical cure rates were superior to penicillin in the ITT population. Cefdinir QD and cefdinir BID were equivalent based on the fixed criterion for equivalence, although observed microbiologic and clinical response rates were consistently higher for cefdinir BID than cefdinir QD. Relapse rates were low for all treatment groups, with cefdinir BID having the lowest relapse rate, followed by cefdinir QD, and finally penicillin.

5.2.2. Evaluable Analyses and Qualified Analyses

5.2.2.1. Test-of-Cure Visit (4-9 Days Posttherapy)

5.2.2.1.1. Microbiologic Eradication

The microbiologic eradication rates were 91% for the cefdinir QD group (192/210), 92% for the cefdinir BID group (199/217), and 83% for the penicillin group (181/217). According to the sponsor, the 95% CI about the difference between cefdinir QD vs penicillin (cefdinir QD minus penicillin) was (1.8%, 14.3%) and between cefdinir BID vs penicillin (cefdinir BID minus penicillin) was (2.1%, 14.5%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above zero. The exploratory CMH test showed that the eradication rates for both the cefdinir QD group and cefdinir BID group were significantly higher than the penicillin group ($p = 0.02$ for QD vs penicillin and $p = 0.01$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-5.5%, 5.0%), showing that these treatments were equivalent (fixed criteria $\pm 10\%$). All persistent pathogens were susceptible to assigned study drug except for 1 pathogen in the penicillin group with unknown susceptibility to penicillin.

Statistical Reviewer's notes:

The statistical calculations and derived inferences are acceptable.

5.2.2.1.2. Clinical Cure

The clinical response rates were 95% for the cefdinir QD treatment group (199/210), 96% for the cefdinir BID group (209/217), and 89% for the penicillin group (193/217). According to the sponsor, the 95% CI about the difference between cefdinir QD vs penicillin was (0.7%, 11.0%), and between cefdinir BID vs penicillin was (2.5%, 12.2%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above zero. The exploratory CMH test showed that the response rates for both cefdinir treatment groups were significantly higher than the penicillin group ($p = 0.02$ for QD vs penicillin and $p < 0.01$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-5.5%, 2.4%), showing that these treatments were equivalent (fixed criteria $\pm 10\%$).

The response rates were based on the combined investigator/sponsor assessment of clinical cure. Only 2 patients, both in the cefdinir BID treatment group, were considered Not Assessable by the investigator and thus were assessed according to the sponsor definition. One patient was assessed as Cure and the other as

Failure. The combined investigator/sponsor assessments for the other 642 evaluable patients were the same as the investigators' assessments.

Statistical Reviewer's notes:

The statistical calculations and derived inferences are acceptable.

5.2.2.1.3. Microbiologic Versus Clinical Response Rates

Most patients (86%; 556/644) had successful microbiologic and clinical responses (ie, microbiological eradication plus clinical cure); another 27 had failing responses (ie, persistent pathogen(s) plus clinical failure) (Table 13). Among those who had different microbiologic and clinical outcomes (eg, eradication plus failure or persistence plus cure), McNemar's test did not detect a significant pattern to the discordant assessments in the cefdinir QD group ($p = 0.09$), but did in the cefdinir BID ($p = 0.01$) and penicillin ($p = 0.02$) groups. In these groups, a disproportionate number of patients experienced a clinical cure, yet had a persistent pathogen. This may be due to a resolution of symptoms in the absence of complete eradication, or may represent a small number of patients who were reinfected with the identical strain of *S. pyogenes* prior to the TOC visit.

TABLE 13. Microbiologic Versus Clinical Response at TOC - Evaluable Patients-per applicant
(Number of Patients)

Microbiologic Response	Clinical Response	
	Cure	Failure
Cefdinir QD		
Eradication	187	5
Persistence	12	6
Cefdinir BID		
Eradication	196	3
Persistence	13	5
Penicillin		
Eradication	173	8
Persistence	20	16

Statistical Reviewer's notes:

The statistical calculations and derived inferences are acceptable.

5.2.2.2. Long-Term Follow-Up Visit (17-24 Days Posttherapy)**5.2.2.2.1. Microbiologic Eradication**

Medical Officer's Note: It was noted on the electronic submission, that the micro lab results did not mostly appear (except with local lab data) either in the CANDATA or the hard copy submission of the CRF. This was subsequently added as a hard copy NDA amendment. This was discussed in a teleconference with the sponsor on 4/11/97.

Of the qualified patients who had *S. pyogenes* eradicated at the TOC visit, 95% (166/175) in the cefdinir QD group, 96% (174/181) in the cefdinir BID group, and 92% (144/156) in the penicillin group also had microbiologic eradication at the LTFU visit. Thus, the observed relapse rate was higher in the penicillin group than in the cefdinir treatment groups.

5.2.2.2.2. Clinical Cure

In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 96% (175/183) for the cefdinir QD group, 98% (188/191) for the cefdinir BID group, and 93% (154/166) for the penicillin group. Clinical cure rates were based on the combined investigator/sponsor determination, which was identical to the investigator determination in this case.

5.2.3. Modified Intent-to-Treat Analyses**5.2.3.1. Test-of Cure Visit (4-9 Days Posttherapy)**

In the MITT population, the microbiologic eradication rates were 91% (212/232) for the cefdinir QD group, 92% (215/234) for the cefdinir BID group, and 84% (199/237) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir QD vs penicillin was (1.5%, 13.3%), and between cefdinir BID vs penicillin was (2.1%, 13.8%), showing that the MITT cefdinir treatment groups were superior to penicillin because the intervals lie above zero. The exploratory CMH test showed that the response rates for both cefdinir treatment groups were significantly higher than the penicillin group ($p = 0.02$ for QD vs penicillin and $p = 0.01$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-5.5%, 4.5%), showing that these treatments were equivalent (fixed criteria $\pm 10\%$).

Statistical Reviewer's notes:

The statistical calculations and derived inferences are acceptable.

5.2.4. Intent-to-Treat Analyses

5.2.4.1. Test-of-Cure Visit (4-9 Days Posttherapy)

5.2.4.1.1. Microbiologic Eradication

The ITT microbiologic eradication rates were 70% (212/305) for the cefdinir QD group, 71% (215/304) for the cefdinir BID group, and 64% (199/310) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir QD vs penicillin was (-2.1%, 12.7%), and between cefdinir BID vs penicillin was (-0.9%, 13.9%), showing that the ITT cefdinir treatment groups were equivalent to penicillin (fixed criteria $\pm 20\%$). The exploratory CMH test showed no significant difference between cefdinir and penicillin treatment ($p = 0.15$ for QD vs penicillin and $p = 0.06$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-8.5%, 6.1%), showing that these treatments were also equivalent (fixed criteria $\pm 20\%$).

Statistical Reviewer's notes:

The statistical calculations and derived inferences are acceptable.

5.2.4.1.2. Clinical Cure

The ITT clinical response rates were 90% (275/305) for the cefdinir QD treatment group, 92% (279/304) for the cefdinir BID group, and 85% (264/310) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir QD vs penicillin was (-0.2%, 10.2%), and between cefdinir BID vs penicillin was (1.6%, 11.6%), showing that cefdinir QD is at least equivalent to penicillin (fixed criteria $\pm 10\%$) and cefdinir BID is superior to penicillin because the interval lies above zero. The exploratory CMH test showed no significant difference between cefdinir QD vs penicillin treatment ($p = 0.06$) but did show that the response rate with cefdinir BID treatment was significantly higher than that of the penicillin group ($p = 0.01$). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-6.2%, 2.9%), showing that these treatments were equivalent (fixed criteria $\pm 10\%$).

Statistical Reviewer's notes:

The statistical calculations and derived inferences are acceptable.

5.2.4.2. Long-Term Follow-Up Visit (18-24 Days Posttherapy)

Both cefdinir groups had higher microbiologic eradication and observed clinical cure rates at LTFU than the penicillin group. The microbiologic eradication rates for the cefdinir QD, cefdinir BID, and penicillin groups were 60%, 61%, and 53%, respectively. The clinical cure rates for the cefdinir QD, cefdinir BID, and penicillin groups were 67%, 71%, and 58%, respectively.

5.2.5. Other Population Analyses

5.2.5.1. Clinically Evaluable Patients

In the clinically evaluable patient population, the cefdinir BID group had the highest clinical response rate (93%), followed by the cefdinir QD group (91%), and the penicillin group (85%). The 95% CI about the difference between cefdinir QD vs penicillin was (0.1%, 11.3%), and between cefdinir BID vs penicillin was (2.8%, 13.5%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above zero. The exploratory CMH test showed that the response rates of the cefdinir groups were significantly higher than the penicillin group ($p = 0.03$ for QD vs penicillin and $p < 0.01$ for BID vs penicillin). According to the sponsor, the 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-7.1%, 2.3%), showing that these treatments were equivalent (fixed criteria $\pm 10\%$).

Statistical Reviewer's notes:

The statistical calculations and derived inferences are acceptable.

5.2.5.2. Patients Who Took Iron During Treatment

Five patients took iron-containing vitamin supplements during cefdinir treatment. Two patients were in the cefdinir QD treatment group and both were evaluable at TOC. Both had a clinical assessment of Cure and both had eradication at TOC. Three patients who took iron were in the cefdinir BID treatment group. One of these patients was evaluable at TOC and had a clinical assessment of Cure but persistence of *S. pyogenes*. The other 2 patients were clinically assessed as Cure at TOC but were not evaluable because they had no *S. pyogenes* at baseline.

5.2.5.3. Patients Who Took Maalox® or Other Aluminum- or Magnesium-Containing Antacids During Treatment

Magnesium- or aluminum-containing antacids may interfere with the absorption of cefdinir.⁽²⁶⁾ Three patients took magnesium- and aluminum-containing antacids concomitantly with cefdinir. Two patients, both in the cefdinir QD group, were not evaluable because neither had *S. pyogenes* at baseline. One of these patients had a clinical assessment of Cure at TOC and the other was assessed as Failure. The third patient, in the cefdinir BID group, was evaluable and had eradication of *S. pyogenes* at TOC and a clinical assessment of Cure.

5.2.6. Summary of Efficacy Results

A summary of the statistical analyses is shown below (Table 14).

TABLE 14. Summary of Efficacy Analyses at TOC-per applicant

Pairwise Comparison	Population	Rates (%)	95% CI	Interpretation
Microbiologic Eradication				
QD vs Penicillin	Evaluable*	91 vs 83	1.8, 14.3	QD Superior
	MITT	91 vs 84	1.5, 13.3	QD Superior
	ITT	70 vs 64	-2.1, 12.7	Equivalent
BID vs Penicillin	Evaluable*	92 vs 83	2.1, 14.5	BID Superior
	MITT	92 vs 84	2.1, 13.8	BID Superior
	ITT	71 vs 64	-0.9, 13.9	Equivalent
QD vs BID	Evaluable	91 vs 92	-5.5, 5.0	Equivalent
	MITT	91 vs 92	-5.5, 4.5	Equivalent
	ITT	70 vs 71	-8.5, 6.1	Equivalent
Clinical Response				
QD vs Penicillin	Evaluable	95 vs 89	0.7, 11.0	QD Superior
	Clinically Evaluable	91 vs 85	0.1, 11.3	QD Superior
	ITT	90 vs 85	-0.2, 10.2	QD at Least Equivalent
BID vs Penicillin	Evaluable	96 vs 89	2.5, 12.2	BID Superior
	Clinically Evaluable	93 vs 85	2.8, 13.5	BID Superior
	ITT	92 vs 85	1.6, 11.6	BID Superior
QD vs BID	Evaluable	95 vs 96	-5.5, 2.4	Equivalent
	Clinically Evaluable	91 vs 93	-7.1, 2.3	Equivalent
	ITT	90 vs 92	-6.2, 2.9	Equivalent

* Primary efficacy analysis

Statistical Reviewer's notes:*The statistical calculations and derived inferences are acceptable.***5.2.6. Appearance of New Pathogens During the Study****5.2.6.1. Superinfections**

Two patients in the cefdinir QD group, 4 patients in the cefdinir BID group, and 6 patients in the penicillin group developed superinfections on or before the TOC visit (Table 15). All superinfecting pathogens in the cefdinir QD and BID groups were susceptible to cefdinir. In the penicillin group, 4 pathogens were susceptible to penicillin and 2 pathogens (*Staphylococcus aureus* and *Streptococcus* Group C) had unknown susceptibility.

TABLE 15. Patients With Superinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir 600 mg QD	Cefdinir 300 mg BID	Penicillin
Gram Positive			
<i>Streptococcus agalactiae</i>	0	0	1
<i>Staphylococcus aureus</i>	0	0	1
<i>Streptococcus pyogenes</i> *	1	1	0
<i>Streptococcus</i> Group C	0	3	3
<i>Streptococcus</i> Group F	1	0	0
β -Hemolytic <i>Streptococcus</i> , not Group A, B, C, F, or G	0	0	1

* Different genotype than baseline *S. pyogenes*

5.2.6.2. Reinfections

Two patients in the cefdinir QD group, 3 patients in the cefdinir BID group, and 5 patients in the penicillin group developed reinfections after the TOC visit (Table 16). All of the reinfecting pathogens were susceptible to the assigned study drug with the exception of 1 *S. pyogenes* isolate in the penicillin group, for which susceptibility was unknown.

TABLE 16. Patients With Reinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir 600 mg QD	Cefdinir 300 mg BID	Penicillin
Gram Positive			
<i>Streptococcus pyogenes</i> *	1	1	2
<i>Streptococcus</i> Type C	0	2	0
β -Hemolytic <i>Streptococcus</i> , not Group A, B, C, F, or G	1	0	2
Multiple			
<i>Streptococcus pyogenes</i> * + <i>Streptococcus</i> Type C	0	0	1

* Different genotype than baseline *S. pyogenes*

Medical Officer's Note: I agree with the different outcome responses by the sponsor.

5.3. Safety

5.3.1. Adverse Events

5.3.1.1. Overview

A total of 466 (51%) patients experienced at least 1 adverse event during this study (Table 17). The incidence was highest in patients treated with cefdinir QD, 55% of whom experienced an adverse event. In the cefdinir BID group, 52% of patients experienced an adverse event, and in the penicillin group, 45% of patients experienced an adverse event. During the 10-day treatment period, the incidence of adverse events was 43%, 39%, and 30% for the cefdinir QD, cefdinir BID, and penicillin groups, respectively. There was no significant difference in the incidence of adverse events between the cefdinir treatment groups, but the incidence of adverse events in the cefdinir QD group was significantly higher than the penicillin group ($p = 0.01$).

Statistical Reviewer's notes:

The safety profile is based on the reports submitted by the sponsor. It was felt that the sponsor had adequately responded to the issues and concerns so that no further analyses were felt warranted.

The incidence of associated adverse events showed a similar trend: 33%, 30%, and 18% of patients in the cefdinir QD, cefdinir BID, and penicillin groups, respectively. Both cefdinir treatment groups had a significantly higher incidence of associated adverse events than the penicillin group ($p < 0.001$ for cefdinir QD and $p = 0.001$ for cefdinir BID).

No deaths occurred during this study and only 3 patients (1 in the cefdinir QD group and 2 in the cefdinir BID group) experienced a serious adverse event. Twenty-six patients discontinued treatment as a result of an adverse event: 9 (3%) in the cefdinir QD group, 13 (4%) in the cefdinir BID group, and 4 (1%) in the penicillin group. The rate of treatment discontinuation was significantly higher for the cefdinir BID group than the penicillin group ($p = 0.02$). Twenty-one of the discontinuations were due to an associated adverse event. Twelve additional patients withdrew from the study because of adverse events after completing treatment but before the LTFU visit (3 patients treated with cefdinir QD, 6 treated with cefdinir BID, and 3 treated with penicillin). Three of these adverse events were considered drug-associated.

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TABLE 17. Summary of Adverse Events - All Patients-Applicant
[Number (%) of Patients]
(Page 1 of 2)

	Cefdinir		Penicillin N = 310
	QD N = 305	BID N = 304	
Adverse Events During Study			
All Adverse Events	169 (55.4)	157 (51.6)	140 (45.2)
Associated* Adverse Events	102 (33.4)	91 (29.9)	57 (18.4)
Adverse Events During Treatment			
All Adverse Events	130 (42.6)	118 (38.8)	93 (30.0)
Adverse Events by Sex^b			
All Adverse Events			
Male	65 (56.5)	41 (41.0)	51 (40.5)
Female	104 (54.7)	116 (56.9)	89 (48.4)
Associated Adverse Events			
Male	42 (36.5)	19 (19.0)	19 (15.1)
Female	60 (31.6)	72 (35.3)	38 (20.7)
Adverse Events by Race^c			
All Adverse Events			
White	144 (56.7)	136 (52.3)	115 (43.4)
Hispanic	13 (46.4)	15 (55.6)	14 (51.9)
Black	5 (45.5)	5 (35.7)	6 (54.5)
Asian	3 (50.0)	1 (100.0)	4 (80.0)
Other	4 (66.7)	0 (0.0)	1 (50.0)
Associated Adverse Events			
White	84 (33.1)	79 (30.4)	46 (17.4)
Hispanic	8 (28.6)	9 (33.3)	6 (22.2)
Black	4 (36.4)	2 (14.3)	3 (27.3)
Asian	2 (33.3)	1 (100.0)	2 (40.0)
Other	4 (66.7)	0 (0.0)	0 (0.0)
Adverse Events by Age^d			
All Adverse Events			
6 to <13 years	1 (100.0)	1 (100.0)	1 (50.0)
13 to <18 years	32 (50.0)	25 (41.7)	26 (33.8)
18 to <65 years	135 (56.5)	131 (54.1)	113 (48.9)
≥65 years	1 (100.0)	0 (0.0)	0 (0.0)
Associated Adverse Events			
6 to <13 years	0 (0.0)	1 (100.0)	0 (0.0)
13 to <18 years	15 (23.4)	10 (16.7)	8 (10.4)
18 to <65 years	86 (36.0)	80 (33.1)	49 (21.2)
≥65 years	1 (100.0)	0 (0.0)	0 (0.0)

- * Considered by the investigator to be possibly, probably, or definitely related to study medication
- ^b Percentages based on total numbers of males or females in a treatment group
- ^c Percentages based on total numbers of patients of each race in a treatment group
- ^d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.

TABLE 17. Summary of Adverse Events - All Patients-Applicant
 [Number (%) of Patients]
 (Page 2 of 2)

	Cefdinir		Penicillin
	QD N = 305	BID N = 304	N = 310
Adverse Events by Maximum Intensity*			
All Adverse Events			
Mild	122 (40.0)	100 (32.9)	91 (29.4)
Moderate	74 (24.3)	77 (25.3)	64 (20.6)
Severe	10 (3.3)	9 (3.0)	5 (1.6)
Associated Adverse Events			
Mild	73 (23.9)	55 (18.1)	36 (11.6)
Moderate	40 (13.1)	44 (14.5)	22 (7.1)
Severe	5 (1.6)	2 (0.7)	3 (1.0)
Serious Adverse Events			
	1 (0.3)	2 (0.7)	0 (0.0)
Deaths			
	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation of Treatment Due to Adverse Events			
All Adverse Events	9 (3.0)	13 (4.3)	4 (1.3)
Associated Adverse Events	6 (2.0)	11 (3.6)	4 (1.3)
Withdrawals After Treatment Due to Adverse Events			
All Adverse Events	3 (1.0)	6 (2.0)	3 (1.0)
Associated Adverse Events	0 (0.0)	2 (0.7)	1 (0.3)

* Patients with multiple adverse events were counted once in each applicable category.

5.3.1.2. All and Drug-Associated Adverse Events

More patients in the cefdinir treatment groups experienced adverse events related to the digestive system than to other body systems. The adverse event most frequently associated with cefdinir treatment was diarrhea, which was experienced by 19% of patients in both the cefdinir QD and BID treatment groups and was considered associated with cefdinir treatment in 17% of patients in each group. In the cefdinir QD treatment group, other adverse events that occurred in at least 3% of patients were headache (13% of patients); vaginal moniliasis (6% of women); nausea (7% of patients); infection (6% of patients); abdominal pain (5% of patients); vomiting (4% of patients); cough (3% of patients); and vaginitis (3% of women). In the cefdinir BID treatment group, adverse events in addition to diarrhea that occurred in at least 3% of patients were headache (10% of patients), vaginal moniliasis (8% of women), infection (6% of patients), nausea (5% of patients), and abdominal pain (3% of patients). Frequently occurring adverse events that were most often associated with either cefdinir treatment regimen were vaginal moniliasis and nausea.

Patients in the penicillin treatment group were most likely to experience adverse events in the body as a whole. Headache was the most frequent adverse event, occurring in 10% of patients. Other frequently occurring adverse events were nausea (5% of patients), diarrhea (4% of patients), and cough (4% of patients). The events most likely to be associated with penicillin treatment were diarrhea and nausea. The rates of occurrence of diarrhea were significantly higher in both cefdinir treatment groups than in the penicillin group ($p < 0.001$).

5.3.1.8. Deaths

No deaths occurred during this study.

5.3.1.9. Serious Adverse Events

One patient in the cefdinir QD group and 2 patients in the cefdinir BID group experienced a serious adverse event (Table 20). Only 1 of these events occurred during the treatment period, none was considered treatment-associated, and none resulted in treatment discontinuation. No patient in the penicillin group experienced a serious adverse event. Narratives for patients who experienced a serious adverse event are found in Appendix B.2.

TABLE 20. Serious Adverse Events - All Patients-Sponsor

Center	Patient Number	Age, Sex	Adverse Event*	Relationship to Study Medication*	Study Day of Onset	Intensity	Outcome
Cefdinir 600 mg QD							
4	18	29, F	Severe depression (Depression)	Unlikely	15	Severe	Recovered
Cefdinir 300 mg BID							
8	2	24, M	Infectious mononucleosis (Lymphocytosis)	Unlikely	2	Severe	Recovered
20	33	33, F	Bone fracture, leg (Accidental Injury)	Definitely not	13	Severe	Recovered/ Sequelae

* Investigator term (COSTART preferred term)

* Investigator assessment

NDA 50-739 (CEFDINIR)
600 MG QD OR 300 MG BID VS.
PEN VK 250 MG QID

PHARYNGITIS / TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-7

5.3.3. Clinical Laboratory Measurements

5.3.3.1. Changes From Baseline

The median difference between baseline and final clinical laboratory values was negligible for most laboratory parameters. WBC and polymorphonuclear leukocyte counts declined in all treatment groups, as would be expected with resolving infection. Platelet counts increased in all treatment groups but were within normal limits both at baseline and the final visit.

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Discussion:

Cefdinir treatment resulted in consistently higher microbiologic eradication and clinical cure rates than penicillin treatment, and statistical analyses showed that these differences were statistically significant in most populations, including the evaluable population. The cefdinir BID treatment group tended to be somewhat more effective than the cefdinir QD group, although these 2 dosage regimens were statistically equivalent in terms of response rates.

All *S. pyogenes* isolates were susceptible to both cefdinir and penicillin, so differential resistance cannot explain the difference in clinical cure or microbiologic eradication rates. However, penicillin is β -lactamase-sensitive, so it is possible for it to be destroyed by β -lactamase produced by commensal organisms in the pharynx before it can eradicate *S. pyogenes*. Also, while penicillin may inhibit the growth of GABHS, it may not be bactericidal, resulting in failure to completely eradicate the pathogen.⁽²⁷⁾ Lower response rates may also be a reflection of lack of compliance with the QID dosing regimen of penicillin, although in this study setting, all evaluable patients fulfilled the protocol criteria for compliance.

All 3 treatments were well-tolerated. The overall incidence of adverse events was 55% for the cefdinir QD treatment group, 52% for the cefdinir BID treatment group, and 45% for the penicillin group. The majority of adverse events were mild or moderate; only 3% of patients in both of the cefdinir groups and 2% of patients in the penicillin group experienced a severe adverse event. The highest incidence of drug-associated adverse events occurred in cefdinir QD-treated patients (33%), followed by cefdinir BID-treated patients (30%), and the lowest incidence in penicillin-treated patients (18%). Only 2% of events in the cefdinir QD group, and 1% in each of the cefdinir BID and penicillin groups were considered by the investigators to be severe. Diarrhea was the adverse event most frequently associated with cefdinir treatment, occurring in 17% of patients in both the QD and BID treatment groups. Other frequently occurring cefdinir-associated adverse events included vaginal moniliasis and nausea. This is consistent with the safety profile of cephalosporins seen in other studies.^(13,28,29) In contrast, treatment-associated diarrhea was also one of the most frequently occurring adverse events in the penicillin group, but it occurred in only 4% of patients. Other penicillin-associated adverse events that occurred most frequently were nausea and headache.

Three patients, 1 in the cefdinir QD group and 2 in the cefdinir BID group, experienced a serious adverse event, none of which were considered drug-related or resulted in treatment discontinuation. No deaths occurred during this study. Treatment discontinuation due to drug-related adverse events occurred in a small percentage of patients in all treatment groups; 2% in the cefdinir QD group, 4% in the cefdinir BID group, and 1% in the penicillin group. Thus, slightly more cefdinir-treated patients discontinued treatment prematurely than did penicillin-treated patients.

Rates of successful courses of therapy can also be calculated from the number of patients who completed treatment and had their baseline pathogen eradicated. Conversely, an unsuccessful course of treatment was defined as one in which a patient was unable to complete treatment or had microbiologic persistence. By this method of comparing treatment groups, which combines efficacy and safety data, cefdinir still has a greater success rate than penicillin, with rates of 86% (QD) and 88% (BID) versus 80% (penicillin).

The results of this study show that penicillin may no longer be the drug of choice in the treatment of streptococcal pharyngitis in adults. The rising failure rate of penicillin treatment has prompted concerns that rheumatic fever and other serious complications of bacterial pharyngitis may once again become a serious public health issue.^(30,31) In addition, the waning ability of penicillin to completely eradicate *S. pyogenes* may give rise to a carrier state in a portion of the population.⁽²⁵⁾ The sponsor suggests that the superior microbiologic eradication rate of cefdinir suggests that it is the drug of choice for the treatment of this disease.

NDA 50-739 (CEFDINIR)
600 MG QD OR 300 MG BID VS.
PEN VK 250 MG QID

PHARYNGITIS / TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-7

7. CONCLUSIONS

- Cefdinir 600 mg QD and 300 mg BID are more effective microbiologically and clinically than penicillin in the treatment of GABHS pharyngitis in adult patients.
- Although the incidence of adverse events is greater with cefdinir than penicillin, cefdinir is well-tolerated by most patients. Most adverse events experienced by cefdinir-treated patients are mild and do not require treatment discontinuation.

Medical Officer's Note: The Reviewer agrees with the design and conduct of the clinical study as presented by the applicant.

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NDA 50-739 (CEFDINIR)
600 MG QD OR 300 MG BID VS.
PEN VK 250 MG QID

PHARYNGITIS / TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-7

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NDA 50-739 (CEFDINIR)
600 MG QD OR 300 MG BID VS.
PEN VK 250 MG QID

PHARYNGITIS / TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-7

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NDA 50-739 (CEFDINIR)
300 MG BID X5DAYS
PEN VK 250 MG QID X10 DAYS

PHARYNGITIS/TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-58

II. PROTOCOL 983-58: AN INVESTIGATOR-BLINDED, RANDOMIZED, COMPARATIVE, MULTICENTER STUDY OF A 5-DAY REGIMEN OF CEFDINIR VERSUS A 10-DAY REGIMEN OF PENICILLIN V IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS/TONSILLITIS INFECTIONS IN ADULT PATIENTS

1. OBJECTIVES:

The objectives of this study were to evaluate the efficacy and safety of a 5-day dosage regimen of cefdinir (300 mg BID) versus a 10-day regimen of penicillin V (250 mg QID) in the treatment of adult (≥ 13 years) patients with Group A β -hemolytic streptococcal pharyngitis/tonsillitis infections.

2. STUDY MANAGEMENT

Twenty-three centers in the United States, each with identical protocols and case report forms (CRFs), participated in the study monitored by Parke-Davis Pharmaceutical Research. This study was conducted according to Good Clinical Practice Guidelines. Investigators met with representatives of Parke-Davis individually between July 8, 1994, and December 13, 1994, to review the protocol. The final protocol, dated May 24, 1994, was approved by the Institutional Review Board at each site prior to enrollment of patients. Informed consent was obtained from each patient (or guardian) prior to enrollment in the study. Clinical laboratory and microbiological data were measured by a central laboratory.

The first patient received the first dose of medication on July 26, 1994, and the last patient had the last follow-up visit on April 6, 1995. No treatment codes were broken during this study.

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TABLE 1. List of Investigators

Center 983-58-	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable ^a
1	J. Adelglass	20	14	14
2	H. Collins	11	9	7
3	V. A. Elinoff	20	20	18
4	W. M. Gooch	85	74	69
5	J. H. Hedrick	10	7	6
6	D. C. Henry	119	97	96
7	J. McCarty	82	74	58
8	R. Z. Paster	32	26	20
9	A. D. Puopolo	31	30	25
10	M. J. Sperling	15	12	12
11	B. Cochran	20	17	14
12	S. Wiederhold	18	18	17
13	M. Drechobl	17	14	14
14	D. McCluskey	17	14	14
15	T. W. Littlejohn	19	17	17
16	F. Mazzone	8	7	6
17	S. Roberts	13	11	8
18	J. Ondrejicka ^b	0	0	0
19	R. Black ^b	0	0	0
20	J. Downing	5	5	5
21	J. D. Smucker	3	2	2
22	L. Kirkegaard	2	2	2
23	R. Gore	11	9	8
Total		558	479	432

^a Microbiologically and clinically evaluable^b Investigator received drug but did not enroll patients.

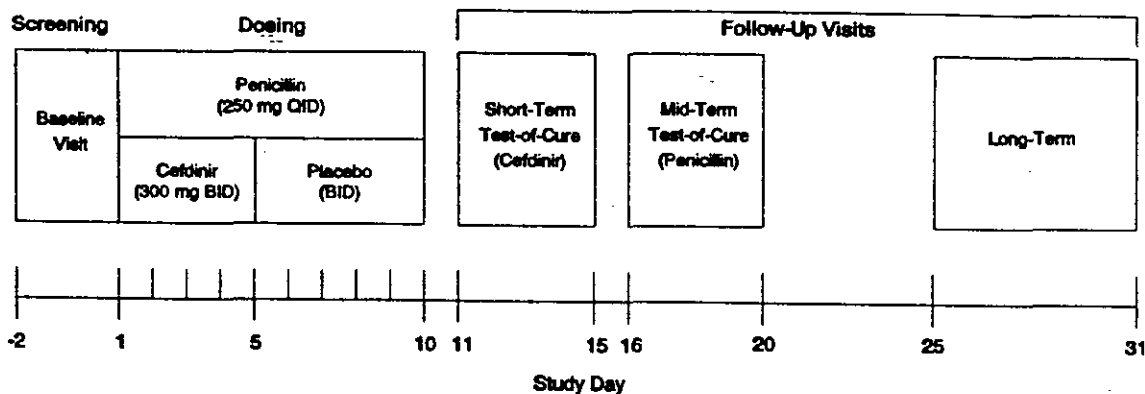
3. MATERIALS AND METHODS

3.1. Study Design

This was an investigator-blinded, randomized, comparative, multicenter study. Adult patients (aged 13 years or older) with GABHS pharyngitis/tonsillitis were randomly assigned to receive either cefdinir capsules (300 mg BID) for 5 days followed by placebo for 5 days or penicillin capsules (250 mg QID) for 10 days (Figure 1). According to the protocol, the test-of-cure (TOC) visit was to occur 6 to 10 days after active study drug treatment was complete (Study Days 11-15 for cefdinir; Study Days 16-20 for penicillin). However, in some cases patients began treatment at midday on Day 1 and therefore, did not finish study medication until Day 6 (if given cefdinir) or Day 11 (if given penicillin). In order to include these patients in the analyses, the TOC window was widened to 5 to 10 days after completion of study drug (Study Days 11-16 for cefdinir and Study Days 16-21 for penicillin). The long-term follow-up (LTFU) visit was to occur within Study Days 25 through 31 for both treatment groups. Patients were to keep a diary (case report form) to record their assessment of throat pain (absent, mild, moderate, severe) at baseline and on each day of study treatment.

NDA 50-739 (CEFDINIR)
300 MG BID X5DAYS
PEN VK 250 MG QID X10 DAYS

PHARYNGITIS/TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-58



VLAMP/CLC/121295/STUDY056
983/058/RR
HGW3/983.PRS/01

FIGURE 1. Study Design

3.1.1. Treatment

3.1.1.1. Materials

All study medications were provided by Parke-Davis Pharmaceutical Research in capsule or tablet form and packaged individually for each patient (Table 2). Each patient received 2 bottles containing medication, 1 marked for Days 1 to 5 and 1 marked for Days 6 to 10. For those patients in the cefdinir treatment group, the first bottle contained capsules with active drug and the second contained placebo capsules that matched the cefdinir capsules. Cefdinir or placebo was administered BID. For patients in the penicillin treatment group, both bottles contained penicillin tablets which were administered QID.

TABLE 2. Study Medication

Medication	Lot	Formulation
Cefdinir 300-mg Capsules	CR 0470393	134393-25
Placebo Capsules	CM 0520494	14964-1PAM2
	CM 1541092	14964-1PAM2
Penicillin 250-mg Tablets	5EE30A	Marketed
	8MA90N	Marketed

3.1.1.2. Drug Administration

Patients were randomly assigned to receive 5 days of treatment with cefdinir (300 mg BID) followed by 5 days of placebo (BID) or 10 days of treatment with penicillin (250 mg QID).

NDA 50-739 (CEFDINIR)
300 MG BID X5DAYS
PEN VK 250 MG QID X10 DAYS

PHARYNGITIS/TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-58

MEDICAL OFFICER'S NOTE: The following sections are identical to protocol 983-7. Please refer to the 983-7 review for details.

3.1.1.3. Method of Assigning Patients to Treatment

3.2. Patient Selection

3.2.1. Inclusion Criteria

3.2.2. Exclusion Criteria

3.2.3. Prohibited Medications or Precautions

3.2.4. Guidelines for Treatment Discontinuation

3.3. Criteria for Evaluation

3.3.1. Efficacy

3.3.1.1. Microbiologic Response

3.3.1.2. Clinical Response

Medical Officer's note, please refer to the table in Protocol 7 with all the patients that were given a combined score.

3.3.1.3. Appearance of New Pathogens

3.3.1.4. Symptomatic Relief of Throat Pain

3.3.2. Safety

3.3.2.1. Adverse Events

3.3.2.2. Physical Examinations

3.3.2.3. Clinical Laboratory Values

3.3.3. Clinical Observations and Laboratory Measurements

The schedule of clinical observations and laboratory measurements is shown in Table 4.

MEDICAL OFFICER'S NOTE: Please note the minor changes in this table as compared with protocol 7.

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TABLE 4. Clinical Observations and Laboratory Measurements

	Baseline	Day 1	Days 3-5	Day 5	Day 6	Day 10	Posttherapy Visits		
							STFU	MTFU	LTFU
							Days 11-15 ^a	Days 16-20 ^b	Days 25-31
Throat Swab for Strep Screen ^a	X								
Culture/Susceptibility Testing ^d	X						X	X	X
Medical History	X								
Physical Examination ^d	X						X	X	X
Clinical Assessment	X						X	X	X
Adverse Events and Concurrent Medications	X	X	X			X	X	X	
Telephone Call to Patient			X						
Clinical Laboratory Tests ^{a,f}	X						X	X ^d	X ^d
Dosing (Cefdinir)		X	X						
Dosing (Placebo)					X	X			
Dosing (Penicillin)		X	X		X				

STFU = Short-term follow-up visit.

MTFU = Mid-term follow-up visit.

- Test-of-cure (TOC) visit, cefdinir
- Test-of-cure (TOC) visit, penicillin
- Must be positive for patients to enter study
- Performed also after early treatment discontinuation or withdrawal (see Section 4.2.4).
- See protocol, Appendix A.2.
- If abnormalities detected at the TOC visit

NDA 50-739 (CEFDINIR)
300 MG BID X5DAYS
PEN VK 250 MG QID X10 DAYS

PHARYNGITIS/TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-58

3.3.4. Data Acceptability and Evaluability

3.3.4.1. Method of Assigning Study Days

3.3.4.2. Data Acceptability

3.3.4.3. Patient Populations for Analysis

3.3.5. Statistical Methodology

3.3.5.1. Sample Size

Medical Officer's Note: This investigator-blinded, comparative study of cefdinir versus penicillin was designed with a sample size of 190 evaluable patients per randomized group for a targeted total of 380 evaluable patients. Other details of sample size calculation are the same.

4.3.5.2. Methods

Medical Officer's Note: please refer to the list of patients in the random patient selection listed in protocol 7.

Efficacy:

Medical Officer's Note: The only differences noted were the following: Study centers contributing 8 or fewer patients, or 2 or fewer patients in any treatment group, were pooled for center-adjusted analyses. Pooling was performed independently for each analysis population after any required data exclusions were made (Appendix D.1).

3.3.5.2.2. Safety

4. PATIENT DEMOGRAPHICS, TREATMENT, AND DISPOSITION

4.1. Patient Characteristics

4.1.1. Patient Sample

TABLE 7. Patient Characteristics - Evaluable^a Patients
[Number (%) of Patients]

Variable	Cefdinir N = 218	Penicillin N = 214	Total N = 432	CMH p-value
Sex				0.265
Male	94 (43.1)	81 (37.9)	175 (40.5)	
Female	124 (56.9)	133 (62.1)	257 (59.5)	
Race				0.711
White	196 (89.9)	191 (89.3)	387 (89.6)	
Black	7 (3.2)	5 (2.3)	12 (2.8)	
Asian	4 (1.8)	5 (2.3)	9 (2.1)	
Hispanic	9 (4.1)	12 (5.6)	21 (4.9)	
Other ^b	2 (0.9)	1 (0.5)	3 (0.7)	
Age, years				0.920
Median	26	26	26	
Range	(13-76)	(13-64)	(13-76)	
Distribution:				
13 to <18	60 (27.5)	56 (26.2)	116 (26.9)	
18 to <65	156 (71.6)	158 (73.8)	314 (72.7)	
≥65	2 (0.9)	0 (0.0)	2 (0.5)	

- ^a Microbiologically and clinically
- ^b Biracial, Chinese, Eastern Indian

Statistical Reviewer's notes:

Two treatment arms are balanced with respect to sex, race and age of the enrolling population.

4.1.2. Confirmed Microbiologic Diagnosis and Baseline Susceptibility

At the baseline visit, *S. pyogenes* was isolated from throat swabs from 484 of 558 (87%) patients randomized to treatment. All *S. pyogenes* isolates were susceptible to both cefdinir and penicillin. Initially, 7 (1%) of the isolates were reported by the reference laboratory as intermediately sensitive to penicillin. However, these samples were found to be fully sensitive to penicillin when reanalyzed at the sponsor's request.

4.1.3. Clinical Signs and Symptoms

All patients who entered the study had both pain and erythema of the pharyngeal cavity, as required by the protocol. Most patients also had exudate, tonsillar swelling, dysphagia, and cervical lymph node tenderness. Approximately 16% of patients presented with fever. Baseline signs and symptoms were similar between treatment groups and patient populations.

4.1.4. Medical History and Secondary Diagnoses

There were no differences in significant medical/surgical history between the treatment groups. The most commonly reported history items were headache, allergic rhinitis, asthma, bronchitis, and nasal congestion. Approximately equal numbers of patients in each group had a history of pharyngitis in the 12 months preceding the study: 19% in the cefdinir group and 16% in the penicillin group. Most patients with a history of pharyngitis had only 1 prior episode in the 12 months preceding the study. Only 1 patient in the cefdinir group and 4 patients in the penicillin group had 3 prior episodes, and 2 patients in the penicillin group had 4 or more prior episodes in the 12 months preceding the study.

4.1.5. Prior Medications for Pharyngitis

Eight patients in the cefdinir group and 10 patients in the penicillin group had received other anti-infective medications for pharyngitis or tonsillitis within 30 days prior to the study. The most frequently used were amoxicillin and penicillin.

4.1.6. Concurrent Medications, Nondrug Therapies, Elective Surgeries/Procedures

The most commonly used concurrent medications were acetaminophen (25%), ibuprofen (24%), and aspirin (7%). No clinically relevant concurrent nondrug therapies, elective surgeries, or elective procedures were used or performed during this study.

4.2. Patient Treatment

The majority of patients in the cefdinir group (154) finished the complete course of study medication on Day 10, which indicates that they completed cefdinir on Day 5. Most penicillin-treated patients (180) completed therapy on Day 11. Patients who took their first dose of study medication in the afternoon or evening of Day 1 would have completed their course of treatment on Day 11. Patients who missed doses during the course of treatment and took them at the end of the course account for the number of patients whose duration of exposure to study medication was longer than that specified in the protocol. Eighty-three percent of patients in the cefdinir treatment group completed the entire course of treatment (active drug followed by

placebo) on Day 10 or 11. Eighty-one percent of patients in the penicillin treatment group completed the course of treatment on Day 10 or 11.

4.3. Patient Disposition

Of the 558 patients who entered the study, 479 (86%) completed the treatment phase, 461 (83%) completed the TOC visit, and 378 (68%) completed the LTFU visit (Table 9). It should be noted that 2 patients in the cefdinir treatment group (Patient 63, Center 4; and Patient 62, Center 9) who are included in the number given as withdrawn from treatment due to an adverse event actually discontinued during the placebo phase, and therefore did complete the course of cefdinir. The percentage of patients completing the treatment phase was similar in the cefdinir and penicillin groups (87% and 85%, respectively).

TABLE 9. Patient Disposition - All Patients
(Number (%) of Patients)

Disposition	Number (%) of Patients					
	Cefdinir		Penicillin		Total	
Randomized to Treatment	278		280		558	
Withdrawn Prior to End of Treatment						
Lack of Compliance	5	(1.8)	9	(3.2)	14	(2.5)
Lack of Efficacy	3	(1.1)	1	(0.4)	4	(0.7)
No Baseline Pathogen	15	(5.4)	19	(6.8)	34	(6.1)
Adverse Event	7*	(2.5)	6	(2.1)	13	(2.3)
Other/Administrative*	6	(2.2)	8	(2.9)	14	(2.5)
Completed Treatment†	242	(87.1)	237	(84.6)	479	(85.8)
Completed Follow-Up Visits						
TOC‡	249	(89.6)	212	(75.7)	461	(82.6)
LTFU	193	(69.4)	185	(66.1)	378	(67.7)

- * Includes 2 patients who were withdrawn during placebo phase of treatment.
- * Reasons include exclusionary baseline laboratory values (7 patients), lost to follow-up (4), medication error (1), patient withdrawal of consent (1), and previous enrollment in cefdinir study (1).
- * Based on investigator assessment of patient status at end of treatment
- * Short-term follow-up visit for cefdinir-treated patients; mid-term follow-up visit for penicillin-treated patients

5. RESULTS

5.1. Protocol Variations

The most common protocol variation was the enrollment of patients with $\geq 2 \times$ ULN for baseline aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values and/or failure to withdraw such patients from treatment when follow-up tests confirmed the baseline results (18 patients). A second protocol variation involved patients enrolled out of numerical sequence. At Site 6, 2 patients (Patients 30 and 61) were enrolled with a patient number 1 digit higher than they should have had according to their study start dates. At Site 7, Patient Numbers 67 to 80 were not used because the date on which these numbers would have been assigned was later than the "Use Before" date of the study drug (penicillin) which was randomly assigned to this group of numbers. New medication bottles were supplied for Patient Numbers 81 through 140 containing penicillin with a later "Use Before" date. Finally, at Site 9, the Patient Number 9 was inadvertently excluded by the investigator. None of these protocol variations were considered intentional by the study sponsor.

Statistical Reviewer's notes:

The Medical Officer agreed with the outcome measures of patients, as classified by the sponsor. In 10% of the patients selected randomly from the database, no discrepancy was found. Thus the sponsor's results and inferences are accepted, unless specified. It is to be noted that the sponsor did not incorporate Yates' continuity correction factor in calculation of confidence intervals, but based on the underlying sample sizes, this is not expected to result in any significant changes.

5.1.1. Efficacy Evaluations

Patients were most often considered not evaluable because *S. pyogenes* was not isolated at baseline (Table 10). Other common reasons for exclusion from the evaluable analyses were that the clinical assessment of signs and symptoms or the throat culture were performed outside the range of days specified in the protocol for baseline or TOC visits. Evaluable patients were most frequently disqualified from LTFU because they missed their clinical assessment of signs and symptoms or follow-up throat culture. The definition of each exclusion and disqualification criterion is given in Appendix A.8. A summary of the number of patients included in the efficacy analysis for each population is given in Table 11.

TABLE 10. Reasons Patients Were Not Evaluable at TOC or Were Disqualified at LTFU
(Number of Patients)

	Cefdinir	Penicillin
Reasons For Exclusion From Evaluable Analyses at TOC*		
Clinical Assessment Missed	11	11
Clinical Assessment Out of Range	25	34
Concurrent Antibacterial	0	4
Culture Out of Range	25	34
Culture Missed	20	12
Medication Not as Prescribed	16	30
No Proven Pathogen	36	38
Wrong Indication	0	1
Total Not Evaluable	60	66
Reasons For Disqualification From Qualified Analyses at LTFU*		
Clinical Assessment Missed	28	43
Clinical Assessment Out of Range	17	6
Concurrent Antibacterial	5	1
Culture Out of Range	19	8
Culture Missed	27	45
Total Disqualified*	50	54

* Patients may have multiple reasons for exclusion or disqualification.

TABLE 11. Patients Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir	Penicillin
Intent-to-Treat (ITT)	278 (100.0)	280 (100.0)
Modified Intent-to-Treat (MITT)	232 (83.5)	233 (83.2)
Clinically Evaluable	240 (86.3)	228 (81.4)
Microbiologically-Clinically Evaluable	218 (78.4)	214 (76.4)
Qualified at LTFU	168 (60.4)	160 (57.1)

5.1.2. Safety Evaluations

All patients randomized to treatment received study medication and were included in the safety evaluations.

5.2. Efficacy

Medical Officer's Note: Please note that no patient outcomes were changed in 10% of the patients randomly selected to validate the patient database.

5.2.1. Overview

The response rates and confidence intervals presented in the efficacy results sections are estimates obtained from pooled analyses. Center-adjusted analyses were also performed and results are consistent between the 2 methods except where noted. A side-by-side comparison of all results from the 2 analysis methods can be found in Appendix D.1.

Comparisons of the microbiologic eradication and clinical cure rates for cefdinir and penicillin treatments at TOC showed that cefdinir treatment was statistically equivalent to penicillin treatment in all analysis populations examined except for the microbiologic eradication rate in the MITT population, where cefdinir was equivalent or superior to penicillin. At LTFU, microbiologic eradication and clinical cure rates in the qualified and ITT populations were similar for both treatment groups.

5.2.2. Evaluable Analyses and Qualified Analyses

5.2.2.1. Test-of-Cure Visit (5-10 Days Posttherapy)

5.2.2.1.1. Microbiologic Eradication

The microbiologic eradication rates were 89% (193/218) for the cefdinir group and 82% (176/214) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir versus penicillin (cefdinir minus penicillin) was (-0.4%, 12.9%), showing that the cefdinir and penicillin treatment groups were equivalent based on the fixed criteria for equivalence ($\pm 15\%$). The exploratory CMH test indicated that there was a marginally significant treatment difference in favor of cefdinir ($p = 0.053$).

5.2.2.1.2. Clinical Cure

The clinical response rates were 89% (194/218) for the cefdinir group and 85% (181/214) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir versus penicillin was (-2.0%, 10.8%), indicating that the cefdinir and penicillin treatment groups were equivalent based on the fixed

criteria for equivalence ($\pm 15\%$). The exploratory CMH test did not show a statistical difference ($p = 0.15$) between the 2 treatment groups. The response rates were based on the combined investigator/sponsor assessment of clinical cure, which was the same as the investigator assessment in this case.

5.2.2.1.3. Microbiologic Versus Clinical Response Rates

Most (83%; 358/432) patients had successful microbiologic and clinical responses (ie, they had microbiologic eradication and were clinically cured; Table 12). According to the sponsor, among those who had different microbiologic and clinical assessments, McNemar's test showed no significant pattern to the discordant assessments in the cefdinir ($p = 0.80$) or the penicillin ($p = 0.17$) groups.

TABLE 12. Microbiologic Versus Clinical Response at TOC - Evaluable Patients
(Number of Patients)

Microbiologic Response	Clinical Response	
	Cure	Failure
Cefdinir N = 218		
Eradication	186	7
Persistence	8	17
Penicillin N = 214		
Eradication	172	4
Persistence	9	29

5.2.2.2. Long-Term Follow-Up Visit (Study Day 25-31)

5.2.2.2.1. Microbiologic Eradication

Of the qualified patients who had *S. pyogenes* eradicated at the TOC visit, 94% (156/166) in the cefdinir group and 97% (152/157) in the penicillin group also had microbiologic eradication at the LTFU visit.

5.2.2.2.2. Clinical Cure

In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 94% (158/168) for the cefdinir group and 96% (152/159) for the penicillin group. Clinical cure rates were based on the combined investigator/sponsor determination, which was identical to the investigator determination in this case.

5.2.3. Modified Intent-to-Treat Analyses

5.2.3.1. Test-of Cure Visit (5-10 Days Posttherapy)

In the MITT population, the microbiologic eradication rates were 89% (206/232) for the cefdinir group and 83% (193/233) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (-0.4%, 12.3%) under the pooled analysis and (+0.02%, 16.6%) under the center-adjusted analysis, showing that cefdinir was equivalent to penicillin based on the pooled analysis (fixed criteria, $\pm 15\%$) and superior to penicillin based on the center-adjusted analysis (because the interval lies above 0). The exploratory CMH test indicated that the treatment difference was marginally significant in favor of cefdinir ($p = 0.06$).

5.2.4. Intent-to-Treat Analyses

5.2.4.1. Test-of-Cure Visit (5-10 Days Posttherapy)

5.2.4.1.1. Microbiologic Eradication

The ITT microbiologic eradication rates were 74% (206/278) for the cefdinir group, and 69% (193/280) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (-2.3%, 12.6%) showing that the microbiologic eradication rate in the cefdinir treatment group was equivalent to the penicillin group based on the predefined fixed criteria for equivalence ($\pm 20\%$). The exploratory CMH test indicated that the treatment difference was not significant.

5.2.4.1.2. Clinical Cure

The ITT clinical response rates were 83% (231/278) for the cefdinir group and 80% (223/280) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir versus penicillin was (-3.0%, 9.9%), indicating that cefdinir treatment was equivalent to penicillin based on the fixed criteria for equivalence. The exploratory CMH test indicated that the treatment difference was not significant.

5.2.4.2. Long-Term Follow-Up Visit (Study Day 25-31)

The microbiologic eradication rates for the cefdinir and penicillin groups were 65% (180/278) and 60% (167/280), respectively. It should be noted that 2 patients in the cefdinir group who were unevaluable (Patient 5, Center 12; and Patient 23, Center 7) and who were treatment failures at TOC but had no pathogen at LTFU were counted as microbiologic failures at LTFU. The clinical cure rates for the cefdinir and penicillin treatment groups were 68% (190/278) and 62% (174/280), respectively.

5.2.5. Other Population Analyses

5.2.5.1. Clinically Evaluable Patients

In the clinically evaluable patient population, the clinical response rate was 87% (208/240) for the cefdinir group and 82% (186/228) for the penicillin group. According to the sponsor, the 95% CI about the difference between treatment groups (cefdinir minus penicillin) was (-1.5%, 11.7%), showing that the cure rate in the cefdinir group was equivalent to that seen in the penicillin group based on the predefined fixed criteria for equivalence ($\pm 15\%$). The exploratory CMH test indicated that the treatment difference was not significant.

5.2.5.2. Patients Who Took Iron During Treatment

Concurrent administration of iron-containing supplements may interfere with the bioavailability of cefdinir. None of the patients in the cefdinir group reported taking iron-containing supplements during the study.

5.2.5.3. Patients Who Took Maalox® or Other Aluminum- or Magnesium-Containing Antacids During Treatment

Magnesium- or aluminum-containing antacids may interfere with the absorption of cefdinir.⁽²⁶⁾ Six patients took magnesium- or aluminum-containing antacids concomitantly with cefdinir. Two patients did not have *S. pyogenes* at baseline, and thus were not evaluable. One of these patients had a clinical assessment of Cure at TOC and the other was assessed as Failure. Four patients were evaluable at TOC, and all 4 had eradication at TOC and a clinical assessment of Cure.

5.2.6. Appearance of New Pathogens During the Study

5.2.6.1. Superinfections

Two patients in the cefdinir group and 1 patient in the penicillin group developed superinfections on or before the TOC visit. One patient in each group had a different strain of *S. pyogenes* than present at baseline and 1 patient in the cefdinir group had *Streptococcus* Group G. All were susceptible to the assigned study drug.

5.2.6.2. Reinfections

Three patients in the cefdinir group and 2 patients in the penicillin group developed reinfections after the TOC visit but on or before the LTFU visit. One patient in each treatment group had *Streptococcus agalactiae* and 1 patient in each group had *Streptococcus* Group C. In addition, 1 patient in the cefdinir group had *S. pyogenes* of a different strain than that present at baseline. All pathogens were susceptible to the assigned study drug.

5.2.6.3. Time to Onset of Symptomatic Relief

Complete patient diary data for assessment of throat pain was available for 97% (541/558) of patients. Diary data were unavailable for 17 patients because they withdrew from the study, were lost to follow-up, did not record baseline assessment, or did not return the diary. Data from the remaining 541 patients (270 in the cefdinir group and 271 in the penicillin group) were analyzed by survival analysis methods to determine the time to onset of symptomatic relief for each treatment group.

The percentage of patients who experienced symptomatic relief of throat pain was similar for the 2 treatment groups (97% for the cefdinir group and 99% for the penicillin group; Figure 2). The mean and median time to symptomatic relief was 3 days for each treatment group. According to the sponsor, there was no significant difference between the treatment groups in the distribution of symptomatic relief of throat pain, according to the log-rank test ($p = 0.74$).

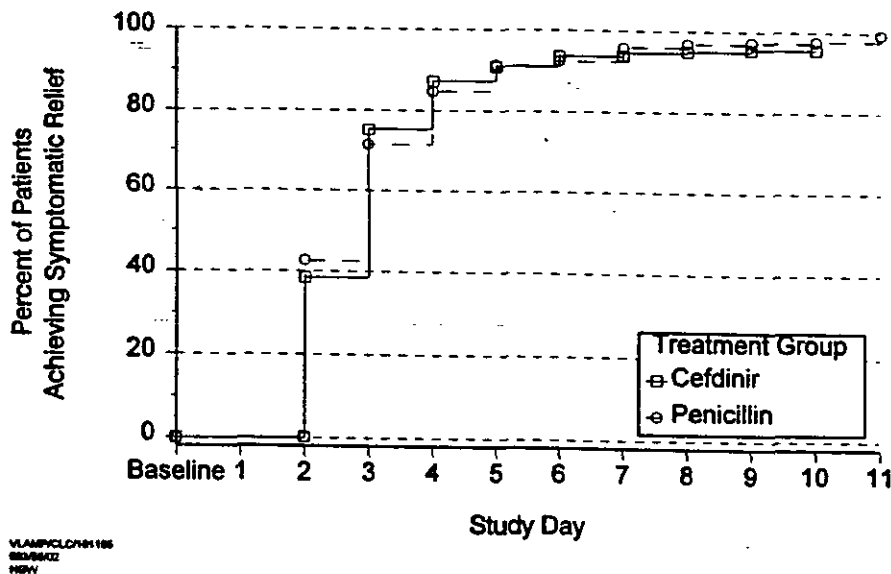


FIGURE 2. Time to Onset of Symptomatic Relief

5.3. Safety

5.3.1. Adverse Events

5.3.1.1. Overview

The safety review is based on the sponsor's reports and results unless otherwise specified.

A total of 304 (54%) patients experienced at least 1 adverse event during this study (Table 13). Fifty-eight percent (161/278) of cefdinir-treated patients and 51% (143/280) of penicillin-treated patients experienced at least 1 adverse event during the course of the study. These rates were not significantly different ($p = 0.08$). The incidence of associated adverse events showed a similar trend, with 22% (61/278) of cefdinir-treated patients and 17% (47/280) of penicillin-treated patients experiencing an associated adverse event during the study. The difference between the treatment groups was not significant ($p = 0.11$).

No deaths occurred during this study and only 1 patient (in the cefdinir-treatment group) experienced a serious adverse event, which was not related to study drug. Three percent (7 patients) of the cefdinir group discontinued study drug treatment due to an adverse event. It should be noted that 2 of these patients discontinued treatment while on placebo. Two percent (6 patients) of the penicillin group discontinued treatment due to an adverse event. Six patients in the cefdinir group (1 on placebo) and 3 patients in the penicillin group discontinued treatment due to an associated adverse event. The number of withdrawals after treatment due to adverse events was similar between the 2 treatment groups; 3 in the cefdinir group and 5 in

NDA 50-739 (CEFDINIR)
300 MG BID X5DAYS
PEN VK 250 MG QID X10 DAYS

PHARYNGITIS/TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-58

the penicillin group. Only 1 of these adverse events (in a penicillin-treated patient) was considered drug-associated.

(See summary table of adverse events on next page.)

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TABLE 13. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 2 of 2)

	Cefdinir N = 278	Penicillin N = 280
Adverse Events by Age^a		
All Adverse Events		
13 to <18 years	40 (54.8)	34 (45.3)
18 to <65 years	119 (58.9)	109 (53.2)
≥65 years	2 (66.7)	0 (0.0)
Associated Adverse Events		
13 to <18 years	6 (8.2)	9 (12.0)
18 to <65 years	53 (26.2)	38 (18.5)
≥65 years	2 (66.7)	0 (0.0)
Adverse Events by Maximum Intensity^a		
All Adverse Events		
Mild	104 (37.4)	98 (35.0)
Moderate	80 (28.8)	58 (20.7)
Severe	14 (5.0)	11 (3.9)
Associated Adverse Events		
Mild	36 (12.9)	37 (13.2)
Moderate	32 (11.5)	13 (4.6)
Severe	3 (1.1)	2 (0.7)
Serious Adverse Events	1 (0.4)	0 (0)
Deaths	0	0
Discontinuation of Treatment Due to Adverse Events		
All Adverse Events	7 ^f (2.5)	6 (2.1)
Associated Adverse Events	6 ^g (2.2)	3 (1.1)
Withdrawals After Treatment Due to Adverse Events		
All Adverse Events	3 (1.1)	5 (1.8)
Associated Adverse Events	0 (0.0)	1 (0.4)

^a Percentages equal the number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range

^b Patients with multiple adverse events were counted once in each applicable category.

^c Includes 2 patients on placebo.

^d Includes 1 patient on placebo.

5.3.1.2. All and Drug-Associated Adverse Events

The adverse event profiles of cefdinir and penicillin were similar. Adverse events relating to the body as a whole occurred with the highest frequency in both treatment groups, with headache occurring most frequently (16% of cefdinir-treated patients and 12% of penicillin-treated patients). The incidence of diarrhea was significantly higher in cefdinir-treated patients (13%) compared to penicillin-treated patients (8%; $p = 0.02$). In the cefdinir group, other adverse events occurring in at least 3% of patients were rhinitis (7%), abdominal pain and infection (4% each), increased cough, dyspepsia, nausea, pain, and sinusitis (3% each). Vaginal moniliasis or vaginitis occurred in 4% of women treated with cefdinir. Frequently occurring adverse events that were most often associated with cefdinir treatment were diarrhea (11% of patients) and vaginal moniliasis or vaginitis (4% of women).

In the penicillin group, additional adverse events experienced by at least 3% of patients included rhinitis (7%), infection, increased cough, and nausea (6% each), and pain (3%). Vaginal moniliasis or vaginitis occurred in 3% of penicillin-treated women. Adverse events associated with penicillin treatment which were found most frequently were diarrhea (6% of patients), nausea (4% of patients), and vaginal moniliasis or vaginitis (4% of women).

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5.3.1.8. Deaths

No deaths occurred during this study.

5.3.1.9. Serious Adverse Events

One patient experienced a serious adverse event during this study. Patient 92 (983-58-6), who received cefdinir, developed pelvic inflammatory disease on Day 5. This adverse event was considered definitely not related to cefdinir (see Appendix B.2 for complete patient narrative).

5.3.1.10. Withdrawals Due to Adverse Events

Thirteen patients (2%) discontinued study treatment because of an adverse event; 7 (3%) from the cefdinir treatment group (2 while on placebo) and 6 (2%) from the penicillin treatment group. Six of 7 adverse events resulting in discontinuation of cefdinir treatment were considered treatment-associated. The event not considered treatment-associated (pelvic inflammatory disease) occurred while the patient was taking placebo. Three of 6 events resulting in discontinuation of penicillin were considered associated with treatment. An additional 8 patients, 3 from the cefdinir treatment group and 5 from the penicillin treatment group, were withdrawn from the study due to adverse events after completing study drug treatment but before the end of follow-up. None of the adverse events which resulted in withdrawal following cefdinir treatment were considered treatment-associated. One adverse event (urticaria) which resulted in withdrawal following penicillin treatment was considered treatment-associated.

No significant differences were found between the rates of discontinuation from treatment due to adverse events in the cefdinir versus the penicillin treatment groups ($p = 0.77$). The most common reasons for treatment discontinuation or study withdrawal were diarrhea in the cefdinir treatment group (3 patients) or urticaria in the penicillin treatment group (3 patients; Table 17). The only other adverse event experienced by more than 1 patient was sinusitis, which occurred in 2 penicillin-treated patients.

Narratives for patients who discontinued treatment or withdrew from the study due to an adverse event are in Appendix B.2.

5.3.3. Clinical Laboratory Measurements

5.3.3.1. Changes From Baseline

The median difference between baseline and final clinical laboratory values was negligible for most laboratory parameters. White blood cell and polymorphonuclear leukocyte counts decreased in both treatment groups, as would be expected with resolving infection. Platelet counts increased slightly in both treatment groups but were within normal limits both at baseline and the final visit.

TABLE 18. Median Differences Between Baseline and Final Clinical Laboratory Values - All Patients

Parameter	Cefdinir		Penicillin	
	Median Difference	N	Median Difference	N
Hematology				
Hemoglobin (g/dL)	-0.3	255	-0.3	261
Hematocrit (%)	-1	251	-1	258
Erythrocytes ($\times 10^6/L$)	-0.1	255	-0.1	261
Mean Cell Hemoglobin (pg)	0	255	0	261
Mean Cell Hemoglobin Concentration (%)	0	251	0	258
Mean Cell Volume (fL)	-1	251	-0.5	258
White Blood Cells ($\times 10^3/\mu L$)	-3.89	255	-4.18	261
Polymorphonuclear Leukocytes ($\times 10^3/\mu L$)	-3.92	255	-4.29	261
Bands ($\times 10^3/\mu L$)	0	255	0	261
Lymphocytes ($\times 10^3/\mu L$)	0.58	255	0.58	261
Monocytes ($\times 10^3/\mu L$)	-0.27	255	-0.26	261
Eosinophils ($\times 10^3/\mu L$)	0.02	255	0.01	261
Basophils ($\times 10^3/\mu L$)	-0.01	255	-0.01	261
Platelets ($\times 10^3/\mu L$)	46	255	42	259
Blood Chemistry				
Glucose, Random (mg/dL)	-2	256	1	262
Blood Urea Nitrogen (mg/dL)	2	261	1	266
Creatinine (mg/dL)	0	261	0	266
Alkaline Phosphatase (U/L)	-3	260	-4.5	266
Bilirubin (mg/dL)	-0.1	258	0	265
Lactate Dehydrogenase (U/L)	-5	258	-4	264
Aspartate Aminotransferase (U/L)	0	261	0	266
Alanine Aminotransferase (U/L)	1	261	0	266
Sodium (mEq/L)	1	261	1	266
Potassium (mEq/L)	0	258	0.1	264
Total Protein (g/dL)	-0.1	261	-0.1	266
Calcium (mg/dL)	0.1	261	0	266
Phosphorus (mg/dL)	0.3	255	0.2	263
Chloride (mEq/L)	1	261	1	266
Bicarbonate (mEq/L)	0.55	258	0.4	265
Urinalysis				
Casts	0	254	0	261
Granular Casts	0	254	0	261
Hyaline Casts	0	254	0	261
pH	0	254	0	261
Specific Gravity	0	254	0	261

5.3.3.2. Category Shifts

For each treatment group, most clinical laboratory values remained in the same category (ie, above, within, or below normal values) at baseline and at the last observation (Table 19). Shifts in laboratory values were similar for both treatment groups. Decreases in white blood cells and polymorphonuclear leukocytes were observed in both treatments, consistent with resolving infection. More increases than decreases were noted in bicarbonate levels, possibly because patients were acidotic at baseline. There were decreases in a number of urinary abnormalities that were present at study admission, such as protein, ketones, hematuria, and bacteria. These abnormalities were most likely related to acute pharyngitis. Urine specific gravity also decreased, consistent with initial mild dehydration at baseline.

5.3.3.3. Markedly Abnormal Clinical Laboratory Values

In certain cases the central laboratory's age/gender-specific normal range limits exceeded the sponsor's criteria for markedly abnormal. For these patients, the attending physician would have considered the values within the normal ranges and no follow-up data are available. These patients are listed separately in Appendix E.2.

Increased white blood cell counts were observed in 2% of patients in the cefdinir treatment group but were not seen in the penicillin treatment group. Otherwise, there were essentially no differences between the 2 treatment groups in the percentage of patients with markedly abnormal laboratory values. The most frequently occurring markedly abnormal laboratory values observed in both treatment groups were increased alanine aminotransferase and phosphorus levels, increased urine red blood cells, and urine protein.

Discussion:

This study was designed to evaluate a 5-day regimen of cefdinir compared to a 10-day regimen of penicillin in the treatment of adult GABHS. Patients treated with a 5-day course of cefdinir demonstrated microbiologic eradication and clinical cure rates comparable to those observed in patients treated with a 10-day course of penicillin. Slightly higher relapse rates were observed in cefdinir-treated patients, most likely due to the fact that the long-term follow-up visit for cefdinir-treated patients occurred at a longer posttherapy interval than that of penicillin-treated patients. Statistical analyses (using a confidence interval approach) of microbiologic eradication and clinical cure rates at TOC showed equivalence between the 2 treatment regimens, indicating that the shorter course of cefdinir treatment is as effective as the longer course of penicillin treatment in adult patients with GABHS pharyngitis/tonsillitis.

Both cefdinir and penicillin treatments were well-tolerated. The safety profile of cefdinir was similar to that of penicillin, with 58% of cefdinir-treated patients and 51% of penicillin-treated patients experiencing an adverse event over the course of the study. A slightly higher incidence of drug-associated adverse events was observed in the cefdinir-treated group (22%) than was seen in the penicillin-treated group (17%), but the difference was not statistically significant ($p = 0.11$). In both treatment groups, the majority of drug-associated adverse events were mild or moderate; only 5% and 4% of adverse events in the cefdinir and penicillin groups, respectively, were considered severe by the investigator. The only treatment-associated adverse event

experienced by >5% of patients in either treatment group was diarrhea, which was observed in a greater number of cefdinir-treated patients (11%) than penicillin-treated patients (6%).

Only 1 patient, in the cefdinir-treatment group, experienced a serious adverse event, which was not related to study drug. No deaths occurred during this study. Treatment discontinuation due to drug-related adverse events occurred in only a small number of patients in either treatment group; 7 patients in the cefdinir group (2 while on placebo) and 6 patients in the penicillin group.

Although penicillin has historically been considered the drug of choice for the treatment of GABHS, a rise in the failure rate of this drug has been observed in recent years, prompting concerns that rheumatic fever and other serious complications of bacterial pharyngitis may once again become a serious public health issue.^(22,26) The decreased effectiveness of penicillin may be due, at least in part, to the fact that it can be destroyed by β -lactamase-producing commensal organisms in the pharynx before effectively eradicating *S. pyogenes*. Treatment of tonsillitis with penicillin may actually select for β -lactamase-producing organisms^(21,25), and 1 study reported that β -lactamase-producing anaerobic bacteria were recovered from 45% of patients with recurrent tonsillitis.⁽²³⁾ In addition, a correlation between the presence of pharyngeal β -lactamase-producing streptococci and failure of penicillin treatment has been demonstrated.⁽²⁴⁾ Thus, the fact that cefdinir is not susceptible to β -lactamase may give it an advantage over penicillin.

In the sponsor's opinion, another advantage of cefdinir is that it is effective given in a short course of therapy. Shortening the standard 10-day course of penicillin treatment decreases its effectiveness^(25,26), but the present study shows that a 5-day course of cefdinir results in microbiologic eradication and clinical cure rates comparable to those obtained with a 10-day course of penicillin. This finding is supported by other recent studies which have demonstrated the effectiveness of short-course oral cephalosporin treatment in patients with pharyngitis/tonsillitis.^(9,29) One study demonstrated that 5 days of cefpodoxime therapy was as effective as 10 days of therapy with this compound, and that both cefpodoxime regimens were superior to a 10-day regimen of penicillin V in bacteriological eradication of GABHS in children.⁽¹⁹⁾ Another study conducted in adults and children ≥ 10 years old found no significant difference in clinical response, bacteriologic eradication, or relapse rates in patients treated with 5 days of cefpodoxime proxetil compared to patients treated with 10 days of phenoxymethyl penicillin.⁽²⁰⁾ The results of the present study show that cefdinir given in a short course of therapy is also effective in treating adults with pharyngitis/tonsillitis. Thus, the fact that cefdinir offers effective microbiologic eradication and clinical cure rates in conjunction with a 5-day course of therapy makes it a favorable treatment option in the management of adult GABHS pharyngitis/tonsillitis.

7. CONCLUSIONS

- All *S. pyogenes* isolates were susceptible to both cefdinir and penicillin.
- Five days of cefdinir therapy (300 mg BID) is as effective microbiologically and clinically as 10 days of penicillin therapy (250 mg QID) in the treatment of adult patients with GABHS pharyngitis/tonsillitis.

NDA 50-739 (CEFDINIR)
300 MG BID X5DAYS
PEN VK 250 MG QID X10 DAYS

PHARYNGITIS/TONSILLITIS-ADULTS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-58

- Although the incidence of adverse events is somewhat higher with cefdinir treatment than with penicillin treatment, the overall difference is not statistically significant. However, the rate of diarrhea is significantly higher in patients in the cefdinir treatment group. Most adverse events experienced by cefdinir-treated patients are mild to moderate and do not require treatment discontinuation. The rate of discontinuation from treatment due to adverse events was comparable between the 2 treatment groups.

Medical Officer's Note: The reviewer agrees with the design and conduct of the clinical study as presented by the applicant.

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NDA 56-739(CEFDINIR)
14 MG/KG QD OR 7 MG/KG BIDX10 DAYS VS.
PEN VK 10 MG/KG QID

PHARYNGITIS/TONSILLITIS-PEDIATRICS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-51

V. PROTOCOL 983-51: AN INVESTIGATOR-BLINDED, RANDOMIZED, COMPARATIVE, MULTICENTER STUDY OF CEFDINIR (CI-983) VERSUS PENICILLIN V-K IN THE TREATMENT OF PEDIATRIC PATIENTS WITH GROUP A β -HEMOLYTIC STREPTOCOCCAL PHARYNGITIS/TONSILLITIS INFECTIONS

1. OBJECTIVES

The objectives of this study were to evaluate the efficacy and safety of two 10-day dosage regimens of cefdinir (14 mg/kg QD or 7 mg/kg BID) versus a 10-day regimen of penicillin V-K (10 mg/kg QID) in the treatment of pediatric patients with Group A β -hemolytic streptococcal (GABHS) pharyngitis/tonsillitis infections.

2. STUDY MANAGEMENT

Thirteen centers in the United States and Canada participated in this study, which was monitored by Parke-Davis Pharmaceutical Research. The final protocol, dated March 23, 1993, was approved by the Institutional Review board or Ethical Committee for each site prior to enrollment of patients. Addendum A contained additions to the selection and exclusion criteria and to the precautions section in accordance with Canadian Health Protection Bureau requirements and applied only to Canadian sites. All study participants supplied written informed consent before they were enrolled. An investigator's meeting was not held for this study. On-site training was conducted individually with each investigator and study coordinator. This study was conducted according to Good Clinical Practice Guidelines. Clinical laboratory and microbiological data were measured by a central laboratory. The first patient received the first dose of medication on May 5, 1993, and the last patient had the last follow-up visit on March 7, 1994. The blind was broken on November 22, 1994.

TABLE 1. List of Investigators

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable
1	G. Aronovitz	39	39	37
2	H. Collins	8	7	7
3	W. Gooch, III	156	147	141
4	J. Hedrick	148	136	126
5	D. Henry	58	54	49
7	J. McCarty	39	32	28
8	M. Pichichero	73	70	64
9	E. Rothstein	62	60	59
10	E. Slosberg	75	68	66
11	M. Sperling	40	40	39
12	S. Arndt	4	4	3
14	A. Irvani	77	72	70
15	S. McLinn	90	76	63
Total		869	805	752

Medical Officer's Note: Eliminating data from Dr. Irvani's site (center 14) reduced the number of patients randomized to treatment, who completed treatment and who were evaluable by 9%. . Please see Table one Appendix P51.

3. MATERIALS AND METHODS

3.1. Study Design

This was a investigator-blind, randomized, comparative, multicenter study with 3 parallel treatment groups (Figure 1). Pediatric patients with GABHS pharyngitis or tonsillitis were randomly assigned to receive cefdinir QD, cefdinir BID, or penicillin QID for 10 days. The protocol and CRFs specified that efficacy assessments were to be performed once during the 5- to 9-day posttherapy interval (test-of-cure visit; TOC) and once during the 18- to 24-day posttherapy interval (long-term follow-up visit; LTFU). However, in some cases the TOC visit occurred on Day 15 and the LTFU visit on Day 28. These were Days 4 and 17 posttherapy, respectively, for patients who began BID or QID treatments at midday on Day 1 and therefore did not

finish treatment until Day 11. For purposes of analysis, the TOC window was widened to 4 to 9 days posttherapy and the LTFU window to 17 to 24 days posttherapy to include these patients.

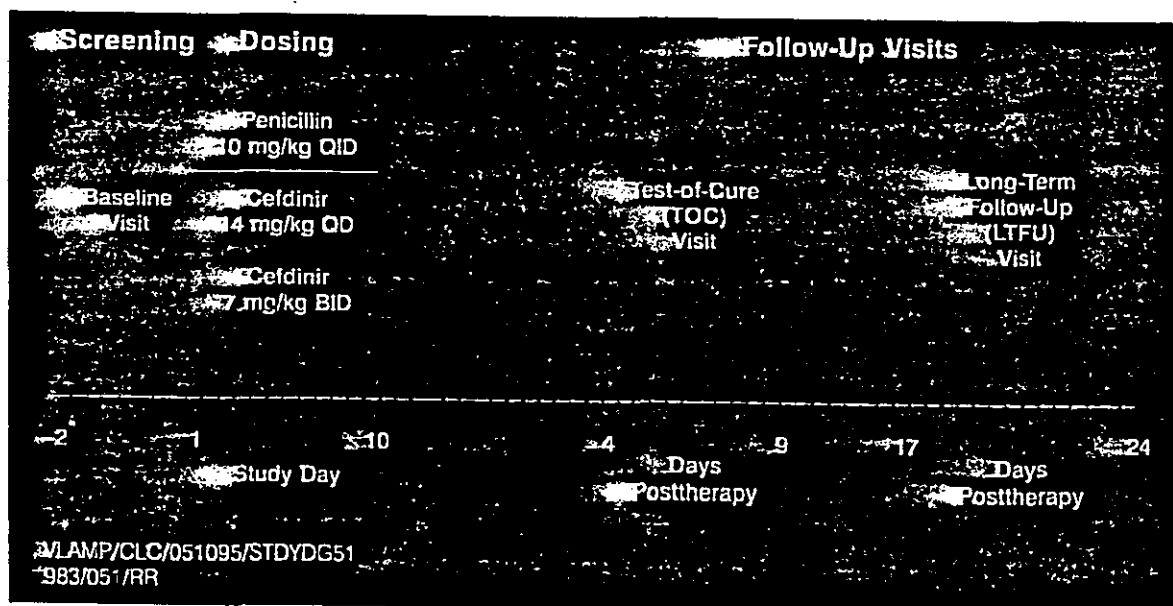


FIGURE 1. Study Design

3.1.1. Treatment

3.1.1.1. Materials

Cefdinir and penicillin were provided in powder form and were reconstituted by a third party to maintain investigator blinding (Table 2).

TABLE 2. Study Medication

Lot	Formulation
Cefdinir 125 mg/5 mL Suspension	
CM1080692	134393-27
CM1090692	134393-27
CR0450393	134393-27
Penicillin V-K 250 mg/5 mL Solution	
6MW66A	Marketed
6MW78A	Marketed
7CU98A	Marketed

3.1.1.2. Drug Administration

Cefdinir suspension was administered orally, either once in the morning (QD) or once in the morning and afternoon (BID). Penicillin solution was administered orally QID. Study medications were taken without regard to meals.

MEDICAL OFFICER'S NOTE: *The following sections are identical to protocol 983-7. Please refer to the 983-7 review for details. Please note that variations are in italicized text.*

3.1.1.3. Methods of Assigning Patients to Treatment

At each center, patients who met the entry criteria at screening were given the next consecutive patient number and, according to the randomization schedule, were dispensed the corresponding study medication. The patient number and milliliter unit dose were recorded on each bottle of reconstituted study medication; the treatment group and total daily dose prescribed were recorded on the appropriate case report form by the third party who dispensed the medication (not by the investigator).

3.2. Patient Selection

3.2.1. Inclusion Criteria

Patients were to be between the ages of 6 months and 12 years, of either sex, and postmenarchal girls were to have a negative pregnancy test prior to receiving study medication.

3.2.2. Exclusion Criteria

- Serum creatinine > 1.5 times the upper limit of normal;*

3.2.3. Prohibited Medications or Precautions

3.2.4. Guidelines for Patient Withdrawal

3.3. Criteria for Evaluation

3.3.1. Efficacy

3.3.1.1. Microbiologic Response

3.3.1.2. Clinical Response

Medical Officer's Note: *Please refer to the table in protocol 7 with all the patients that were given a combined score.*

3.3.1.3. Appearance of New Pathogens

NDA 50-739(CEFDINIR)
14 MG/KG QD OR 7 MG/KG BIDX10 DAYS VS.
PEN VK 10 MG/KG QID

PHARYNGITIS/TONSILLITIS-PEDIATRICS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-51

- 3.3.2. Safety
 - 3.3.2.1. Adverse Events
 - 3.3.2.2. Physical Examinations
 - 3.3.2.3. Clinical Laboratory Values
- 3.3.3. Clinical Observations and Laboratory Measurements
- 3.3.4. Data Acceptability and Evaluability
 - 3.3.4.1. Method of Assigning Study Days
 - 3.3.4.2. Data Acceptability
 - 3.3.4.3. Patient Populations for Analysis
- 3.3.5. Statistical Methodology
 - 3.3.5.1. Sample Size

Medical Officer's Note: This investigator-blinded, comparative study of cefdinir versus penicillin was designed with a sample size of 190 evaluable patients per randomized group for a total of 570 evaluable patients.

3.3.5.2. Methods

Medical Officer's Note: Please refer to the random numbers generated in protocol seven for random patient selection.

- 3.3.5.2.1. Efficacy
- 3.3.5.2.2. Safety

4. PATIENT DEMOGRAPHICS, TREATMENT, AND DISPOSITION

4.1. Patient Characteristics

4.1.1. Patient Sample

RR 720-03468 contains the patient listings for this study. Listings contain all of the data collected on the CRFs and are organized by topic (eg, patient characteristics, infection history).

Approximately equal numbers of females and males entered this study. Most patients were white and the median age was 7 years, with most patients in the 6 to <13 age group. There were no differences between treatment groups. One patient was randomized to treatment (cefdinir BID) but did not receive drug.

Baseline characteristics of the evaluable population were similar to those of all patients (Table 7).

TABLE 7. Patient Characteristics - Evaluable^a Patients
[Number (%) of Patients]

Variable	Cefdinir				Penicillin		Total	
	QD N = 252		BID N = 250		N = 250		N = 752	
Sex								
Male	142	(56.3)	134	(53.6)	124	(49.6)	400	(53.2)
Female	110	(43.7)	116	(46.4)	126	(50.4)	352	(46.8)
Race								
White	229	(90.9)	225	(90.0)	219	(87.6)	673	(89.5)
Hispanic	15	(6.0)	13	(5.2)	12	(4.8)	40	(5.3)
Black	5	(2.0)	10	(4.0)	16	(6.4)	31	(4.1)
Asian	1	(0.4)	0	(0.0)	2	(0.8)	3	(0.4)
Other ^b	2	(0.8)	2	(0.8)	1	(0.4)	5	(0.7)
MH p-value	Cefdinir QD vs penicillin = 0.159; Cefdinir BID vs penicillin = 0.329							
Age, yr								
Median	7.5		6.9		7.4		7.3	
Range	1-13		1-13		2-13		1-13	
Distribution								
<2	4	(1.6)	3	(1.2)	3	(1.2)	10	(1.3)
2 to <6	72	(28.6)	86	(34.4)	75	(30.0)	233	(31.0)
6 to <13	175	(69.4)	161	(64.4)	172	(68.8)	508	(67.6)
13 to <18	1	(0.4)	0	(0.0)	0	(0)	1	(0.1)
CMH p-value	Cefdinir QD vs penicillin = 0.814; Cefdinir BID vs penicillin = 0.326							

^a Microbiologically and clinically

^b Afghanistan, American Indian, Indian

Medical officer's note: Excluding the Iravani data did not substantially change the demographic characteristics of either the total patient population or the evaluable patient population. Please see (appendix table 6 and 7) in appendix p51.

4.1.2. Confirmed Microbiologic Diagnosis and Baseline Susceptibility

At the baseline visit, *S. pyogenes* was isolated from throat swabs of 832 of the 869 (96%) patients randomized to treatment. One patient had a positive multiple culture for β -hemolytic streptococcus Group A morphology 1 and morphology 2. All isolates were susceptible to both cefdinir and penicillin with the exception of 2 *S. pyogenes* isolates for which susceptibility to penicillin was not tested.

4.1.3. Clinical Signs and Symptoms

Of the 869 patients randomized to treatment, 7 patients (1 in the cefdinir QD group, 2 in the cefdinir BID group, and 4 in the penicillin group) had pharyngeal erythema but not pharyngeal pain at baseline. Eight patients (2 in the cefdinir QD group, 5 in the cefdinir BID group, and 1 in the penicillin group) had pharyngeal pain but not pharyngeal erythema at baseline. Otherwise, all patients who entered the study had

both pain and erythema of the pharyngeal cavity, as required by the protocol. Most patients also had tonsillar swelling, dysphagia, and cervical lymph node tenderness. Approximately half of the patients had baseline exudate and 27% presented with fever. There were no apparent differences in baseline signs and symptoms between treatment groups, or between the ITT and evaluable patient populations.

4.1.4. Medical History and Secondary Diagnoses

There were no differences in prior or concurrent medical conditions between treatment groups. Approximately equal percentages of patients in each treatment group had experienced pharyngitis/tonsillitis within 1 year prior to the start of the study: 32% in the cefdinir QD group, 29% in the cefdinir BID group, and 29% in the penicillin group. Twelve patients in the cefdinir QD group, 6 patients in the cefdinir BID group, and 5 patients in the penicillin group had experienced 3 or more prior episodes.

4.1.5. Prior Medications for Pharyngitis

Twelve patients (4%) in the cefdinir QD group, 18 patients (6%) in the cefdinir BID group, and 7 patients (2%) in the penicillin group had received prior antibiotic medications for pharyngitis/tonsillitis within the 30-day period before the study. Amoxicillin was the most commonly used prior medication (28 patients). Five patients had received a prior cephalosporin: cefadroxil monohydrate (4 patients) or cefaclor (1 patient).

4.1.6. Concurrent Medications, Nondrug Therapies, Elective Surgeries/Procedures

Concurrent medications taken by at least 5% of patients included acetaminophen (23%), amoxicillin (7%), and ibuprofen (6%).

No patient received a concurrent nondrug therapy for pharyngitis. Patient 21 (983-51-5) underwent a tonsillectomy/adenoidectomy on Day 12 after failing treatment with 7 mg cefdinir BID for 10 days.

4.2. Patient Treatment

The median number of days on study medication was 10 days in the 2 cefdinir treatment groups and 11 days in the penicillin group (Table 8). Patients in the cefdinir BID group and penicillin group who took their first dose in the afternoon or evening of Day 1 would have completed their course of treatment on Day 11. Other patients who missed doses during the 10-day course of treatment and took them at the end of the course also contributed to the patients whose exposure to study medication was greater than 10 days. Over 95% of patients in all treatment groups completed treatment in 10 or 11 days.

TABLE 8. Patient Exposure to Study Medication - All Patients

Days of Study Medication	Cefdinir		Penicillin N = 290
	QD N = 289	BID N = 290	
1	2	2	0
2	3	1	2
3	2	1	1
4	1	3	1
5	2	0	1
6	0	1	1
7	1	5	1
8	4	4	3
9	0	1	1
10	253	212	96
11	13	51	172
12	4	2	4
13	0	1	0
14	0	1	1
16	1	0	1
17	0	1	0
Median	10	10	11
Unknown	3	4*	5

* One patient did not receive any study medication.

Medical Officer's Note: Patient exposure to study medication remained the same, with the majority of cefdinir patients (both QD and BID groups) finishing study medication on Day 10 and most penicillin patients finishing medication on Day 11. Please see table (appendix8) in appendix p51.

4.3. Patient Disposition

Of the 869 patients who entered the study, 805 (93%) completed the treatment phase, 810 (93%) completed the TOC visit, and 689 (79%) completed the LTFU visit (Table 9).

TABLE 9. Patient Disposition - All Patients
[Number (%) of Patients]

Disposition	Cefdinir				Penicillin		Total	
	QD		BID					
Randomized to Treatment	289		290		290		869	
Withdrawn Prior to End of Treatment								
No Baseline Pathogen	6	(2.1)	10	(3.4)	8	(2.8)	24	(2.8)
Adverse Event	4	(1.4)	2	(0.7)	3	(1.0)	9	(1.0)*
Lack of Compliance	2	(0.7)	4	(1.4)	7	(2.4)	13	(1.5)
Other/Administrative ^b	6	(2.1)	8	(2.8)	4	(1.4)	18	(2.1)
Completed Treatment ^c	27	(93.8)	266	(91.7)	26	(92.4)	805	(92.6)
	1				8			
Completed Follow-Up Visits ^c								
TOC	27	(94.1)	270	(93.1)	26	(92.4)	810	(93.2)
	2				8			
LTFU	25	(86.5)	237	(81.7)	20	(69.7)	689	(79.3)
	0				2			

- * Twenty-six other patients were withdrawn due to an adverse event after treatment but before the LTFU visit.
- * Reasons include lost to follow-up (6 patients), medication errors or missed doses (4 patients), parent request (4 patients), elevated liver enzymes (2 patients), erroneous report of no baseline pathogen (1 patient), and child vomited after first dose (1 patient).
- * Based on the investigator assessment of patient status at the end of treatment (Case Report Form 9).

Medical Officer's Note: The number of patients who completed the treatment, TOC visit, and LTFU visit phases of the study decreased 9%, 9%, and 10% respectively; however, the overall percentages of patients completing each phase remained relatively constant at 92.6%, 93.1%, and 78.0% respectively. Please see table (appendix 9) in appendix p51.

5. RESULTS

5.1. Protocol Variations

Protocol variations that did not exclude patients from the evaluable analyses included not having pain and erythema at baseline (14 patients), being outside the specified age range (1 patient), entering the study out of numerical order (8 patients), receiving a different treatment than specified by the randomization code (3 patients), receiving more medication than specified by the protocol (15 patients), having baseline clinical laboratory values above the limit specified in the protocol (11 patients), and being previously enrolled in a cefdinir study (3 patients).

5.1.1. Efficacy Evaluations

Patients were most often considered not evaluable because the medication was not taken as prescribed (Table 10). Other common reasons for exclusion from the evaluable analyses were that the clinical assessment of signs and symptoms at baseline or TOC was outside the range of days specified in the protocol (clinical assessment out of range), the culture at baseline or TOC was performed outside the range of days

specified in the protocol (culture out of range), or there was no proven baseline pathogen. Evaluable patients were most frequently disqualified from LTFU because they missed their clinical assessment of signs and symptoms or missed their follow-up throat culture. The definition of each exclusion and disqualification criterion is given in Appendix A.8. A summary of the number of patients in each population is given in Table 11.

TABLE 10. Reasons Patients Were Not Evaluable at TOC or Were Disqualified at LTFU
(Number of Patients)

	Cefdinir		Penicillin
	14 mg/kg QD	7 mg/kg BID	
Reasons For Exclusion From Evaluable Analyses at TOC*			
Clinical Assessment Missed	5	7	5
Clinical Assessment Out of Range	17	21	24
Concurrent Antibacterial	1	5	2
Medication Not as Prescribed	24	23	17
Randomization Violation	0	0	2
Culture Out of Range	16	19	21
Culture Missed	7	9	10
No Baseline Susceptibility Tests	0	1	0
No Proven Pathogen	10	16	10
Total Not Evaluable	37	40	40
Reasons For Disqualification From Qualified Analyses at LTFU*			
Clinical Assessment Missed	19	23	59
Clinical Assessment Out of Range	9	3	10
Concurrent Antibacterial	9	7	9
Culture Out of Range	8	4	11
Culture Missed	19	23	58
Total Disqualified	34	33	78

* A patient can be counted under more than 1 reason.

Medical Officer's Note: No substantial change was seen in the frequency distribution of reasons for exclusion from evaluable analyses at TOC and reasons for disqualification from qualified analyses at LTFU. Please see table (appendix 10) in appendix p51.

TABLE 11. Patients Included in Efficacy Summaries
(Number (%) of Patients)

Patient Population	Cefdinir		Penicillin
	14 mg/kg QD	7 mg/kg BID	
Intent-to-Treat (ITT)	289 (100.0)	290 (100.0)	290 (100.0)
Modified Intent-to-Treat (MITT)	272 (94.1)	266 (91.7)	271 (93.4)
Clinically Evaluable	258 (89.3)	255 (87.9)	254 (87.6)
Evaluable	252 (87.2)	250 (86.2)	250 (86.2)
Qualified	218 (75.4)	217 (74.8)	172 (59.3)

Medical Officer's Note: The percentages of patient's included in each population analyzed changed minimally after exclusion of Dr. Iravani's patients. Please see table 11 in appendix P51. Also, when Dr. Iravani's data was not included in the analysis for clinical and microbiologic efficacy, and there was very little effect on response rates. Please see appendix P51 page 1, 2, and 3.

Please see the FDA's statistical evaluation below with Yates continuity correction. This is minimally changed from the sponsor's analysis.

Summary of cure rates in protocol 51.

Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with c correction)
Clinical Efficacy				
All sites	246/252(97.6%)	241/250(96.4%)	217/250(86.8%)	<u>Cefdinir QID vs Cefdinir BID</u> 252,250(-0.0216, 0.0459) 97.6%, 96.4% <u>Cefdinir QID vs Penn</u> 252,250(0.0582, 0.1582) 97.6%, 86.8% <u>Cefdinir BID vs Penn</u> 250,250(0.0441, 0.1479) 96.4%, 86.8%
Sites 14 excluding Iravani	222/228(97.3%)	218/227(96%)	196/227(86.3%)	<u>Cefdinir QID vs Cefdinir BID</u> 228,227(-0.0238, 0.0505) 97.3%, 96% <u>Cefdinir QID vs Penn</u> 228,227(0.0566, 0.1639) 96%, 86.3% <u>Cefdinir BID vs Penn</u> 227,227(0.0411, 0.1527) 96%, 86.3%
Microbiologic Eradication				
All sites	233/252(92.4%)	237/250(94.8%)	177/250(70.8%)	<u>Cefdinir QD vs Cefdinir BID</u> 252,250(-0.0701, 0.0232) 92.4%, 94.8% <u>Cefdinir QD vs pen</u> 252,250(0.1475, 0.2857) 92.4%, 70.8% <u>Cefdinir BID vs Pen</u> 250,250(0.1732, 0.3067) 94.8%, 70.8%
Sites 14 excluding Iravani	215/228(94.3%)	214/227(94.3%)	159/227(70%)	<u>Cefdinir QD vs Cefdinir BID</u> 228,227(-0.0468, 0.0473) 94.3%, 94.3% <u>Cefdinir QD vs Pen</u> 228,227(0.1713, 0.3137) 94.3%, 70% <u>Cefdinir BID vs Pen</u> 227,227(0.1711, 0.3135) 94.3%, 70%

Statistical Reviewer's Comments:

For both clinical efficacy as well as for microbiologic eradication, Cefdinir QD is therapeutically equivalent to Cefdinir BID. Both Cefdinir QD and BID regimens are statistically superior to penicillin with respect to clinical efficacy and microbiologic eradication. These results hold true with or without the information from Site 14 (Dr. Iravani).

5.1.2. Safety Evaluations

All patients randomized to treatment and who received study medication were included in safety evaluations.

5.2. Efficacy

Medical Officer's Note: Please note that the outcomes for the the-patients-below have been changed:

Outcomes Changed by Medical officer and Statistician:			
Patient Number	Applicant	FDA	Reason:
51	MICRO: TOC/LTFU (Not Asse/Not Asse)	MICRO: TOC/LTFU (Erad/Eradication)	<i>S. pyogenes</i> was isolated at baseline with a non pathogen (<i>S. Aureus</i>) and was not considered
199	Clin: TOC/LTFU cure/cure	clin: toc/ltfu failure/failure	Patient had moderate swelling and erythema clinically with a positive culture.
203	Clin: TOC/LTFU cure/cure	clin: toc/ltfu failure/failure	Patient had erythema/sweling/ and cervical lymph node tenderness
260	MICRO: TOC/LTFU (Not Asse/Not Asse)	MICRO: TOC/LTFU (Erad/Eradication)	<i>S. pyogenes</i> was isolated at baseline with a non pathogen (<i>P. aeruginosa</i>) and was not considered
476	Clin: TOC/LTFU cure/cure	clin: toc/ltfu failure/failure	Patient had moderate swelling and erythema clinically
727	MICRO: TOC/LTFU (Not Asse/Not Asse)	MICRO: TOC/LTFU (Erad/Eradication)	<i>S. pyogenes</i> was isolated at baseline with a non pathogen (<i>Citrobacter freundii</i>) and was not considered

5.2.1. Overview

The response rates and confidence intervals presented in the efficacy results sections are estimates obtained from pooled analyses. Center-adjusted analyses were also performed and results are consistent between the 2 methods. A side-by-side comparison of all results from the 2 analysis methods can be found in Appendix D.1.

Cefdinir-treated patients had significantly higher microbiologic and clinical response rates than patients with penicillin in all cases. Cefdinir QD and cefdinir BID were equivalent in all cases based on the fixed criteria for equivalence. Relapse rates were low for all treatment groups with cefdinir QD having the lowest relapse rate.

5.2.2. Evaluable and Qualified Analyses

5.2.2.1. Test-of-Cure Visit (4-9 Days Posttherapy)

5.2.2.1.1. Microbiologic Eradication

The microbiologic eradication rates were 93% for the cefdinir QD group (233/252), 95% for the cefdinir BID group (237/250), and 71% for the penicillin group (177/250). The 95% CI about the difference between cefdinir QD vs penicillin (cefdinir QD minus penicillin) was (15.1%, 28.2%) and between cefdinir BID vs penicillin (cefdinir BID minus penicillin) was (17.7%, 30.3%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above 0. The exploratory CMH test showed that the eradication rates for both the cefdinir QD group and cefdinir BID group were significantly higher than the penicillin group ($p < 0.001$ for QD vs penicillin and $p < 0.001$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-6.6%, 1.9%), showing that these treatments were equivalent.

All persistent pathogens were susceptible to assigned study drug except for 1 *S. pyogenes* isolate from the penicillin group whose susceptibility to penicillin was unknown.

5.2.2.1.2. Clinical Cure

The clinical response rates were 98% for the cefdinir QD treatment group (246/252), 96% for the cefdinir BID group (241/250), and 87% for the penicillin group (217/250). The 95% CI about the difference between cefdinir QD vs penicillin (cefdinir QD minus penicillin) was (6.2%, 15.4%) and between cefdinir BID vs penicillin (cefdinir BID minus penicillin) was (4.8%, 14.4%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above 0. The exploratory CMH test showed that the eradication rates for both the cefdinir QD group and cefdinir BID group were significantly higher than the penicillin group ($p < 0.001$ for QD vs penicillin and $p < 0.001$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-1.8%, 4.2%), showing that these treatments were equivalent.

The response rates were based on the combined investigator/sponsor assessment of clinical cure, which was identical to the investigator assessment because no patient was considered Not Assessable by the investigator.

5.2.2.1.3. Microbiologic Versus Clinical Response Rates

Most patients (85%; 638/752) had successful microbiologic and clinical responses (ie, microbiological eradication plus clinically cured); another 39 had failing responses (ie, persistent pathogen(s) plus clinical failure) (Table 12). Among those who had different microbiologic and clinical outcomes (eg, eradication plus failure or persistence plus cure), McNemar's test did not detect a significant pattern to the discordant assessments in the cefdinir BID group ($p = 0.28$), but did in the cefdinir QD ($p = 0.002$) and penicillin ($p < 0.001$) groups. In these groups, a disproportionate number of patients experienced a clinical cure, yet had a persistent pathogen. This may be due to a resolution of symptoms in the absence of complete eradication, or may represent a small number of patients who were reinfected with the identical strain of *S. pyogenes* prior to the TOC visit.

TABLE 12. Clinical Versus Microbiologic Response at TOC -
Evaluable Patients

Microbiologic Response	Clinical Response	
	Cure	Failure
Cefdinir QD		
Eradication	231	2
Persistence	15	4
Cefdinir BID		
Eradication	232	5
Persistence	9	4
Penicillin		
Eradication	175	2
Persistence	42	31

Medical Officer's Note: The correlation between clinical and microbiological responses remained good, with the majority of patients having clinical cure associated with microbiologic eradication. Please see table 12 in appendix P51.

5.2.2.2. Long-Term Follow-Up Visit (17-24 Days Posttherapy)

5.2.2.2.1. Microbiologic Eradication

Of the qualified patients who had their baseline pathogen eradicated at the TOC visit, 94% (197/210) in the cefdinir QD group, 89% (190/214) in the cefdinir BID group, and 90% (136/152) in the penicillin group also had microbiologic eradication at the LTFU visit. Thus, the relapse rate was lowest in the cefdinir QD group and similar for the other 2 groups.

5.2.2.2.2. Clinical Cure

The qualified clinical cure rate at LTFU was 95% (208/218) for the cefdinir QD treatment group, 94% (202/216) for the cefdinir BID group, and 94% (160/171) for the penicillin group. Clinical cure rates were based on the combined investigator/sponsor determination, which was identical to the investigator determination in this case, since no patients were Not Assessable.

5.2.3. Modified Intent-to-Treat Analyses

5.2.3.1. Test-of Cure Visit (4-9 Days Posttherapy)

In the MITT population, the microbiologic eradication rates were 92% (250/272) for the cefdinir QD group, 95% (252/266) for the cefdinir BID group, and 70% (189/271) for the penicillin group. The 95% CI about the difference between cefdinir QD vs penicillin (cefdinir QD minus penicillin) was (15.8%, 28.5%) and between cefdinir BID vs penicillin (cefdinir BID minus penicillin) was (18.9%, 31.1%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above 0. The exploratory CMH test showed that the eradication rates for both the cefdinir QD group and cefdinir BID group were

significantly higher than the penicillin group ($p < 0.001$ for QD vs penicillin and $p < 0.001$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-7.0%, 1.4%), showing that these treatments were equivalent.

5.2.4. Intent-to-Treat Analyses

5.2.4.1. Test-of-Cure Visit (4-9 Days Posttherapy)

5.2.4.1.1. Microbiologic Eradication

The ITT microbiologic eradication rates were 87% (250/289) for the cefdinir QD group, 87% (252/290) for the cefdinir BID group, and 65% (189/290) for the penicillin group. The 95% CI about the difference between cefdinir QD vs penicillin (cefdinir QD minus penicillin) was (14.6%, 28.1%) and between cefdinir BID vs penicillin (cefdinir BID minus penicillin) was (15.0%, 28.4%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above 0. The exploratory CMH test showed that the eradication rates for both the cefdinir-QD group and cefdinir BID group were significantly higher than the penicillin group ($p < 0.001$ for QD vs penicillin and $p < 0.001$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-5.9%, 5.1%), showing that these treatments were equivalent.

5.2.4.1.2. Clinical Cure

The ITT clinical response rates were 95% (275/289) for the cefdinir QD treatment group, 93% (271/290) for the cefdinir BID group, and 82% (238/290) for the penicillin group. The 95% CI about the difference between cefdinir QD vs penicillin (cefdinir QD minus penicillin) was (8.0%, 18.1%) and between cefdinir BID vs penicillin (cefdinir BID minus penicillin) was (6.1%, 16.6%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above 0. The exploratory CMH test showed that the eradication rates for both the cefdinir QD group and cefdinir BID group were significantly higher than the penicillin group ($p < 0.001$ for QD vs penicillin and $p < 0.001$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-2.1%, 5.5%), showing that these treatments were equivalent.

5.2.4.2. Long-Term Follow-Up Visit (17-24 Days Posttherapy)

Both cefdinir groups had higher microbiologic eradication and observed clinical response rates than the penicillin group. The microbiologic eradication rates were 76% for the cefdinir QD group, 72% for the cefdinir BID group, and 53% for the penicillin group. The clinical response rates were 82% for the cefdinir QD group, 76% for the cefdinir BID group, and 64% for the penicillin group.

5.2.5. Other Population Analyses

5.2.5.1. Clinically Evaluable Patients

In the clinically evaluable patient population, the clinical response rate was 97% (251/258) for the cefdinir QD group, 97% (246/255) for the cefdinir BID group, and 86% (219/254) for the penicillin group. The 95% CI about the difference between cefdinir QD vs penicillin (cefdinir QD minus penicillin) was (6.4%, 15.7%) and between cefdinir BID vs penicillin (cefdinir BID minus penicillin) was (5.4%, 15.1%), showing that both cefdinir treatment groups were superior to penicillin because the intervals lie above 0. The exploratory CMH test showed that the eradication rates for both the cefdinir QD group and cefdinir BID group were significantly higher than the penicillin group ($p < 0.001$ for QD vs penicillin and $p < 0.001$ for BID vs penicillin). The 95% CI about the difference between the cefdinir treatment groups (QD minus BID) was (-2.2%, 3.8%), showing that these treatments were equivalent.

A summary of the statistical analyses is shown below (Table 13).

TABLE 13. Summary of Efficacy Analyses at TOC

Pairwise Comparison	Population	Rates (%)	95% CI	Interpretation
Microbiologic Eradication				
QD vs Penicillin	Evaluable*	93 vs 71	15.1, 28.2	QD Superior
	MITT	92 vs 70	15.8, 28.5	QD Superior
	ITT	87 vs 65	14.6, 28.1	QD Superior
BID vs Penicillin	Evaluable*	95 vs 71	17.7, 30.3	BID Superior
	MITT	95 vs 70	18.9, 31.1	BID Superior
	ITT	87 vs 65	15.0, 28.4	BID Superior
QD vs BID	Evaluable	93 vs 95	-6.6, 1.9	Equivalent
	MITT	92 vs 95	-7.0, 1.4	Equivalent
	ITT	87 vs 87	-5.9, 5.1	Equivalent
Clinical Response				
QD vs Penicillin	Evaluable	98 vs 87	6.2, 15.4	QD Superior
	Clinically Evaluable	97 vs 86	6.4, 15.7	QD Superior
	ITT	95 vs 82	8.0, 18.1	QD Superior
BID vs Penicillin	Evaluable	96 vs 87	4.8, 14.4	BID Superior
	Clinically Evaluable	97 vs 86	5.4, 15.1	BID Superior
	ITT	93 vs 82	6.1, 16.6	BID Superior
QD vs BID	Evaluable	98 vs 96	-1.8, 4.2	Equivalent
	Clinically Evaluable	97 vs 97	-2.2, 3.8	Equivalent
	ITT	95 vs 93	-2.1, 5.5	Equivalent

* Primary efficacy analysis

Medical Officer's Note: Exclusion of Site 14 had very little effect on response rates. Both cefdinir QD and cefdinir BID are still statistically superior to penicillin for both clinical and microbiological response rates, across patient populations. Cefdinir QD and cefdinir BID remain equivalent by CI testing for both clinical response rate and microbiological response rate. Please see table 13 in appendix P51. Following Table 13, the same information for the evaluable patient population is presented in a slightly different format and includes p-values (Table 13A) in appendix P51.

5.2.6. Appearance of New Pathogens During the Study

5.2.6.1. Superinfections

Two patients in the cefdinir QD group, 2 patients in the cefdinir BID group, and 1 patient in the penicillin group developed superinfections on or before the TOC visit (Table 14). All superinfecting pathogens in the cefdinir QD and BID groups were susceptible to cefdinir. In the penicillin group, 1 pathogen was susceptible to penicillin and 1 pathogen (*Enterobacter sakazakii*) had unknown susceptibility.

TABLE 14. Patients With Superinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir 14 mg/kg QD	Cefdinir 7 mg/kg BID	Penicillin
Gram Positive			
<i>Streptococcus pyogenes</i> *	2	1	0
<i>Streptococcus</i> Type G	0	1	0
Gram Negative			
<i>Enterobacter sakazakii</i>	0	0	1

* Genotypically distinct from baseline isolate

Medical Officer's Note: The patient with E. Sakazakii was eliminated with exclusion of site 14. Please see table (appendix 14) in appendix P51.

5.2.6.2. Reinfections

Three patients in the cefdinir QD group, 4 patients in the cefdinir BID group, and 3 patients in the penicillin group developed reinfections after the TOC visit but before the LTFU visit (Table 15). All of the reinflecting pathogens were susceptible to the assigned study drug.

TABLE 15. Patients With Reinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir 14 mg/kg QD	Cefdinir 7 mg/kg BID	Penicillin
Gram Positive			
<i>Streptococcus pyogenes</i> *	2	4	3
Gram Negative			
<i>Acinetobacter calcoaceticus</i> var <i>lwoffi</i>	1	0	1

* Genotypically distinct from baseline isolate

Medical Officer's Note: The number of patients with reinfections did not change. I agree with the different outcome responses by the sponsor.

5.3. Safety

Medical Officer's Note: When Dr. Irvani's data was not included in the analysis for safety (both the adverse event rates and drug-associated adverse event rates), there was very little effect on the adverse event rates. Please see appendix P51 page 1, 2, and 3.

One patient randomized to treatment (cefdinir BID) did not receive drug and was not evaluated for safety.

5.3.1. Adverse Events

5.3.1.1. Overview

A total of 358 (41%) patients experienced at least 1 adverse event during this study (Table 16). The incidence was highest in patients treated with cefdinir BID, 45% of whom experienced an adverse event. In the cefdinir QD group, 41% of patients experienced an adverse event, and in the penicillin group, 38% of patients experienced an adverse event. There was no significant difference in the incidence of adverse events among the 3 treatment groups.

The incidence of adverse events that occurred during the treatment period was approximately half of the incidence of adverse events that occurred throughout the study period: 22% of cefdinir QD-treated patients, 19% of cefdinir BID-treated patients, and 18% of penicillin-treated patients experienced an adverse event while receiving study medication.

The incidence of associated adverse events showed a similar trend: 8%, 9%, and 7% of patients in the cefdinir QD, cefdinir BID, and penicillin groups, respectively, experienced an associated adverse event during the study, and there were no significant differences between treatment groups.

No deaths occurred during this study and only 1 patient (in the cefdinir BID group) experienced a serious adverse event, which was not drug-associated. Nine patients discontinued treatment as a result of an adverse event: 4 (1%) in the cefdinir QD group, 2 (1%) in the cefdinir BID group, and 3 (1%) in the penicillin group. The rates of discontinuation were not significantly different for the 3 treatment groups. Only 3 of the discontinuations were due to an associated adverse event. An additional 26 patients withdrew from the study because of adverse events after completing treatment but before the LTFU visit (7 patients treated with cefdinir QD, 10 treated with cefdinir BID, and 9 treated with penicillin). None of these adverse events were considered drug-associated.

TABLE 16. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 1 of 2)

	Cefdinir		Penicillin N = 290
	QD N = 289	BID N = 289	
Adverse Events During Study			
All Adverse Events	119 (41.2)	129 (44.6)	110 (37.9)
Associated* Adverse Events	24 (8.3)	27 (9.3)	21 (7.2)
Adverse Events During Treatment			
All Adverse Events	62 (21.5)	55 (19.0)	52 (17.9)
Adverse Events by Sex^b			
All Adverse Events			
Male	60 (38.7)	61 (39.6)	50 (35.0)
Female	59 (44.0)	68 (50.4)	60 (40.8)
Associated Adverse Events			
Male	8 (5.2)	8 (5.2)	11 (7.7)
Female	16 (11.9)	19 (14.0)	10 (6.8)
Adverse Events by Race^c			
All Adverse Events			
White	116 (44.4)	118 (45.2)	103 (40.4)
Hispanic	0 (0.0)	5 (33.3)	3 (21.4)
Black	2 (40.0)	5 (45.5)	3 (18.8)
Asian	0 (0.0)	0 (0.0)	1 (33.3)
Other	1 (50.0)	1 (50.0)	0 (0.0)
Associated Adverse Events			
White	24 (9.2)	25 (9.5)	21 (8.2)
Hispanic	0 (0.0)	1 (6.7)	0 (0.0)
Black	0 (0.0)	1 (9.1)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Events by Age^d			
All Adverse Events			
<2 years	3 (60.0)	3 (100.0)	3 (60.0)
2 to <6 years	32 (37.6)	44 (44.9)	36 (40.9)
6 to <13 years	84 (42.4)	82 (43.3)	71 (36.0)
Associated Adverse Events			
<2 years	1 (20.0)	1 (33.3)	1 (20.0)
2 to <6 years	4 (4.7)	10 (10.2)	7 (8.0)
6 to <13 years	19 (9.6)	16 (8.5)	13 (6.6)

- * Considered by the investigator to be possibly, probably, or definitely related to study medication
- ^b Percentages based on total numbers of males or females in a treatment group
- ^c Percentages based on total numbers of patients of each race in a treatment group
- ^d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range

TABLE 16. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 2 of 2)

(page 2 of 2)

	Cefdinir		
	QD N = 289	BID N = 289	Penicillin N = 290
Adverse Events by Intensity*			
All Adverse Events			
Mild	90 (31.1)	99 (34.3)	80 (27.6)
Moderate	39 (13.5)	39 (13.5)	42 (14.5)
Severe	0 (0.0)	3 (1.0)	3 (1.0)
Associated Adverse Events			
Mild	18 (6.2)	24 (8.3)	15 (5.2)
Moderate	7 (2.4)	4 (1.4)	6 (2.1)
Severe	0 (0.0)	0 (0.0)	1 (0.3)
Patients With Serious Adverse Events	0 (0.0)	1 (0.3)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Patients Who Discontinued Treatment Due to Adverse Events			
All Adverse Events	4 (1.4)	2 (0.7)	3 (1.0)
Associated Adverse Events	0 (0.0)	1 (0.3)	2 (0.7)
Patients Withdrawn Due to Adverse Events After Completing Treatment			
All Adverse Events	7 (2.4)	10 (3.5)	9 (3.1)
Associated Adverse Events	0 (0.0)	0 (0.0)	0 (0.0)

* Patients with multiple adverse events were counted once in each applicable category.

Medical Officer's Note: Dr Iravani's site reported an incidence of adverse events that was much lower than the overall reported rates: 8% for cefdinir QD, 15% for cefdinir BID, and 15% for penicillin. Because of this, the incidence of all adverse events increased slightly in all treatment groups when data from this site was excluded. Rates of all adverse events increased from 41.2% to 44.3% (a factor of 1.08) in the cefdinir QD group, from 44.6% to 47.5% (a factor of 1.07) in the cefdinir BID group, and from 37.9% to 40.2% (a factor of 1.06) in the penicillin group. As shown below, no statistically significant difference in adverse event rates was detected between cefdinir QD and penicillin, cefdinir BID and penicillin, or cefdinir QD and cefdinir BID.

	Cef. QD vs Pen CMH p-Value	Cef. BID vs Pen CMH p-Value	Cef. QD vs Cef. BID CMH p-Value
All Adverse Events			
All Sites	0.393	0.087	0.350
Excluding Site 14	0.295	0.078	0.433
Drug-Associated Adverse Events			
All Sites	0.612	0.364	0.620
Excluding Site 14	0.727	0.364	0.512

Rates of drug-associated adverse events increased from 8.3% to 8.7% (a factor of 1.05) in the cefdinir QD group, from 9.3% to 10.3% (a factor of 1.11) in the cefdinir BID group, and from 7.2% to 8.0% (a factor of 1.11) in the penicillin group. Again, no statistically significant differences were detected between groups. Overall, the adverse event profile in the revised analysis is similar to that seen in the original analysis.

Similar trends were seen when adverse events and drug-associated adverse events were examined by age, sex, and race.

5.3.1.2. All and Drug-Associated Adverse Events

Adverse events related to the body as a whole occurred more frequently than adverse events in other body systems in all treatment groups. The most frequently occurring adverse event was infection, which occurred in 9% of patients in the cefdinir QD group, 11% of patients in the cefdinir BID group, and 10% of patients in the penicillin group. Infection was a COSTART term that included upper respiratory infections, viral illnesses, and cold symptoms. In the cefdinir QD treatment group, other adverse events that occurred in at least 3% of patients were cough (8% of patients), diarrhea (8%), rhinitis (6%), otitis media (5%), vomiting (5%), abdominal pain (4%), and headache (3%). In the cefdinir BID treatment group, frequently occurring adverse events were similar to those of the QD treatment group: cough (6%), diarrhea (6%), otitis media (5%), rhinitis (5%), and abdominal pain (3%). Adverse events that occurred frequently in the penicillin-treated patients were cough (6%), vomiting (6%), otitis media (5%), headache (3%), and diarrhea (3%). The difference in the rates of diarrhea between treatment groups was only significant when comparing the cefdinir QD group with the penicillin group. In this case, patients in the cefdinir QD group had a significantly higher rate of diarrhea than did patients in the penicillin group ($p = 0.01$). Diarrhea was also the adverse event most frequently considered associated with both cefdinir and penicillin. It was considered treatment-associated in 5% of patients in the cefdinir QD group, 4% of patients in the cefdinir BID group, and 3% of patients in the penicillin group.

Medical Officer's Note: When site 14 was excluded, small increases were also seen in most individual adverse event rates and drug-associated adverse event rates as a result of the smaller denominator. The largest increase in rate for a particular event was for infection, where the rate increased by 0.8% in the cefdinir QD and BID groups and by 0.7% in the penicillin group. Lesser increases in the rates of diarrhea were seen, 0.4% in the cefdinir QD group, 0.6% in the cefdinir BID group, and 0.3% in the penicillin group. Please see table 17 in appendix P51.

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5.3.1.7. Adverse Events by Day of Onset

TABLE 18. Adverse Events by Study Day of Onset* - All Patients

Study Day	Cefdinir				Penicillin	
	14 mg/kg QD		7 mg/kg BID		Patients at Risk ^b	Patients (%) With Onset of AE
	Patients at Risk ^b	Patients (%) With Onset of AE	Patients at Risk ^b	Patients (%) With Onset of AE		
1	289	10 (3.5)	289	8 (2.8)	290	4 (1.4)
2	286	12 (4.2)	287	8 (2.8)	289	11 (3.8)
3	285	18 (6.3)	286	13 (4.5)	288	9 (3.1)
4	280	17 (6.1)	286	13 (4.5)	285	11 (3.9)
5	280	6 (2.1)	285	10 (3.5)	283	2 (0.7)
6	278	3 (1.1)	283	1 (0.4)	281	3 (1.1)
7	277	9 (3.2)	282	1 (0.4)	281	3 (1.1)
8	277	1 (0.4)	278	5 (1.8)	280	4 (1.4)
9	275	1 (0.4)	275	0 (0.0)	278	6 (2.2)
10	274	3 (1.1)	273	2 (0.7)	276	2 (0.7)
11	274	5 (1.8)	272	2 (0.7)	275	2 (0.7)
12	273	4 (1.5)	271	4 (1.5)	271	6 (2.2)
13	273	9 (3.3)	270	4 (1.5)	269	7 (2.6)
14	272	4 (1.5)	269	6 (2.2)	264	6 (2.3)
15	271	7 (2.6)	269	12 (4.5)	255	12 (4.7)
16	263	3 (1.1)	262	6 (2.3)	244	10 (4.1)
17	261	4 (1.5)	259	5 (1.9)	230	5 (2.2)
18	258	2 (0.8)	256	5 (2.0)	227	4 (1.8)
19	255	2 (0.8)	252	4 (1.6)	217	1 (0.5)
20 ^c	252	2 (0.8)	247	5 (2.0)	208	3 (1.4)

- * Patients with multiple occurrences of an adverse event were counted once for each occurrence that started on a different study day.
- ^b Number of patients receiving study drug or in the follow-up period. Patients who experienced an adverse event on a particular day were not removed from the number of patients at risk unless they were withdrawn from the study.
- ^c Patients were followed through Day 50. The last adverse events occurred on Day 34.

Medical Officer's Note: With or without data from center 14, the adverse events occurred most commonly within the first 5 days of treatment. Please see table 18 in Appendix P51.

5.3.1.8. Deaths

No deaths occurred during this study.

5.3.1.9. Serious Adverse Events

Only 1 patient experienced a serious adverse event. Patient 4 (983-51-40), who received cefdinir BID, experienced a laceration to her heel on Day 14. This event was considered definitely not related to treatment (see Appendix B.2 for complete patient narrative).

5.3.1.10. Withdrawals Due to Adverse Events

Medical Officer's Note: No patient at Dr. Iravani's site discontinued study medication or withdrew from the study due to an adverse event. This data is unchanged from the original NDA.

5.3.3. Clinical Laboratory Measurements

5.3.3.1. Changes From Baseline

5.3.3.2. Category Shift Changes

Medical Officer's Note: Two tables in each study report have not been revised: 1) Median Differences Between Baseline and Final Clinical Laboratory Values - All Patients, and 2) Category Shifts in Clinical Laboratory Values - All Patients (Tables 21 and 22 in Protocol 983-051 study report). These tables contain laboratory data that are run using a different system of programs. Extensive reprogramming would be required to exclude data.

5.3.3.3. Markedly Abnormal Clinical Laboratory Values

Patients who had markedly abnormal laboratory value at the first posttherapy visit according to the criteria in Appendix A.7 are listed in Table 23. In certain cases the central laboratory's age/gender-specific normal range limits exceeded the sponsor's criteria for markedly abnormal. For these patients, the attending physician would have considered the values within the normal ranges and no follow-up data are available. These patients are listed separately in Appendix E.22.

Table 24 summarizes the percentage of patients in each treatment group with markedly abnormal values. Included in this table are patients with clinical laboratory values that became markedly abnormal during the study regardless of drug association. This table does not include patients with markedly abnormal values at the first posttherapy visit that were improved relative to the baseline visit or the patients listed in Appendix E.22.

The most frequent markedly abnormal laboratory values were increased alkaline phosphatase and urine protein levels, increased polymorphonuclear leukocyte and eosinophil counts, and decreased lymphocyte counts. There were no differences between treatment groups in the number and type of markedly abnormal laboratory values.

Medical Officer's Note: The total number of patients experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) remained constant at 27 in the cefdinir QD treatment group, decreased to 23 in the cefdinir BID treatment group and decreased to 25 in the penicillin group, but the overall percentages remained relatively constant at 10.2%, 8.8%, and 9.5% respectively.

The largest change among individual parameters was seen in polymorphonuclear leukocytes, where one fewer patient in the cefdinir BID group and 2 fewer patients in the penicillin group experienced an increase. Other parameters showing changes only decreased by one patient. Please see table 24 in appendix P51.

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6. DISCUSSION

Cefdinir treatment resulted in consistently higher microbiologic eradication and clinical cure rates than penicillin treatment, and statistical analyses showed that these differences were statistically significant. The rates for the 2 cefdinir treatment groups were statistically equivalent to one another.

All *S. pyogenes* isolates were susceptible to both cefdinir and penicillin, so differential resistance cannot explain the difference in microbiologic eradication or clinical cure rates. However, penicillin is β -lactamase-sensitive, so it is possible for it to be destroyed by β -lactamase-producing commensal organisms in the pharynx before it can eradicate *S. pyogenes*. Also, while penicillin may inhibit the growth of GABHS, it may not be bactericidal, and therefore be unable to eradicate the pathogen. It has been suggested that lower response rates to penicillin may be due to lack of compliance with the QID dosing regimen, although lack of compliance in this research setting was not a problem.

All 3 treatments were well-tolerated. The overall incidence of adverse events was 41% for the cefdinir QD group, 45% for the cefdinir BID group, and 38% for the penicillin group. Most adverse events were mild or moderate; no patient in the cefdinir QD group, and only 1% of patients in the cefdinir BID and penicillin groups experienced a severe adverse event. The incidence of drug-associated adverse events was low and was similar among treatment groups. The highest incidence of drug-associated adverse events occurred in the cefdinir BID treatment group (9%), followed by cefdinir QD (8%), and finally the penicillin group (7%). Only 1 patient, in the penicillin group, experienced a severe, drug-associated adverse event (urticaria). Diarrhea was the adverse event most frequently considered associated with both cefdinir and penicillin treatment. Drug-associated diarrhea occurred in 5% of cefdinir QD-treated patients, 4% of cefdinir BID-treated patients, and 4% of penicillin-treated patients.

Only 1 patient, in the cefdinir BID treatment group, experienced a serious adverse event (heel laceration) during the study, and it did not result in treatment discontinuation nor was it considered treatment-associated. No deaths occurred during this study. Treatment discontinuation due to drug-associated adverse events occurred in 1 patient in the cefdinir BID group and 2 patients in the penicillin group.

One way of defining a successful course of therapy is to calculate the number of patients who completed treatment and had their baseline pathogen eradicated. Conversely, an unsuccessful course of treatment is defined as one in which a patient was unable to complete treatment or had microbiologic persistence. By this method of comparing treatment groups, which combines efficacy and safety data, cefdinir is markedly better than penicillin, with success rates of 90% (QD) and 93% (BID) compared to 68% for penicillin.

Medical Officer's Note: Exclusion of data from Dr Iravani's site did not affect results of the cefdinir capsule studies, as his site enrolled only pediatric patients taking the suspension.

*In the study comparing 10 days treatment of QD and BID cefdinir to penicillin, exclusion of data from Dr Iravani's site did not affect efficacy conclusions. Either cefdinir regimen was superior to penicillin in eradication of *S. pyogenes* from the pharynx, by both CI testing (the confidence interval did not cross zero),*

and p-value (CMH) testing. Both of the cefdinir regimens were statistically superior to the penicillin regimen in achieving clinical cures as well.

As reported adverse event rates were lower at Dr Iravani's site than the overall rate observed in the study, exclusion of data from his site resulted in increased adverse event rates in all treatment groups. Exclusion of data from Dr Iravani's site, however, did not alter analyses, showing that neither adverse event rates nor drug-associated adverse event rates were statistically significantly different between treatment groups at the $p < 0.05$ level, for either study.

The primary objective of therapy of streptococcal pharyngitis is eradication of *S. pyogenes* from the pharynx, in order to decrease the risk of complications such as rheumatic fever. The study included in the cefdinir NDA, with or without data from Dr Iravani's site, demonstrate that cefdinir effectively eradicates streptococci from the pharynx, and does so more reliably than penicillin.

7. CONCLUSIONS

- Cefdinir QD and cefdinir BID are superior microbiologically and clinically to penicillin in the treatment of GABHS pharyngitis in pediatric patients.
- Although the incidence of adverse events is somewhat higher with cefdinir treatment than penicillin treatment, cefdinir is well-tolerated. Most adverse events experienced by cefdinir-treated patients are mild and do not require treatment discontinuation.

Medical Officer's Note: The reviewer agrees with the design and conduct of the clinical study as presented by the applicant.

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APPENDIX P 51

Study 983-051

Pediatric Pharyngitis -10 days

Evaluable Patients

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding Site 14 (Iravani).

	Cefdinir QD	Cefdinir BID	Penicillin
Clinical Response Rates			
All Sites	97.6% (246/252)	96.4% (241/250)	86.8% (217/250)
Excluding Site 14	97.4% (222/228)	96.0% (218/227)	86.3% (196/227)

Microbiological Response by Patient

All Sites	92.5% (233/252)	94.8% (237/250)	70.8% (177/250)
Excluding Site 14	94.3% (215/228)	94.3% (214/227)	70.0% (159/227)

	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	(6.2%, 15.4%)	<0.001	(4.8%, 14.4%)	<0.001
Excluding Site 14	(6.1%, 15.9%)	<0.001	(4.6%, 14.8%)	<0.001
Microbiological Response by Patient				
All Sites	(15.1%, 28.2%)	<0.001	(17.7%, 30.3%)	<0.001
Excluding Site 14	(17.6%, 30.9%)	<0.001	(17.5%, 30.9%)	<0.001

Excluding Site 14 had very little effect on response rates. Both cefdinir QD and cefdinir BID are still shown to be superior to penicillin for both clinical response rate and microbiological response by patient for the evaluable population.

Clinically Evaluable Patients

The table below presents the clinical response rates and analysis results for the clinically evaluable patient population, both including and excluding Site 14.

	Cefdinir QD	Cefdinir BID	Penicillin	
Clinical Response Rates				
All Sites	97.3% (251/258)	96.5% (246/255)	86.2% (219/254)	
Excluding Site 14	97.0% (226/233)	96.1% (222/231)	85.7% (198/231)	
	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin	
	Unadjusted	CMH	Unadjusted	CMH p-value
	95% CI	p-value	95% CI	
All Sites	(6.4%, 15.7%)	<0.001	(5.4%, 15.1%)	<0.001
Excluding Site 14	(6.3%, 16.3%)	<0.001	(5.2%, 15.5%)	<0.001

Excluding Site 14 had very little effect on the clinical response rates. Both cefdinir QD and cefdinir BID are still shown to be superior to penicillin for the clinically evaluable population.

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NDA 50-739(CEFDINIR)
14 MG/KG QD OR 7 MG/KG BID X10 DAYS VS.
PEN VK 10 MG/KG QID
APPENDIX P 51

PHARYNGITIS/TONSILLITIS-PEDIATRICS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-51

Summary of Microbiologic Response Rates by Patient
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Protocol 983-051
NDA Analysis - All Sites

Microbiologic Response	Number (%) of Patients					
	Cefdinir 14 mg/kg QD		Cefdinir 7 mg/kg BID		Penicillin V-K	
	N	%	N	%	N	%
Patients w/ eradication	233	92.5	237	94.8	177	70.8
Patients w/ persistence	19	7.5	13	5.2	73	29.2
Total	252	100.0	250	100.0	250	100.0

Protocol 983-051 (Subset=51_noinv.txt)

All sites except Iravani

		Number (%) of Pathogens											
		Cefdinir 14 mg/kg QD				Cefdinir 7 mg/kg BID				Penicillin V-K			
		Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce
		N	%	N	%	N	%	N	%	N	%	N	%
ve	S pyogen	215	94.4	13	5.7	214	94.4	13	5.7	159	70.1	68	30.0
	Pathogens	215	94.3	13	5.7	214	94.3	13	5.7	159	70.0	68	30.0

Protocol 983-051

enter = 983-051-014 Iravani Only

Pathogen		Number (%) of Pathogens											
		Cefdinir 14 mg/kg QD				Cefdinir 7 mg/kg BID				Penicillin V-K			
		Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce	Eradicati- on	Persisten- ce
		N	%	N	%	N	%	N	%	N	%	N	%
Gram Positive	S pyogen	18	75.0	6	25.0	23	100.0	18	78.3	5	21.7		
otal	Pathogens	18	75.0	6	25.0	23	100.0	18	78.3	5	21.7		

The preceding page summarized the microbiologic response by pathogen patients at the test of cure visit for all patients (NDA analysis); all sites except Iravani's (14); and Site 14 alone.

Adverse Events

The table below presents the adverse event rates and drug-associated adverse event rates, and the analysis results, for patients who took drug both including and excluding site 14.

	Cefdinir QD	Cefdinir BID	Penicillin	Cef. QD vs Penicillin CMH p-value	Cef. BID vs Penicillin CMH p-value
All Adverse Events					
All Sites	41.2% (119/289)	44.6% (129/289)	37.9% (110/290)	0.393	0.087
Excluding Site 14	44.3% (117/264)	47.5% (125/263)	40.2% (106/264)	0.295	0.078
Drug-Associated Adverse Events					
All Sites	8.3% (24/289)	9.3% (27/289)	7.2% (21/290)	0.620	0.612
Excluding Site 14	8.7% (23/264)	10.3% (27/263)	8.0% (21/264)	0.727	0.364

Excluding Site 14 had very little effect on adverse event rates. No significant differences in adverse events or drug-associated adverse events were detected between patients receiving cefdinir QD and penicillin or cefdinir BID and penicillin when either including or excluding Site 14.

Dr. Iravani reported no serious adverse events in this study.

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CEFDINIR IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS**INTRODUCTION**

This package contains the revised research report tables from Studies 983-051 and 983-056 requested by Dr Roopa Viraraghavan, medical reviewer, with the clinical trial data from Dr Abdollah Iravani removed. The format is as follows:

Each tab number represents the corresponding table number in the study report. Behind each tab is the original NDA study report table, followed by the revised table. In addition to this summary, the following revised tables are in WordPerfect and are included on the accompanying WordPerfect diskette:

Protocol	Revised Table Number
983-051	1, 11, 13, 13A, 17, 24
983-056	1, 11, 13, 15, 20

The remainder of the revised information is presented as SAS output and included on the accompanying diskette in ASCII format. The terms Subset=51_noinv.txt and Subset=56_noinv.txt that are included as part of the header indicate that the dataset does not include information from Dr Iravani's site. In a few tables, there were no changes, or the change was only a line deletion of text. Only the original NDA tables are included for these cases.

Two tables in each study report have not been revised: 1) Median Differences Between Baseline and Final Clinical Laboratory Values - All Patients, and 2) Category Shifts in Clinical Laboratory Values - All Patients (Tables 21 and 22 in Protocol 983-051; Tables 17 and 18 in Protocol 983-056). These tables contain laboratory data that are run using a different system of programs. Extensive reprogramming would be required to exclude data. The Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at

Baseline (Table 24 for Protocol 983-051 and Table 20 for Protocol 983-056) does exclude data from Dr Iravani's site, and presents the most significant laboratory anomalies during the study. This table is used to drive incidence figures contained in proposed labelling. If still required after review of the data, the 2 tables not included and listed above could be revised and sent in approximately 3 weeks.

The tables for each study are listed below, and discussion of the changes caused by the deletion of Dr Iravani's data is included here. A discussion of the overall results for the entire pharyngitis indication concludes this summary.

Protocol 983-051

Protocol 983-051 was conducted to obtain information on the clinical and microbiological efficacy and safety of 10 days of cefdinir therapy versus 10 days of penicillin therapy in the treatment of streptococcal pharyngitis.

TABLE 1

Eliminating data from Dr Iravani's site (Center 14) reduced the number of patients randomized to treatment, who completed treatment, and who were evaluable by 9% in each category.

TABLES 6 and 7

Excluding the Iravani data did not substantially change the demographic characteristics of either the total patient population or the evaluable patient population.

TABLE 8

Patient exposure to study medication remained the same, with the majority of cefdinir patients (both QD and BID groups) finishing study medication on Day 10 and most penicillin patients finishing medication on Day 11.

TABLE 9

The number of patients who completed the treatment, TOC visit, and LTFU visit phases of the study decreased 9%, 9%, and 10% respectively; however, the overall percentages of patients completing each phase remained relatively constant at 92.6%, 93.1%, and 78.0% respectively.

TABLE 10

No substantial change was seen in the frequency distribution of reasons for exclusion from evaluable analyses at TOC and reasons for disqualification from qualified analyses at LTFU.

TABLE 11

The percentages of patients included in each population analyzed changed minimally after exclusion of Dr Iravani's patients.

TABLE 12

The correlation between clinical and microbiological responses remained good, with the majority of patients having clinical cure associated with microbiologic eradication.

TABLE 13

Exclusion of Site 14 had very little effect on response rates. Both cefdinir QD and cefdinir BID are still statistically superior to penicillin for both clinical and microbiological response rates, across patient populations. Cefdinir QD and cefdinir BID remain equivalent by CI testing for both clinical response rate and microbiological response rate.

Following Table 13, the same information for the evaluable patient population is presented in a slightly different format and includes p-values (Table 13A).

TABLE 14

The patient with *Enterobacter sakazakii* as a superinfecting pathogen was eliminated.

TABLE 15

The number of patients with reinfections did not change.

TABLE 16

Dr Iravani's site reported an incidence of adverse events that was much lower than the overall reported rates: 8% for cefdinir QD, 15% for cefdinir BID, and 15% for penicillin. Because of this, the incidence of all adverse events increased slightly in all treatment groups when data from this site was excluded. Rates of all adverse events increased from 41.2% to 44.3% (a factor of 1.08) in the cefdinir QD group, from 44.6% to 47.5% (a factor of 1.07) in the cefdinir BID group, and from 37.9% to 40.2% (a factor of 1.06) in the penicillin group. As shown below, no statistically significant difference in adverse event rates was detected between cefdinir QD and penicillin, cefdinir BID and penicillin, or cefdinir QD and cefdinir BID.

NDA 50-739(CEFDINIR)

	Cef. QD vs Pen CMH p-Value	Cef. BID vs Pen CMH p-Value	Cef. QD vs Cef. BID CMH p-Value
All Adverse Events			
All Sites	0.393	0.087	0.350
Excluding Site 14	0.295	0.078	0.433
Drug-Associated Adverse Events			
All Sites	0.612	0.364	0.620
Excluding Site 14	0.727	0.364	0.512

Rates of drug-associated adverse events increased from 8.3% to 8.7% (a factor of 1.05) in the cefdinir QD group, from 9.3% to 10.3% (a factor of 1.11) in the cefdinir BID group, and from 7.2% to 8.0% (a factor of 1.11) in the penicillin group. Again, no

statistically significant differences were detected between groups. Overall, the adverse event profile in the revised analysis is similar to that seen in the original analysis.

Similar trends were seen when adverse events and drug-associated adverse events were examined by age, sex, and race.

TABLE 17

Small increases were also seen in most individual adverse event rates and drug-associated adverse event rates as a result of the smaller denominator. The largest increase in rate for a particular event was for infection, where the rate increased by 0.8% in the cefdinir QD and BID groups and by 0.7% in the penicillin group. Lesser increases in the rates of diarrhea were seen, 0.4% in the cefdinir QD group, 0.6% in the cefdinir BID group, and 0.3% in the penicillin group.

TABLE 18

With or without data from Center 14, adverse events occurred most commonly within the first 5 days of treatment.

TABLES 19 and 20

No patient at Dr Iravani's site discontinued study medication or withdrew from the study due to an adverse event. The content of these tables is unchanged from the original NDA.

TABLES 21 and 22

These tables have not been revised; please see the Introduction for an explanation.

TABLE 23

This table is a list of patients with markedly abnormal values at the first posttherapy visit. The table from the original NDA has been included, with patients from Dr Iravani's site (Center 14) lined out.

TABLE 24

The total number of patients experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) remained constant at 27 in the cefdinir QD treatment group, decreased to 23 in the cefdinir BID treatment group and decreased to 25 in the penicillin group, but the overall percentages remained relatively constant at 10.2%, 8.8%, and 9.5% respectively.

The largest change among individual parameters was seen in polymorphonuclear leukocytes, where one fewer patient in the cefdinir BID group and 2 fewer patients in the penicillin group experienced an increase. Other parameters showing changes only decreased by one patient.

Protocol 983-056

Protocol 983-056 was conducted to obtain information on the clinical and microbiological efficacy and safety of 5 days of cefdinir therapy versus 10 days of penicillin therapy in the treatment of streptococcal pharyngitis.

TABLE 1

Eliminating Dr Iravani's site (Center 5) reduced the number of patients randomized to treatment by 12%, the number completing treatment by 11%, and the evaluable population by 12%.

TABLES 6 and 7

Excluding the Iravani data did not substantially change the demographic characteristics of either the total patient population or the evaluable patient population. The number of black patients decreased from 20 to 11, but this was a very small subgroup; white patients constituted 91% of the population.

TABLE 1. List of Investigators Excluding Site 14

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable
1	G. Aronovitz	39	39	37
2	H. Collins	8	7	7
3	W. Gooch, III	156	147	141
4	J. Hedrick	148	136	126
5	D. Henry	58	54	49
7	J. McCarty	39	32	28
8	M. Pichichero	73	70	64
9	E. Rothstein	62	60	59
10	E. Slosberg	75	68	66
11	M. Sperling	40	40	39
12	S. Arndt	4	4	3
15	S. McLinn	90	76	63
Total		792	733	682

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Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

		Number (%) of Patients			Total
		Cefdinir 14 mg/kg QD	Cefdinir 7 mg/kg BID	Penicillin V-K	
Total	Patients	264	264	264	792
Sex					
Male	N	141	132	133	406
	Percent	53.4	50.0	50.4	51.3
Female	N	123	132	131	386
	Percent	46.6	50.0	49.6	48.7
Race					
White	N	243	245	233	721
	Percent	92.0	92.8	88.3	91.0
Black	N	4	11	15	30
	Percent	1.5	4.2	5.7	3.8
Asian	N	1	0	3	4
	Percent	0.4	0	1.1	0.5
Other	N	16	8	13	37
	Percent	6.1	3.0	4.9	4.7
Age (Years)					
< 2	N	5	3	4	12
	Percent	1.9	1.1	1.5	1.5
2 to < 6	N	77	87	83	247

(CONTINUED)

Summary Specification Table 101
(Page 1 of 2)

NDA 50-739 (CEFIDINIR)

APPENDIX P 51

APRSL.WPD

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

		Number (%) of Patients			Total
		Cefdinir 14 mg/kg QD	Cefdinir 7 mg/kg BID	Penicillin V-K	
Age (Years)					
2 to < 6	Percent	29.2	33.0	31.4	31.2
6 to < 13	N	182	174	177	533
	Percent	68.9	65.9	67.0	67.3
Age Range	Max	13	13	13	13
	Min	1	1	2	1
Baseline Diagnosis					
Pharyngitis	N	86	91	87	264
	Percent	32.6	34.5	33.0	33.3
Tonsillitis	N	20	14	17	51
	Percent	7.6	5.3	6.4	6.4
Pharyngitis & tonsillitis	N	158	159	160	477
	Percent	59.8	60.2	60.6	60.2

Summary Specification Table 101
(Page 2 of 2)

NDA 50-739 (CEFDINIR)

APPENDIX P 51

APR51.WPD

13

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Minimum, Median and Maximum Values
For Demographic and Other Variables
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

	Cefdinir 14 mg/kg QD			Cefdinir 7 mg/kg BID			Penicillin V-K			Total		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Baseline Parameters												
Age (Years)	0.8	7.6	13.0	1.4	7.0	12.9	1.7	7.2	12.8	0.8	7.3	13.0
Weight (kg)	9.1	25.9	65.0	9.9	24.5	70.5	9.0	24.5	79.5	9.0	25.1	79.5
Height (cm)	76.2	126.0	177.3	78.2	123.2	172.7	81.5	124.5	165.1	76.2	124.5	177.3
Systolic BP (mm Hg)	70.0	98.0	150.0	70.0	100.0	128.0	70.0	100.0	140.0	70.0	100.0	150.0
Diastolic BP (mm Hg)	38.0	60.0	90.0	38.0	60.0	90.0	30.0	61.0	92.0	30.0	60.0	92.0
Temperature (C)	35.9	37.2	40.1	35.7	37.3	40.3	34.8	37.4	40.8	34.8	37.3	40.8

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
 Microbiologically-Clinically Evaluable Patients
 Protocol 983-051 (Subset=51_noinv.txt)

		Number (%) of Patients			Total
		Cefdinir 14 mg/kg QD	Cefdinir 7 mg/kg BID	Penicillin V-K	
Total	Patients	228	227	227	682
Sex					
Male	N	129	114	114	357
	Percent	56.6	50.2	50.2	52.3
Female	N	99	113	113	325
	Percent	43.4	49.8	49.8	47.7
Race					
White	N	211	211	199	621
	Percent	92.5	93.0	87.7	91.1
Black	N	4	10	15	29
	Percent	1.8	4.4	6.6	4.3
Asian	N	1	0	2	3
	Percent	0.4	0	0.9	0.4
Other	N	12	6	11	29
	Percent	5.3	2.6	4.8	4.3
Age (Years)					
< 2	N	4	3	3	10
	Percent	1.8	1.3	1.3	1.5
2 to < 6	N	64	77	70	211

(CONTINUED)

Summary Specification Table 102
 (Page 1 of 2)

NDA 50-739(CEFIDINIR)

APPENDIX P-51

APPFSL.WPD

15

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

Protocol 983-051 (Subset=51_noinv.txt)

		Number (%) of Patients			Total
		Cefdinir 14 mg/kg QD	Cefdinir 7 mg/kg BID	Penicillin V-K	
Age (Years)					
2 to < 6	Percent	28.1	33.9	30.8	30.9
6 to < 13	N	160	147	154	461
	Percent	70.2	64.8	67.8	67.6
Age Range	Max	13	13	13	13
	Min	1	1	2	1
Baseline Diagnosis					
Pharyngitis	N	73	79	73	225
	Percent	32.0	34.8	32.2	33.0
Tonsillitis	N	15	9	15	39
	Percent	6.6	4.0	6.6	5.7
Pharyngitis & tonsillitis	N	140	139	139	418
	Percent	61.4	61.2	61.2	61.3

Summary Specification Table 102
(Page 2 of 2)

NDA 50-739(CEFdinir)

APPENDIX P 51

APP51.WPD

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Minimum, Median and Maximum Values
For Demographic and Other Variables
Microbiologically-Clinically Evaluable Patients

Protocol 983-051 (Subset=51_noinv.txt)

NDA 50-739 (CEFDINIR)

APPENDIX P 51

	Cefdinir 14 mg/kg QD			Cefdinir 7 mg/kg BID			Penicillin V-K			Total		
	Min	Med	Max	Min	Med	Max	Min	Med	Max	Min	Med	Max
Baseline Parameters												
Age (Years)	0.8	7.6	13.0	1.4	6.9	12.9	1.7	7.2	12.8	0.8	7.3	13.0
Weight (kg)	9.1	25.9	65.0	9.9	23.9	70.5	9.0	25.0	79.5	9.0	25.1	79.5
Height (cm)	76.2	126.5	177.3	78.2	122.0	172.7	81.5	124.5	165.1	76.2	124.5	177.3
Systolic BP (mm Hg)	70.0	98.0	150.0	70.0	100.0	128.0	70.0	100.0	140.0	70.0	100.0	150.0
Diastolic BP (mm Hg)	38.0	60.0	90.0	38.0	60.0	90.0	30.0	62.0	92.0	30.0	60.0	92.0
Temperature (C)	35.9	37.2	40.1	35.7	37.3	40.3	34.8	37.3	40.8	34.8	37.3	40.8

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Exposure to Study Medication
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

Days on Study Medication	Number (%) of Patients					
	Cefdinir 14 mg/kg QD (Median=10.0)		Cefdinir 7 mg/kg BID (Median=10.0)		Penicillin V-K (Median=11.0)	
	N	%	N	%	N	%
1	2	0.8	2	0.8	0	0
2	3	1.1	1	0.4	2	0.8
3	2	0.8	1	0.4	1	0.4
4	1	0.4	3	1.1	1	0.4
5	2	0.8	0	0	1	0.4
6	0	0	1	0.4	0	0
7	1	0.4	4	1.5	0	0
8	4	1.5	4	1.5	3	1.1
9	0	0	1	0.4	0	0
10	228	86.4	193	73.4	96	36.4
11	13	4.9	45	17.1	149	56.4
12	4	1.5	2	0.8	4	1.5
13	0	0	1	0.4	0	0
14	0	0	1	0.4	1	0.4
16	1	0.4	0	0	1	0.4
17	0	0	1	0.4	0	0
Unknown	3	1.1	3	1.1	5	1.9
Total	264	100.0	263	100.0	264	100.0

Summary Specification Table 265
(Page 1 of 1)

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Treatment Phase

All Patients

Protocol 983-051 (Subset=51_noinv.txt)

		Number of Patients							
		Cefdinir 14 mg/kg QD N=264		Cefdinir 7 mg/kg BID N=264		Penicill- in V-K N=264		Total N=792	
		N	%	N	%	N	%	N	%
Completed Phase		246	93.2	241	91.3	246	93.2	733	92.6
Reason for Withdrawal	Lack of Compliance	2	0.8	4	1.5	6	2.3	12	1.5
	Adverse Event	4	1.5	2	0.8	3	1.1	9	1.1
	No Baseline Pathogen	6	2.3	9	3.4	5	1.9	20	2.5
	Other/Administrati- ve	6	2.3	8	3.0	4	1.5	18	2.3

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Test-Of-Cure Visit

All Patients

Protocol 983-051 (Subset=51_noinv.txt)

		Number of Patients							
		Cefdinir 14 mg/kg QD N=264		Cefdinir 7 mg/kg BID N=264		Penicill- in V-K N=264		Total N=792	
		N	%	N	%	N	%	N	%
Completed Phase		247	93.6	245	92.8	245	92.8	737	93.1
Reason for Withdrawal	Lack of Compliance	4	1.5	4	1.5	7	2.7	15	1.9
	Adverse Event	4	1.5	2	0.8	3	1.1	9	1.1
	Failure at end of therapy	0	0	0	0	2	0.8	2	0.3
	No Baseline Pathogen	6	2.3	9	3.4	6	2.3	21	2.7
	Other/Administrati- ve	3	1.1	4	1.5	1	0.4	8	1.0

Summary Specification Table 270
(Page 1 of 1)

NDA 50-739 (CEFDINIR)

APPENDIX P 51

APPENDIX P 51

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Long-Term Follow-Up Visit

All Patients

Protocol 983-051 (Subset=51_noinv.txt)

		Number of Patients							
		Cefdinir 14 mg/kg QD N=264		Cefdinir 7 mg/kg BID N=264		Penicill- in V-K N=264		Total N=792	
		N	%	N	%	N	%	N	%
Completed Phase		225	85.2	213	80.7	180	68.2	618	78.0
Reason for Withdrawal	Lack of Compliance	5	1.9	9	3.4	12	4.5	26	3.3
	Adverse Event	11	4.2	12	4.5	11	4.2	34	4.3
	Failure at end of therapy	14	5.3	14	5.3	54	20.5	82	10.4
	No Baseline Pathogen	6	2.3	10	3.8	6	2.3	22	2.8
	Other/Administrati- ve	3	1.1	6	2.3	1	0.4	10	1.3

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Reasons for Exclusion of Patients from Evaluable Analyses
Test-of-Cure Visit

Protocol 983-051 (Subset=51_noinv.txt)

		Number (%) of Patients							
		Cefdinir 14 mg/kg QD		Cefdinir 7 mg/kg BID		Penicillin V-K		Total	
		N	%	N	%	N	%	N	%
Exclusions from Clinical Analyses	*** Total ***	31	11.7	33	12.5	33	12.5	97	12.2
	Clin asmt missed	5	1.9	7	2.7	5	1.9	17	2.1
	Clin out of range	17	6.4	19	7.2	21	8.0	57	7.2
	Concurrent antibac	1	0.4	5	1.9	2	0.8	8	1.0
	Med not as prescrib	24	9.1	22	8.3	15	5.7	61	7.7
	Randomiz violation	0	0	0	0	2	0.8	2	0.3
Additional Exclusions from Microbiological Analyses	*** Total ***	5	1.9	4	1.5	4	1.5	13	1.6
	Cult out of range	16	6.1	17	6.4	19	7.2	52	6.6
	Culture missed	7	2.7	9	3.4	10	3.8	26	3.3
	No base suscp tsst	0	0	1	0.4	0	0	1	0.1
	No proven pathogn	9	3.4	14	5.3	7	2.7	30	3.8
Total	*** TOTAL ***	36	13.6	37	14.0	37	14.0	110	13.9

Summary Specification Table 172
(Page 1 of 1)

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients
 Reasons for Disqualification of Microbiologically/Clinically Evaluable Patients from Analysis
 Long-Term Follow-Up Visit

Protocol 983-051 (Subset=51_noinv.txt)

Disqualification	Number (%) of Patients					
	Cefdinir 14 mg/kg QD		Cefdinir 7 mg/kg BID		Penicillin V-K	
	N	%	N	%	N	%
*** Total ***	32	14.0	33	14.5	76	33.5
Clin asmt missed	19	8.3	23	10.1	59	26.0
Clin out of range	8	3.5	3	1.3	9	4.0
Concurrent antibac	7	3.1	7	3.1	8	3.5
Cult out of range	7	3.1	4	1.8	10	4.4
Culture missed	19	8.3	23	10.1	58	25.6

Summary Specification Table 175
 (Page 1 of 1)

APPENDIX P 51

NDA 50-739 (CEFDINIR)

APPENDIX P 51

CI-983
Amendment

TABLE 11. Patients Included in Efficacy Summaries Excluding Site 14
[Number (%) of Patients]

Patient Population	Cefdinir		Penicillin
	14 mg/kg QD	7 mg/kg BID	
Intent-to-Treat (ITT)	264 (100.0)	264 (100.0)	264 (100.0)
Modified Intent-to-Treat (MITT)	248 (93.9)	242 (91.7)	248 (93.9)
Clinically Evaluable	233 (88.2)	231 (87.5)	231 (87.5)
Evaluable	228 (86.3)	227 (86.0)	227 (86.0)
Qualified	196 (74.2)	194 (73.5)	149 (56.4)

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Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Combined Investigator/Sponsor Determination Response Rates Versus Microbiologic Response Rates
 Test-of-Cure Visit
 Microbiologically-Clinically Evaluable Patients

Protocol 983-051 (Subset=51_noinv.txt)

Microbiologic Response	Clinical Response											
	Cefdinir 14 mg/kg QD				Cefdinir 7 mg/kg BID				Penicillin V-K			
	Cure		Failure		Cure		Failure		Cure		Failure	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients w/ eradication	213	93.4	2	0.9	209	92.1	5	2.2	157	69.2	2	0.9
Patients w/ persistence	9	3.9	4	1.8	9	4.0	4	1.8	39	17.2	29	12.8

TABLE 13. Summary of Efficacy Analyses at TOC Excluding Site 14

Pairwise Comparison	Population	Rates (%)	95% CI	Interpretation
Microbiologic Eradication				
QD vs Penicillin	Evaluable ^a	94 vs 70	17.6, 30.9	QD Superior
	MITT	94 vs 69	18.1, 31.1	QD Superior
	ITT	88 vs 65	16.1, 30.1	QD Superior
BID vs Penicillin	Evaluable ^a	94 vs 70	17.5, 30.9	BID Superior
	MITT	94 vs 69	19.0, 31.7	BID Superior
	ITT	86 vs 65	14.5, 28.7	BID Superior
QD vs BID	Evaluable	94 vs 94	-4.2, 4.3	Equivalent
	MITT	94 vs 94	-4.9, 3.6	Equivalent
	ITT	88 vs 86	-4.2, 7.2	Equivalent
Clinical Response				
QD vs Penicillin	Evaluable	97 vs 86	6.1, 15.9	QD Superior
	Clinically Evaluable	97 vs 86	6.3, 16.3	QD Superior
	ITT	95 vs 81	7.8, 18.7	QD Superior
BID vs Penicillin	Evaluable	96 vs 86	4.6, 14.8	BID Superior
	Clinically Evaluable	96 vs 86	5.2, 15.5	BID Superior
	ITT	93 vs 81	5.7, 17.0	BID Superior
QD vs BID	Evaluable	97 vs 96	-1.9, 4.6	Equivalent
	Clinically Evaluable	97 vs 96	-2.4, 4.2	Equivalent
	ITT	95 vs 93	-2.2, 6.0	Equivalent

^a Primary efficacy analysis

TABLE 13A
PROTOCOL 983-051
RESPONSE RATES AND ANALYSIS RESULTS

EVALUABLE PATIENT POPULATION

	Cefdinir QD	Cefdinir BID	Penicillin
Clinical Response Rates			
All Sites	97.6% (246/252)	96.4% (241/250)	86.8% (217/250)
Excluding Site 14	97.4% (222/228)	96.0% (218/227)	86.3% (196/227)
Microbiological Response by Patient			
All Sites	92.5% (233/252)	94.8% (237/250)	70.8% (177/250)
Excluding Site 14	94.3% (215/228)	94.3% (214/227)	70.0% (159/227)

	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin		Cefdinir QD vs. Cefdinir BID	
	Unadjusted	CMH	Unadjusted	CMH	Unadjusted	CMH
	95% CI	p-value	95% CI	p-value	95% CI	p-value
Clinical Response Rates						
All Sites	(6.2%, 15.4%)	<0.001	(4.8%, 14.4%)	<0.001	(-1.8%, 4.2%)	0.380
Excluding Site 14	(6.1%, 15.9%)	0.001	(4.6%, 14.8%)	0.001	(-1.9%, 4.6%)	0.380
Microbiological Response by Patient						
All Sites	(15.1%, 28.2%)	<0.001	(17.7%, 30.3%)	<0.001	(-6.6%, 1.9%)	0.302
Excluding Site 14	(17.6%, 30.9%)	<0.001	(17.5%, 30.9%)	<0.001	(-4.2%, 4.3%)	0.963

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Superinfection Rates
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

Superinfecting Pathogen(s)		Cefdinir 14 mg/kg QD N=264		Cefdinir 7 mg/kg BID N=264	
		Number of Patients with Superinfection	%	Number of Patients with Superinfection	%
Gram Positive	S pyogen	2	0.8	1	0.4
	Strep G	0	0	1	0.4
Total Patients		2	0.8	2	0.8

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Adverse Events
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

	Cefdinir 14 mg/kg OD (N=264)		Cefdinir 7 mg/kg BID (N=263)		Penicillin V-K (N=264)	
	N	%	N	%	N	%
Number of Patients Reporting AE	117	44.3	125	47.5	106	40.2
Number of Patients Reporting Mild AE	88	33.3	96	36.5	77	29.2
Number of Patients Reporting Moderate AE	39	14.8	38	14.4	41	15.5
Number of Patients Reporting Severe AE	0	0.0	3	1.1	3	1.1
Number of Male Patients Reporting AE	60	42.6	58	43.9	49	36.8
Number of Female Patients Reporting AE	57	46.3	67	51.1	57	43.5
Number of Patients < 2 Years Old Reporting AE	3	60.0	3	100.0	3	75.0
Number of Patients 2 to < 6 Years Old Reporting AE	32	41.6	42	48.3	35	42.2
Number of Patients 6 to < 13 Years Old Reporting AE	82	45.1	80	46.2	68	38.4
Number of Patients 13 to < 18 Years Old Reporting AE	0	0.0	0	0.0	0	0.0
Number of White Patients Reporting AE	114	46.9	116	47.5	99	42.5
Number of Black Patients Reporting AE	2	50.0	5	45.5	3	20.0
Number of Asian Patients Reporting AE	0	0.0	0	0.0	1	33.3
Number of Hispanic Patients Reporting AE	0	0.0	3	50.0	3	27.3
Number of Other Patients Reporting AE	1	50.0	1	50.0	0	0.0

(CONTINUED)

Patients who did not discontinue treatment due to an AE
Summary Specification Table 148
(Page 1 of 2)

NDA 50-739 (CEFIDINIR)

APPENDIX F 51

APPENDIX F 51

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Adverse Events
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

	Cefdinir 14 mg/kg QD (N=264)		Cefdinir 7 mg/kg BID (N=263)		Penicillin V-K (N=264)	
	N	%	N	%	N	%
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	4	1.5	2	0.8	3	1.1
Number of Patients Whose Treatment Was Discontinued Due to Non-TESS AE	0	0.0	0	0.0	0	0.0
Number of Patients Withdrawn from Study Due to AE	7	2.7	10	3.8	9	3.4

*Patients who did not discontinue treatment due to an AE
Summary Specification Table 148
(Page 2 of 2)

APPENDIX P 16

NDA 50-739(CEFIDINIR)

APPENDIX P 16

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Associated Adverse Events
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

	Cefdinir 14 mg/kg QD (N=264)		Cefdinir 7 mg/kg BID (N=263)		Penicillin V-K (N=264)	
	N	%	N	%	N	%
Number of Patients Reporting AE	23	8.7	27	10.3	21	8.0
Number of Patients Reporting Mild AE	17	6.4	24	9.1	15	5.7
Number of Patients Reporting Moderate AE	7	2.7	4	1.5	6	2.3
Number of Patients Reporting Severe AE	0	0.0	0	0.0	1	0.4
Number of Male Patients Reporting AE	8	5.7	8	6.1	11	8.3
Number of Female Patients Reporting AE	15	12.2	19	14.5	10	7.6
Number of Patients < 2 Years Old Reporting AE	1	20.0	1	33.3	1	25.0
Number of Patients 2 to < 6 Years Old Reporting AE	4	5.2	10	11.5	7	8.4
Number of Patients 6 to < 13 Years Old Reporting AE	18	9.9	16	9.2	13	7.3
Number of Patients 13 to < 18 Years Old Reporting AE	0	0.0	0	0.0	0	0.0
Number of White Patients Reporting AE	23	9.5	25	10.2	21	9.0
Number of Black Patients Reporting AE	0	0.0	1	9.1	0	0.0
Number of Asian Patients Reporting AE	0	0.0	0	0.0	0	0.0
Number of Hispanic Patients Reporting AE	0	0.0	1	16.7	0	0.0
Number of Other Patients Reporting AE	0	0.0	0	0.0	0	0.0

(CONTINUED)

*Patients who did not discontinue treatment due to an AE
Summary Specification Table 262
(Page 1 of 2)

NDA 50-739 (CEFDINIR)

APPENDIX P 51

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Associated Adverse Events
All Patients

Protocol 983-051 (Subset=51_noinv.txt)

	Cefdinir 14 mg/kg OD (N=264)		Cefdinir 7 mg/kg BID (N=263)		Penicillin V-K (N=264)	
	N	%	N	%	N	%
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	0	0.0	1	0.4	2	0.8
Number of Patients Whose Treatment Was Discontinued Due to Non-TESS AE	0	0.0	0	0.0	0	0.0
Number of Patients Withdrawn from Study Due to AE	0	0.0	0	0.0	0	0.0

*Patients who did not discontinue treatment due to an AE
Summary Specification Table 262
(Page 2 of 2)

APPENDIX P 51

NDA 50-739 (CEFDINIR)

APPENDIX P 51

TABLE 17. All and Associated Adverse Events by Body System: All Patients - Protocol 983-51
[Number (%) of Patients]
(Page 1 of 5)

BODY SYSTEM ^a / Adverse Event	Sites Excluding Iravani					
	Cefdinir				Penicillin	
	14 mg/kg QD N = 264		7 mg/kg BID N = 263		N = 264	
	All	Assoc	All	Assoc	All	Assoc
BODY AS A WHOLE	57 (21.6)	4 (1.5)	54 (20.5)	6 (2.3)	54 (20.5)	5 (1.9)
Infection	25 (9.5)	0 (0.0)	32 (12.2)	0 (0.0)	29 (11.0)	0 (0.0)
Abdominal Pain	12 (4.5)	3 (1.1)	9 (3.4)	6 (2.3)	6 (2.3)	5 (1.9)
Headache	9 (3.4)	1 (0.4)	6 (2.3)	0 (0.0)	7 (2.7)	0 (0.0)
Accidental Injury	6 (2.3)	0 (0.0)	4 (1.5)	0 (0.0)	7 (2.7)	0 (0.0)
Flu Syndrome	3 (1.1)	0 (0.0)	4 (1.5)	0 (0.0)	4 (1.5)	0 (0.0)
Photosensitivity Reaction	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic Reaction	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Back Pain	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Chest Pain	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Face Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Fever	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)
Malaise	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neck Pain	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Neck Rigidity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Pain	4 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Sepsis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RESPIRATORY SYSTEM	41 (15.5)	0 (0.0)	38 (14.4)	0 (0.0)	32 (12.1)	0 (0.0)
Cough Increased	23 (8.7)	0 (0.0)	18 (6.8)	0 (0.0)	16 (6.1)	0 (0.0)
Rhinitis	17 (6.4)	0 (0.0)	12 (4.6)	0 (0.0)	7 (2.7)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	4 (1.5)	0 (0.0)
Lung Disorder	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

^a The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 17. All and Associated Adverse Events by Body System: All Patients - Protocol 983-51
[Number (%) of Patients]
(Page 2 of 5)

BODY SYSTEM ^a / Adverse Event	Sites Excluding Iravani					
	Cefdinir				Penicillin N = 264	
	14 mg/kg QD N = 264		7 mg/kg BID N = 263			
	All	Assoc	All	Assoc	All	Assoc
RESPIRATORY SYSTEM (Continued)						
Pneumonia	2 (0.8)	0 (0.0)	3 (1.1)	0 (0.0)	2 (0.8)	0 (0.0)
Laryngitis	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Asthma	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Pharyngitis	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Voice Alteration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory Disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sputum Increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
DIGESTIVE SYSTEM	34 (12.9)	19 (7.2)	33 (12.5)	17 (6.5)	28 (10.6)	14 (5.3)
Diarrhea	21 (8.0)	12 (4.5)	18 (6.8)	12 (4.6)	9 (3.4)	8 (3.0)
Vomiting	13 (4.9)	3 (1.1)	5 (1.9)	2 (0.8)	15 (5.7)	5 (1.9)
Anorexia	1 (0.4)	1 (0.4)	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)
Gastroenteritis	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gingivitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Glossitis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Liver Function Tests Abnormal	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Mouth Ulceration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Nausea	2 (0.8)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Thirst	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Tooth Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dyspepsia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

^a The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 17. All and Associated Adverse Events by Body System: All Patients - Protocol 983-51
[Number (%) of Patients]
(Page 3 of 5)

BODY SYSTEM ^a / Adverse Event	Sites Excluding Iravani					
	Cefdinir				Penicillin N = 264	
	14 mg/kg QD N = 264		7 mg/kg BID N = 263			
	All	Assoc	All	Assoc	All	Assoc
DIGESTIVE SYSTEM (Continued)						
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Melena	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
SPECIAL SENSES	20 (7.6)	1 (0.4)	17 (6.5)	0 (0.0)	20 (7.6)	0 (0.0)
Otitis Media	13 (4.9)	0 (0.0)	13 (4.9)	0 (0.0)	13 (4.9)	0 (0.0)
Conjunctivitis	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Ear Disorder	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)
Ear Pain	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Amblyopia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Deafness	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)
Eye Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Lacrimation Disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis Externa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Tinnitus	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SKIN AND APPENDAGES	10 (3.8)	0 (0.0)	13 (4.9)	4 (1.5)	12 (4.5)	4 (1.5)
Rash	4 (1.5)	0 (0.0)	4 (1.5)	2 (0.8)	6 (2.3)	3 (1.1)
Cutaneous Moniliasis	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)
Contact Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Exfoliative Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes Simplex	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Maculopapular Rash	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)
Pustular Rash	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

^a The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 17. All and Associated Adverse Events by Body System: All Patients - Protocol 983-51
[Number (%) of Patients]
(Page 5 of 5)

BODY SYSTEM ^a / Adverse Event	Sites Excluding Iravani					
	Cefdinir				Penicillin N = 264	
	14 mg/kg QD N = 264		7 mg/kg BID N = 263			
	All	Assoc	All	Assoc	All	Assoc
NERVOUS SYSTEM (Continued)						
Nervousness	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Somnolence	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Torticollis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
METABOLIC AND NUTRITIONAL SYSTEM	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)
Lactate Dehydrogenase Increased	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Peripheral Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
CARDIOVASCULAR SYSTEM	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cardiovascular Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Postural Hypotension	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MUSCULOSKELETAL SYSTEM	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Arthrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

^a The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Adverse Events by Study Day of Onset*

Patients Who Received Study Medication

Protocol 983-051 (Subset=51_noinv.txt)

Appendix P 51

NDA 50-739 (CEFIDINIR)

Study Day	Treatment Group								
	Cefdinir 14 mg/kg QD N=264			Cefdinir 7 mg/kg BID N=263			Penicillin V-K N=264		
	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE
1	264	9	3.4	263	8	3.0	264	4	1.5
2	261	12	4.6	261	8	3.1	263	11	4.2
3	260	18	6.9	260	13	5.0	262	9	3.4
4	255	17	6.7	260	13	5.0	259	10	3.9
5	255	6	2.4	259	10	3.9	257	2	0.8
6	253	3	1.2	257	1	0.4	255	3	1.2
7	252	9	3.6	256	1	0.4	255	3	1.2
8	252	1	0.4	252	5	2.0	255	4	1.6
9	250	1	0.4	250	0	0.0	254	6	2.4
10	249	3	1.2	248	2	0.8	252	2	0.8
11	249	5	2.0	247	2	0.8	251	2	0.8
12	248	3	1.2	246	3	1.2	247	4	1.6
13	248	9	3.6	245	4	1.6	245	7	2.9
14	247	4	1.6	244	6	2.5	240	6	2.5
15	246	7	2.8	244	12	4.9	231	12	5.2

APPENDIX P 51

(CONTINUED)

* Contains only Adverse Events that occurred after the start of study drug (Study Day 1). Patients reporting multiple occurrences of an Adverse Event are counted once for each occurrence of the Adverse Event starting on a different Study Day.

Summary Specification Table 152

(Page 1 of 4)

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Adverse Events by Study Day of Onset*
 Patients Who Received Study Medication
 Protocol 983-051 (Subset=51_noinv.txt)

Study Day	Treatment Group								
	Cefdinir 14 mg/kg QD N=264			Cefdinir 7 mg/kg BID N=263			Penicillin V-K N=264		
	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE
16	238	3	1.3	237	6	2.5	221	10	4.5
17	236	4	1.7	234	5	2.1	207	5	2.4
18	233	2	0.9	231	5	2.2	204	4	2.0
19	230	2	0.9	227	4	1.8	194	1	0.5
20	227	2	0.9	222	5	2.3	186	3	1.6
21	226	1	0.4	221	3	1.4	183	2	1.1
22	226	3	1.3	219	3	1.4	182	4	2.2
23	225	4	1.8	217	5	2.3	180	0	0.0
24	225	5	2.2	217	3	1.4	180	5	2.8
25	224	1	0.4	216	5	2.3	180	2	1.1
26	224	3	1.3	214	4	1.9	177	4	2.3
27	224	8	3.6	213	5	2.3	175	3	1.7
28	218	6	2.8	212	7	3.3	169	3	1.8
29	174	9	5.2	162	2	1.2	145	7	4.8
30	115	2	1.7	108	7	6.5	97	2	2.1

(CONTINUED)

* Contains only Adverse Events that occurred after the start of study drug (Study Day 1).
 Patients reporting multiple occurrences of an Adverse Event are counted once for each
 occurrence of the Adverse Event starting on a different Study Day.

Summary Specification Table 152

(Page 2 of 4)

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Adverse Events by Study Day of Onset*
 Patients Who Received Study Medication
 Protocol 983-051 (Subset=51_noinv.txt)

Study Day	Treatment Group								
	Cefdinir 14 mg/kg QD N=264			Cefdinir 7 mg/kg BID N=263			Penicillin V-K N=264		
	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE
31	78	6	7.7	71	1	1.4	66	2	3.0
32	52	0	0.0	47	2	4.3	46	1	2.2
33	33	3	9.1	32	3	9.4	31	1	3.2
34	19	1	5.3	19	1	5.3	19	1	5.3
35	10	0	0	12	0	0	13	0	0
36	3	0	0	9	0	0	7	0	0
37	3	0	0	7	0	0	6	0	0
38	2	0	0	6	0	0	5	0	0
39	2	0	0	5	0	0	4	0	0
40	2	0	0	3	0	0	4	0	0
41	2	0	0	2	0	0	3	0	0
42	1	0	0	1	0	0	3	0	0
44	1	0	0	1	0	0	2	0	0
45	1	0	0	1	0	0	1	0	0
46	0	0	0.0	1	0	0	1	0	0

(CONTINUED)

* Contains only Adverse Events that occurred after the start of study drug (Study Day 1).
 Patients reporting multiple occurrences of an Adverse Event are counted once for each
 occurrence of the Adverse Event starting on a different Study Day.

Summary Specification Table 152

(Page 3 of 4)

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Adverse Events by Study Day of Onset^{*}
 Patients Who Received Study Medication
 Protocol 983-051 (Subset=51_noinv.txt)

Study Day	Treatment Group								
	Cefdinir 14 mg/kg QD N=264			Cefdinir 7 mg/kg BID N=263			Penicillin V-K N=264		
	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE	Number of patients at risk	Number with onset of AE	% of patients with onset of AE
47	0	0	0.0	0	0	0.0	1	0	0
50	0	0	0.0	0	0	0.0	0	0	0.0

* Contains only Adverse Events that occurred after the start of study drug (Study Day 1).
 Patients reporting multiple occurrences of an Adverse Event are counted once for each
 occurrence of the Adverse Event starting on a different Study Day.

Summary Specification Table 152
 (Page 4 of 4)

NOTE: Dr. Travani's Data is marked out (Center 14)

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 1 of 8)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinir QD									
1	3	W	6 yr, M	20.9	Eosinophils	13%	3	0-7	No history noted
1	18	W	8 yr, M	25.9	Urine Protein	1+	Neg	Neg	No history noted
1	37	W	5 yr, M	18.6	Lymphocytes	7%	17	10-66	No history noted
					Polymorphonuclear Leukocytes	77%	77	20-75	
3	128	W	11 yr, M	40.9	Urine Protein	2+	Neg	Neg	No history noted
3	138	H	23 mo, M	10.9	Urine Specific Gravity	1.04	--	1.005-1.03	No history noted
4	27	W	9 yr, M	26.5	Lymphocytes	6%	21	10-49	History viral gastroenteritis; failure
4	62	W	5 yr, M	39.0	Eosinophils	12%	10	0-7	ADD; methylphenidate; failure Eosinophils 8% on Day 29
4	77	W	7 yr, M	24.5	Polymorphonuclear Leukocytes	78%	76	20-75	History of otitis media AB: URI PMNs 50% on Day 18
4	85	W	7 yr, M	27.0	Alanine Aminotransferase	104 U/L	121	0-40	Per site, returned to normal limits on Day 12
4	95	W	5 yr, F	17.5	Eosinophils	13%	6	0-7	Asthma, allergies; beclomethasone AB: second degree burn
4	100	W	9 yr, F	26.4	Eosinophils	13%	8	0-7	Eosinophils 14% on Day 29
4	146	W	8 yr, M	33.5	Alkaline Phosphatase	421 U/L	393	25-350	No history noted
5	8	W	12 yr, M	44.5	Phosphorus	5.5 mg/dL	5.5	2.5-5	Adolescent AB: diarrhea
7	30	H	12 yr, F	55.9	Urine Red Blood Cells	21-50/HPF	1-5	0	Adolescent

W = White; H = Hispanic; M = Male; F = Female; Neg = Negative; -- = Not available; ADD = Attention Deficit Disorder; AB = Adverse Event; URI = Upper Respiratory Infection.

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 2 of 8)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinir QD (Continued)									
8	58	W	12 yr, F	47.7	Urine Protein	2+	Trace	Neg	AB: cold symptoms
8	67	W	9 yr, F	31.8	Urine White Blood Cells	21-50/HPF	0	1-5	AB: toothache
9	6	W	5 yr, F	19.8	Phosphorus	6.9 mg/dL	4.7	3.1-6.3	AB: diarrhea, otitis media
9	24	W	11 yr, F	30.0	Eosinophils	11%	2	0-7	No history noted
9	56	W	5 yr, F	22.8	Eosinophils	11%	10	0-7	No history noted
9	61	W	11 yr, M	32.0	Eosinophils	19%	9	0-7	Seasonal allergies; clemastine, albuterol
10	10	W	10 yr, M	39.0	White Blood Cells	$3 \times 10^9/L$	7.5	4.3-13.5	History recurrent otitis media
10	19	W	7 yr, M	24.1	Alkaline Phosphatase	439 U/L	396	25-350	No history noted
10	34	W	11 yr, F	47.3	Eosinophils	16%	12	0-7	No history noted Eosinophils 11% on Day 11
10	37	B	6 yr, M	23.0	Urine Specific Gravity	1.036	1.03	1.005-1.03	AB: abdominal pain, fever, headache
10	57	W	7 yr, F	20.0	White Blood Cells	$20.8 \times 10^9/L$	25.6	5-14.5	Failure Day 15
					Lymphocytes	7%	3	10-66	
					Polymorphonuclear Leukocytes	88%	79	20-75	
10	58	W	9 yr, F	27.7	Platelets	$696 \times 10^9/L$	329	140-450	AB: cough; dextromethorphan
15	6	W	7 yr, F	34.1	White Blood Cells	$2.9 \times 10^9/L$	4.4	5-14.5	No history noted
15	7	W	10 yr, M	46.4	Eosinophils	12%	2	0-7	Allergic rhinitis; albuterol, triamcinolone
15	34	W	12 yr, M	41.4	Urine Protein	1+	Neg	Neg	ADD, myoclonic seizure syndrome; dextroamphetamine

W = White; B = Black; M = Male; F = Female; Neg = Negative; AB = Adverse Event; ADD = Attention Deficit Disorder.

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 3 of 8)

NDA 50739 (CEFDINIR)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinir BID									
1	21	W	10 yr, M	32.3	Lymphocytes	8%	18	10-49	Recurrence AB: viral URI
1	30	W	8 yr, F	27.7	Alkaline Phosphatase	403 U/L	436	25-350	Microscopic hematuria
					Urine Protein	2+	1+	Neg	
3	72	W	5 yr, M	21.0	Polymorphonuclear Leukocytes	79%	78	20-75	Failure
3	73	W	2 yr, F	14.6	Bands	17%	0	0-8	No history noted
3	116	AI	3 yr, F	14.1	Bicarbonate	13 mmol/L	16	22-32	No history noted
3	126	W	8 yr, M	25.9	Urine Protein	2+	1+	Neg	No history noted
3	137	W	10 yr, F	30.0	Urine Protein	2+	2+	Neg	No history noted
3	150	W	22 mo, M	11.3	Bicarbonate	13 mmol/L	19	22-32	AB: mild URI, congestion
4	140	W	11 yr, F	59.5	Urine White Blood Cells	21-50/HPF	1-5	1-5	Migraine
5	38	W	4 yr, F	17.3	Calcium	6.6 mg/dL	9.7	8.4-10.2	Failure Day 12
5	40	W	11 yr, F	42.0	Urine Protein	4+	1+	Neg	No history noted
7	13	W	6 yr, F	35.0	Urine White Blood Cells	21-50/HPF	6-10	1-5	AB: UTI Recurrence Day 20 Urine white blood cells 1-5 on Day 20
8	28	W	9 yr, M	40.9	White Blood Cells	$21.4 \times 10^9/L$	17.8	4.5-13.5	Recurrence Day 18
8	33	W	8 yr, M	27.3	Chloride	84 mEq/L	102	97-110	Asthma, allergies AB: URI
					Sodium	122 mEq/L	141	136-146	
8	45	W	6 yr, M	30.7	Alkaline Phosphatase	407 U/L	416	25-350	History recurrent otitis media

W = White; AI = American Indian; M = Male; F = Female; Neg = Negative; AB = Adverse Event; URI = Upper Respiratory Infection; UTI = Urinary Tract Infection.

APPENDIX F 51

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 4 of 8)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinir BID (Continued)									
8	49	W	5 yr, F	16.8	Hemoglobin	9.6 g/dL	10.3	11.5-14.5	AE: viral gastroenteritis
9	12	W	7 yr, M	20.1	Lymphocytes	7%	13	10-66	Failure Day 13
					Polymorphonuclear Leukocytes	86%	74	20-75	
10	5	W	8 yr, M	27.2	Alkaline Phosphatase	405 U/L	394	25-350	Eczema
10	62	W	6 yr, F	29.2	Eosinophils	13%	2	0-7	AB: abdominal pain, vomiting
11	2	W	3 yr, F	16.0	Eosinophils	14%	4	0-7	History otitis externa Eosinophils 2% on Day 33
11	14	H	11 yr, F	40.1	Urine Specific Gravity	1.036	1.027	1.005-1.03	AB: viral URI
11	36	W	5 yr, F	19.7	Urine Protein	2+	Trace	Neg	No history noted Urine protein negative on Day 28
12	2	W	10 yr, F	44.5	Alanine Aminotransferase	148 U/L	43	0-31	AB: chickenpox ALT 134 on Day 41
~~14~~	~~17~~	~~W~~	~~4 yr, M~~	~~17.7~~	~~Polymorphonuclear Leukocytes~~	~~77%~~	~~67~~	~~20-75~~	~~Hyperactivity, enuresis, imipramine, methylphenidate~~
~~14~~	~~25~~	~~W~~	~~5 yr, M~~	~~20.0~~	~~Aspartate Aminotransferase~~	~~170 U/L~~	~~94~~	~~0-37~~	~~Hay fever, flu symptoms; brompheniramine AST 58 on Day 18~~
					~~Alanine Aminotransferase~~	~~295 U/L~~	~~167~~	~~0-40~~	~~ALT 118 on Day 18~~
~~14~~	~~75~~	~~H~~	~~3 yr, F~~	~~16.6~~	~~Alkaline Phosphatase~~	~~427 U/L~~	~~362~~	~~25-350~~	~~No history noted~~
					~~Eosinophils~~	~~20%~~	~~17~~	~~0-7~~	

W = White; H = Hispanic; M = Male; F = Female; Neg = Negative; AB = Adverse Event; URI = Upper Respiratory Infection; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase.

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 5 of 8)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinir BID (Continued)									
14	77	H	8 yr, M	41.4	Alkaline Phosphatase	426 U/L	365	25-350	No history noted
15	13	W	2 yr, M	12.4	Urine Glucose	1+	Neg	Neg	No history noted
15	72	W	5 yr, M	23.4	White Blood Cells	$3.1 \times 10^9/L$	12.2	5.5-15.5	Reactive airway disease, cough; triamcinolone, albuterol AE: croup; prednisolone, phenylpropanolamine/dextromethorphan
Penicillin V-K									
3	19	W	10 yr, F	56.8	Lymphocytes	6%	9	10-66	Failure
3	21	W	8 yr, M	29.1	Polymorphonuclear Leukocytes	87%	83	20-75	
3	37	W	10 yr, M	33.2	White Blood Cells	$3.2 \times 10^9/L$	8.3	4.5-13.5	Down's syndrome
4	52	W	5 yr, F	16.3	Lactate Dehydrogenase	460 U/L	452	118-273	No history noted
4	96	W	6 yr, F	30.5	Polymorphonuclear Leukocytes	16%	13	40-80	
4	96	W	6 yr, F	30.5	Polymorphonuclear Leukocytes	26%	67	40-80	Testicular hernia, chemosis
4	96	W	6 yr, F	30.5	Alkaline Phosphatase	516 U/L	449	25-350	Stuffy nose AE: URI
4	96	W	6 yr, F	30.5	Urine White Blood Cells	21-50/HPF	--	1-5	AE: URI
5	16	W	11 yr, F	50.5	Urine Specific Gravity	1.038	1.02	1.005-1.03	No history noted

W = White; H = Hispanic; M = Male; F = Female; Neg = Negative; -- = Not available; AE = Adverse Event; URI = Upper Respiratory Infection.

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 6 of 8)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Penicillin V-K (Continued)									
5	58	W	7 yr, M	30.9	White Blood Cells	22.4 x 10 ⁹ /L	13.9	5-14.5	Seasonal allergies, sinusitis; demastine, triamcinolone Failure Day 14
					Lymphocytes	5%	13	10-66	
					Polymorphonuclear Leukocytes	88%	76	20-75	
7	9	H	6 yr, F	21.4	Polymorphonuclear Leukocytes	82%	--	20-75	Failure Day 13 AB: dysuria
8	8	W	4 yr, F	13.6	Urine pH	9	5	5-8	No history noted
8	38	W	10 yr, F	28.4	White Blood Cells	20.7 x 10 ⁹ /L	10.2	4.5-13.5	Failure Day 14
					Lymphocytes	9%	22	10-49	
8	46	W	6 yr, F	23.9	Polymorphonuclear Leukocytes	77%	83	20-75	No history noted
8	59	W	6 yr, F	22.3	White Blood Cells	22.8 x 10 ⁹ /L	14.7	5-14.5	History recurrent otitis media Failure Day 18
					Lymphocytes	6%	13	10-66	
					Polymorphonuclear Leukocytes	88%	78	20-75	
9	15	W	4 yr, F	12.7	Hemoglobin	9.5 g/dL	9.6	11.5-14.5	Anemia, eczema; mupirocin
9	17	W	6 yr, M	19.5	Alkaline Phosphatase	408 U/L	374	25-350	No history noted
9	44	W	5 yr, M	17.5	Urine Protein	1+	Neg	Neg	Failure Day 19
9	60	W	9 yr, F	40.0	Urine Specific Gravity	1.038	1.025	1.005-1.03	Failure Day 14 AB: pustular rash
10	47	W	6 yr, F	22.5	Alkaline Phosphatase	403 U/L	364	25-350	No history noted

W = White; H = Hispanic; M = Male; F = Female; Neg = Negative; -- = Not available; AB = Adverse Event.

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 7 of 8)

NDA 50-739 (CEFDINIR)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Penicillin V-K (Continued)									
10	60	W	5 yr, M	18.2	Bicarbonate	10 mmol/L	17	22-32	AE: influenza, hepatitis, mononucleosis, otitis media
					Aspartate Aminotransferase	642 U/L	31	0-37	
					Alanine Aminotransferase	525 U/L	13	0-40	
					Lactate Dehydrogenase	452 U/L	225	150-300	
10	74	W	11 yr, M	29.1	Urine pH	9	7	5-8	No history noted
11	11	W	3 yr, M	16.3	Eosinophils	15%	3	0-7	Asthma AE: vomiting, rash, cough
					Urine Glucose	2+	Neg	Neg	
11	24	W	7 yr, F	23.2	Eosinophils	14%	9	0-7	No history noted
11	29	W	12 yr, F	46.8	Urine Protein	1+	Neg	Neg	AE: cough
14	19	W	7 yr, F	28.2	Lymphocytes	8%	8	10-66	Failure Day 14
					Polymorphonuclear Leukocytes	87%	82	20-75	
14	26	B	4 yr, M	19.1	Urine Specific Gravity	1.036	1.025	1.005-1.03	Recurrent otitis media, hyperactivity; methylphenidate
14	42	W	7 yr, F	21.1	Eosinophils	13%	5	0-7	Recurrent otitis media
					Urine Protein	1+	2+	Neg	2+ on Day 40
14	47	W	5 yr, M	17.3	White Blood Cells	24.6 x 10 ⁹ /L	29.6	5.5-15.5	Failure Day 12
					Polymorphonuclear Leukocytes	90%	76	20-75	AE: bilateral otitis media, URI, headache, vomiting
					Lymphocytes	5%	14	10-66	
14	65	W	5 yr, F	16.7	Urine White Blood Cells	21-50/HPF	0	1-5	No history noted

W = White; B = Black; M = Male; F = Female; Neg = Negative; AB = Adverse Event; URI = Upper Respiratory Infection.

APPENDIX P 51

TABLE 23. Markedly Abnormal Clinical Laboratory Values at the First Posttherapy Visit
(Page 8 of 8)

NDA 50-139(CERIDINIR)

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Penicillin V-K (Continued)									
15	19	W	5 yr, M	20.8	White Blood Cells	23.6 x 10 ⁹ /L	17.2	5.5-15.5	Failure Day 12
					Polymorphonuclear Leukocytes	84%	79	20-75	
15	71	W	7 yr, F	25.5	Lymphocytes	5%	6	10-66	Failure Day 14
					Polymorphonuclear Leukocytes	91%	87	20-75	
15	85	W	9 yr, M	27.0	Urine Protein	1+	Neg	Neg	No history noted

W = White; M = Male; F = Female; Neg = Negative.

APPENDIX P 51

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TABLE 24. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline Excluding Site 14^a
[Number (%) of Patients]

NDA 50-739(CEFDINIR)

50-739(CEFDINIR)		APPENDIX C Cefdinir		Penicillin	
Parameter	Direction of Change	14 mg/kd QD N = 264	7 mg/kg BID N = 263	N = 264	
Hematology					
Hemoglobin	Decrease	0 (0.0)	1 (0.4)	1 (0.4)	
Platelets	Increase	1 (0.4)	0 (0.0)	0 (0.0)	
White Blood Cells	Decrease	2 (0.8)	1 (0.4)	1 (0.4)	
	Increase	0 (0.0)	1 (0.4)	4 (1.5)	
Polymorphonuclear Leukocytes ^b	Decrease	0 (0.0)	0 (0.0)	1 (0.4)	
	Increase	2 (0.8)	2 (0.8)	6 (2.3)	
Lymphocytes	Decrease	2 (0.8)	2 (0.8)	4 (1.5)	
Eosinophils	Increase	9 (3.4)	2 (0.8)	2 (0.8)	
Bands	Increase	0 (0.0)	1 (0.4)	0 (0.0)	
Blood Chemistry					
Alkaline Phosphatase	Increase	2 (0.8)	1 (0.4)	3 (1.1)	
Lactate Dehydrogenase	Increase	0 (0.0)	0 (0.0)	2 (0.8)	
Aspartate Aminotransferase	Increase	0 (0.0)	0 (0.0)	1 (0.4)	
Alanine Aminotransferase	Increase	0 (0.0)	1 (0.4)	1 (0.4)	
Sodium	Decrease	0 (0.0)	1 (0.4)	0 (0.0)	
Chloride	Decrease	0 (0.0)	1 (0.4)	0 (0.0)	
Calcium	Decrease	0 (0.0)	1 (0.4)	0 (0.0)	
Phosphorus	Increase	1 (0.4)	0 (0.0)	0 (0.0)	
Bicarbonate	Decrease	0 (0.0)	2 (0.8)	1 (0.4)	
Urinalysis					
Protein	Increase	4 (1.5)	4 (1.5)	3 (1.1)	
Glucose	Increase	0 (0.0)	1 (0.4)	1 (0.4)	
White Blood Cells ^b	Increase	1 (0.4)	2 (0.8)	1 (0.4)	
Erythrocytes	Increase	1 (0.4)	0 (0.0)	0 (0.0)	
pH	Increase	0 (0.0)	0 (0.0)	2 (0.8)	
Specific Gravity ^b	Increase	2 (0.8)	1 (0.4)	2 (0.8)	
Any Parameter^c		27 (10.2)	23 (8.8)	25 (9.5)	

- ^a This table does not include data from patients with markedly abnormal values at the STFU visit that were unchanged or improved relative to the baseline value.
- ^b Three patients had no baseline values for comparison, but are included in this summary. One patient was in the cefdinir QD treatment group (Patient 138, Center 3 for Urine Specific Gravity), and 2 were in the penicillin treatment group (Patient 96, Center 4 for Urine White Blood Cells; Patient 9, Center 7 for Polymorphonuclear Leukocytes).
- ^c Total number of patients in a treatment group experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) regardless of the laboratory parameter.

NDA 50-739 (CEFDINIR)
7 MG/KG BIDXSD VS.
PEN VK 10MG/KG QIDX10D

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

VI PROTOCOL 983-56: AN INVESTIGATOR-BLINDED, RANDOMIZED, COMPARATIVE, MULTICENTER STUDY OF A 5-DAY REGIMEN OF CEFDINIR (CI-983) VERSUS PENICILLIN V-K IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS/TONSILLITIS INFECTIONS IN PEDIATRIC PATIENTS (PROTOCOL 983-56)

1. OBJECTIVES

The objectives of this study were to evaluate the efficacy and safety of a 5-day dosage regimen of cefdinir (7 mg/kg BID) versus a 10-day regimen of penicillin V-K (10 mg/kg QID) in the treatment of pediatric patients with GABHS pharyngitis/tonsillitis infections.

2. STUDY MANAGEMENT

Fourteen centers in the United States, each with matching protocols and case report forms, participated in the study monitored by Parke-Davis Pharmaceutical Research. This study was conducted according to Good Clinical Practice Guidelines. Investigators met with representatives of Parke-Davis individually (between January 1994 to April 1994) to review the protocol; Institutional Review Board approval was obtained prior to the study. Informed patient (or guardian) consents were obtained before patients were enrolled in the study. Clinical laboratory and microbiological data were measured by a central laboratory¹

TABLE 1. List of Investigators

Center 983-56-	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable
1	Gerson Aronovitz, MD	12	12	11
2	W. Manford Gooch III, MD, PC	50	47	44
3	James A. Hedrick, MD	59	56	53
4	Dan Henry, MD	47	45	45
5	Abdollah Irvani, MD	57	52	54
6	Kevin Ludwig, MD*	0	0	0
7	James McCarty, MD	33	31	28
8	Samuel McLinn, MD	30	29	29
9	Michael Pichichero, MD	48	48	46
10	Edward Rothstein, MD	53	53	51
11	Sandra Wiederhold, MD	25	24	24
12	Malcolm Sperling, MD	20	19	19
13	Richard Schwartz, MD	32	32	31
14	Margaret Drehobl, MD	16	13	13
Total		482	461	448

* Investigator received drug but did not enroll patients

Medical Officer's note: Eliminating Dr Iravani's site (Center 5) reduced the number of patients randomized to treatment by 12%, the number completing treatment by 11%, and the evaluable population by 12%. Please see Table 1 Appendix P56.

The first patient received the first dose of medication on February 18, 1994, and the last patient had the last follow-up visit on August 3, 1994.

3. MATERIALS AND METHODS

3.1. Study Design

This was an investigator-blinded, randomized, comparative, multicenter study (Figure 1). Pediatric patients with GABHS pharyngitis or tonsillitis were randomly assigned to receive either cefdinir (7 mg/kg BID) for 5 days or penicillin (10 mg/kg QID) for 10 days.

According to the protocol, the test-of-cure (TOC) visit was to occur within 6 to 10 days after study treatment was complete (Study Days 11-15 for cefdinir; Study Days 16-20 for penicillin). However, for purposes of analysis, the TOC visit was expanded to 5 to 10 days posttherapy to accommodate those patients who completed treatment on Study Day 6 (cefdinir) or Study Day 11 (penicillin).

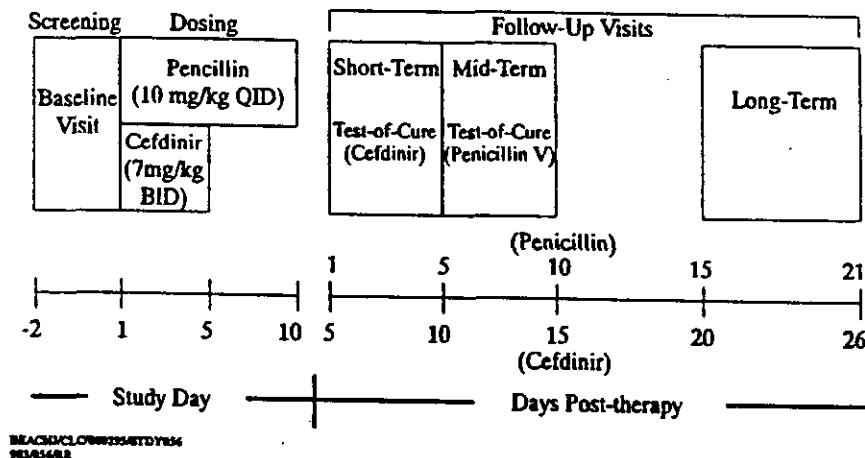


FIGURE 1. Study Design

3.1.1. Treatment

3.1.1.1. Materials

All study medications were provided by Parke-Davis Pharmaceutical Research in powder form to be reconstituted at the site by a third party to maintain investigator blinding (Table 2). The medication CRF was also kept separate from the main CRF notebook to maintain blinding.

TABLE 2. Study Medication

Medication	Lot	Formulation
Cefdinir 125-mg/5-mL Suspension*	CR0450393	134393-27
Penicillin V-K 250-mg/5-mL Suspension*	6MW78A	Marketed
	6MW66A	Marketed
	7CU98A	Marketed

* All suspensions supplied in 100-mL bottles

3.1.1.2. Drug Administration

Cefdinir suspension was administered orally once in the morning and evening (7 mg/kg BID) for 5 days. Penicillin was administered orally (10 mg/kg QID) for 10 days.

MEDICAL OFFICER'S NOTE: FOLLOWING SECTIONS ARE IDENTICAL TO PROTOCOL 983-7. PLEASE REFER TO THAT REVIEW FOR DETAILS. PLEASE NOTE THAT VARIATIONS ARE IN ITALICIZED TEXT.

3.1.1.3. Methods of Assigning Patients to Treatment

An independent randomization scheme was prepared for each study center. The planned treatment group ratio was 1:1 for cefdinir and penicillin. A block size of 4 patients was used with 2 treatment replicates per block.

At each center, patients who met the entry criteria at screening were given the next consecutive patient number and, according to the randomization schedule, were dispensed the corresponding study medication. The patient number and milliliter unit dose were recorded on each bottle of reconstituted study medication; the treatment group and total daily dose prescribed were recorded on the appropriate case report form by the third party who dispensed the medication (not by the investigator).

3.2. Patient Selection

3.2.1. Inclusion Criteria

Children 6 months to 12 years of age with GABHS pharyngitis were included in the study. Pain (or irritability in infants) and erythema of the pharyngeal cavity were required symptoms for inclusion. Postmenarchal girls were to have a negative pregnancy test prior to drug administration.

3.2.2. Exclusion Criteria

* Serum creatinine $>1.5 \times \text{ULN}$;

3.2.3. Prohibited Medications or Precautions

3.2.4. Guidelines for Patient Withdrawal

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

3.3. Criteria for Evaluation

3.3.1. Efficacy

3.3.1.1. Microbiologic Response

3.3.1.2. Clinical Response

Medical Officer's Note: Please refer to the table in protocol 7 with all the patients that were given a combined score.

3.3.1.3. Appearance of New Pathogens

3.3.2. Safety

3.3.2.1. Adverse Events

3.3.2.2. Physical Examinations

3.3.2.3. Clinical Laboratory Values

3.3.3. Clinical Observations and Laboratory Measurements

Medical Officer's Note: The schedule of clinical observations and laboratory measurements is indicated below (Table 4). This is similar to protocol 58.

TABLE 4. Clinical Observations and Laboratory Measurements

	Baseline	Day 1	Days 3-5	Day 5	Day 10	Posttherapy Visits		
						STFU	MTFU	LTFU
						Days 11-15 ^a	Days 16-20 ^b	Days 25-31
Throat Swab for Strep Screen ^c	X							
Culture/Susceptibility Testing ^d	X					X	X	X
Medical History	X							
Physical Examination ^d	X					X	X	X
Clinical Assessment ^d	X					X	X	X
Adverse Events and Concurrent Medications	X	X	X			X	X	X
Telephone Call to Patient			X					
Clinical Laboratory Tests ^d	X					X	X ^e	X ^e
Dosing (Cefdinir)		X	X	X				
Dosing (Penicillin V-K)		X	X	X	X			

^a Test-of-cure (TOC) visit, cefdinir

^b Test-of-cure (TOC) visit, penicillin

^c Must be positive for patients to enter study

^d Perform also after early treatment discontinuation or withdrawal (see Section 4.2.4).

^e If abnormalities detected at the STFU visit

3.3.4. Data Acceptability and Evaluability

3.3.4.1. Method of Assigning Study Days

The first dose of study medication was taken on Day 1. Study days after Day 1 were numbered consecutively. Days before Day 1 were assigned consecutive negative numbers beginning with Day -1.

3.3.4.2. Data Acceptability

3.3.4.3. Patient Populations for Analysis

3.3.5. Statistical Methodology

Medical Officer's Note: Please note that the random number's generated are located in protocol 7.

3.3.5.1. Sample Size

Medical Officer's Note: This investigator-blinded comparative study of cefdinir versus penicillin was designed with a sample size of 190 evaluable patients per randomized group for a targeted total of 380 evaluable patients.

3.3.5.2. Methods

3.3.5.2.1. Efficacy

3.3.5.2.2. Safety

4. PATIENT DEMOGRAPHICS, TREATMENT, AND DISPOSITION

4.1. Patient Characteristics

4.1.1. Patient Sample

Patient characteristics were similar across treatment groups with respect to sex, age, and race for all and evaluable patient populations (Tables 6 and 7).

Approximately equal numbers of males and females participated in the study. The mean age across treatment groups was 7.5 years; 73% of the patients were between 6 to 12 years old. Eighty-nine percent of patients were white.

TABLE 6. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir N = 240	Penicillin N = 242	Total N = 482
Sex			
Male	128 (53.3)	122 (50.4)	250 (51.9)
Female	112 (46.7)	120 (49.6)	232 (48.1)
Race			
White	214 (89.2)	214 (88.4)	428 (88.8)
Black	8 (3.3)	12 (5.0)	20 (4.1)
Asian	4 (1.7)	0 (0.0)	4 (0.8)
Other	14 (5.8)	16 (6.6)	30 (6.2)
Age, years			
Median	7.4	7.7	7.5
Range	(1-13)	(2-18)	(1-18)
Distribution:			
<2	2 (0.8)	1 (0.4)	3 (0.6)
2 to <6	65 (27.1)	62 (25.6)	127 (26.3)
6 to <13	173 (72.1)	177 (73.1)	350 (72.6)
13 to <18 years	0 (0.0)	2 (0.8)	2 (0.4)

TABLE 7. Patient Characteristics - Evaluable* Patients
[Number (%) of Patients]

Variable	Cefdinir N = 224	Penicillin N = 216	Total N = 440	CMH p-value
Sex				0.642
Male	118 (52.7)	109 (50.5)	227 (51.6)	
Female	106 (47.3)	107 (49.5)	213 (48.4)	
Race				0.742
White	199 (88.8)	194 (89.8)	393 (89.3)	
Black	8 (3.6)	9 (4.2)	17 (3.9)	
Asian	4 (1.8)	0 (0.0)	4 (0.9)	
Other	13 (5.8)	13 (6.0)	26 (5.9)	
Age, years				0.762
Median	7.4	7.6	7.5	
Range (Min, Max)	(2-13)	(2-16)	(2-16)	
Distribution:				
<2	1 (0.4)	1 (0.5)	2 (0.5)	
2 to <6	59 (26.3)	55 (25.5)	114 (25.9)	
6 to <13	164 (73.2)	159 (73.6)	323 (73.4)	
13 to <18	0 (0.0)	1 (0.5)	1 (0.2)	

* Microbiologically and clinically

Medical Officer's Note: Excluding the Iravani data did not substantially change the demographic characteristics of either the total patient population or the evaluable patient population. The number of

black patients decreased from 20 to 11, but this was a very small subgroup; white patients constituted 91% of the population. See table 6 and 7 in appendix P56.

Statistical Reviewer's Notes:

Two treatment arms are balance with respect to sex, race and age of the enrolling patient population.

4.1.2. Confirmed Microbiologic Diagnosis and Baseline Susceptibility

At the baseline visit, *S. pyogenes* was isolated from throat swabs from 472 of 482 (98%) patients randomized to treatment. All *S. pyogenes* isolates were susceptible to both cefdinir and penicillin.

4.1.3. Clinical Signs and Symptoms

Of the patients randomized to treatment, all but 1 cefdinir-treated patient (pain absent) had both pharyngeal pain and erythema. Most patients also had tonsillar swelling, dysphagia, and cervical lymph node tenderness. Baseline signs and symptoms were similar between treatment groups and patient populations.

4.1.4. Medical History and Secondary Diagnoses

There were no differences in significant medical/surgical history between the 2 treatment groups. Approximately a third of the patients in each treatment group experienced pharyngitis/tonsillitis within 1 year prior to the study.

4.1.5. Prior Medications for Pharyngitis

Sixteen cefdinir-treated patients and 17 penicillin-treated patients had received prior anti-infective medications for pharyngitis or tonsillitis within 30 days of the study. The most frequently used were penicillin and amoxicillin.

4.1.6. Concurrent Medications, Nondrug Therapies, Elective Surgeries/Procedures

Overall, acetaminophen (20% of patients) and cefadroxil monohydrate (8%) were the most frequently used concurrent medications. No clinically relevant concurrent nondrug therapies, elective surgeries, or elective procedures were used or performed during this study.

4.2. Patient Treatment

The majority of cefdinir-treated patients (175) completed therapy on Day 5; most penicillin-treated patients (150) completed therapy on Day 11 (Table 8). Cefdinir-treated patients who began treatment in the late afternoon or evening of Day 1 completed their course of therapy on Day 6 instead of Day 5. Similarly, penicillin-treated patients who began therapy in the latter part of Day 1 completed therapy on Day 11.

TABLE 8. Patient Exposure to Study Medication - All Patients
(Number of Patients)

Days of Study Medication	Cefdinir N = 240	Penicillin N = 242
1	2	0
2	1	1
3	1	0
4	0	1
5	175	3
6	61	1
7	0	2
8	0	0
9	0	2
10	0	75
11	0	150
12	0	3
Unknown	0	4
Median (Days)	5	11

Medical Officer's Note: Patient exposure to study medication remained the same, with the majority of cefdinir patients finishing study medication on Day 5 and most penicillin patients finishing medication on Day 11. Please see table (appendix 8) in appendix P56.

4.3. Patient Disposition

Of the 482 patients who entered the study, 461 (90%) completed the treatment phase (Table 9). Ninety-eight percent of cefdinir-treated patients completed the TOC follow-up visit compared with 83% of penicillin-treated patients.

The investigators assessed if patients took the full 10 days (penicillin) or 5 days (cefdinir) of study medication as prescribed. Analysis of this indicator of treatment compliance indicated that 93% of cefdinir-treated patients took medication as prescribed compared with 76% of penicillin-treated patients. This suggests that the 5-day course of therapy and/or the BID dosing schedule may improve compliance.

TABLE 9. Patient Disposition - All Patients
(Number (%) of Patients)

Disposition	Cefdinir		Penicillin		Total	
Randomized to Treatment	240		242		482	
Withdrawn Prior to End of Treatment						
Lack of Compliance	2	(0.8)	10	(4.1)	12	(2.5)
Failure at End of Therapy	0	(0.0)	1	(0.4)	1	(0.2)
No Baseline Pathogen	0	(0.0)	1	(0.4)	1	(0.2)
Adverse Event	0	(0.0)	2	(0.8)	2	(0.4)
Other/Administrative	2	(0.8)	3	(1.2)	5	(1.0)
Completed Treatment*	236	(98.3)	225	(93.0)	461	(95.6)
Completed Follow-Up Visits						
TOC ^b	235	(97.9)	200	(82.6)	435	(90.2)
LTFU	182	(75.8)	169	(69.8)	351	(72.8)

* Based on investigator assessment at end of treatment.

^b Short-term follow-up visit for cefdinir-treated patients; mid-term follow-up visit for penicillin-treated patients.

Medical Officer's Note: The overall percentages of patients completing the treatment phase, TOC visit phase, and LTFU visit phase of the study remained relatively constant at 96.2%, 89.1%, and 70.6% respectively. The percentage of patients completing the treatment phase increased by 0.6% when patients from Dr Iravani's site were excluded. See table (Appendix 9) in appendix P56.

5. RESULTS

5.1. Protocol Variations

The most common protocol variation was the enrollment of patients whose baseline clinical laboratory results showed 2 times the upper limit of normal in AST or ALT levels; this affected 6 patients.

5.1.1. Efficacy Evaluations

The most common reasons for exclusion from the evaluable analysis at TOC were that the clinical assessment and throat culture were out of the appropriate study day range (Table 10). A summary of the number of patients included in the efficacy analysis for each population is given in Table 11.

TABLE 10. Reasons Patients Were Not Evaluable at TOC or Were Disqualified at LTFU
(Number of Patients)

	Cefdinir	Penicillin
Reasons For Exclusion From Evaluable Analyses at TOC		
Clinical Assessment Out of Range	7	15
Culture Out of Range	7	15
Medication Not as Prescribed	7	12
No Proven Pathogen	5	5
Concurrent Antibacterial	3	2
Culture Missed	2	8
Clinical Assessment Missed	1	4
No Baseline Signs or Symptoms	0	1
Total Not Evaluable*	16	26
Reasons For Disqualification From Qualified Analyses at LTFU*		
Culture Missed	27	55
Clinical Assessment Missed	25	53
Culture Out of Range	21	15
Clinical Assessment Out of Range	20	16
Concurrent Antibacterial	1	4
Total Disqualified*	48	73

* Patients may have multiple reasons for exclusion or disqualification.

Medical Officer's Note: No substantial change was seen in the frequency distribution of reasons for exclusion from evaluable analyses at TOC and reasons for disqualification from qualified analyses at LTFU. Please see table (appendix 10) in appendix P56.

TABLE 11. Patients (With Data) Included in Efficacy Summaries
(Number of Patients)

Patient Population	Cefdinir	Penicillin
Intent-to-Treat (ITT)	240	242
Modified Intent-to-Treat (MITT)	235	229
Clinically Evaluable	228	220
Microbiologically-Clinically Evaluable	224	216
Qualified at LTFU	176	143

Medical Officer's Note: Please see appendix P56 for the above revised table.

Also note that when Dr. Irvani's data was not included in the analysis for clinical and microbiologic efficacy, there was very little effect on response rates. Please see appendix P56 page 1,2 and 3. The table below is recalculated by the statistical reviewer with Yates' continuity correction.

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

SUMMARY OF CURE RATES IN PROTOCOL 56

Criteria	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Clinical Efficacy (all evaluable patients)			
All sites	205/224(91.5%)	196/216(90.7%)	224,216(-0.0499, 0.0655) _{91.5%, 90.7%}
Sites excluding Dr. Iravani	179/196(91.3%)	173/193(89.6%)	196,193(-0.0465, 0.0804) _{91.3%, 89.6%}
Microbiologic Eradication (all evaluable patients)			
All sites	201/224(89.7%)	155/216(71.7%)	224,216(0.1031, 0.2563) _{89.7%, 71.7%}
Sites excluding Dr. Iravani	176/196(89.7%)	135/193(69.9%)	196,193(0.1160, 0.2809) _{89.7%, 69.9%}
Clinical Efficacy (clinically evaluable patients)			
All sites	209/228(91.6%)	200/220(90.9%)	228,220(-0.0491, 0.0642) _{91.6%, 90.9%}
Sites excluding Dr. Iravani	182/199(91.4%)	175/195(89.7%)	199,195(-0.0455, 0.0798) _{91.4%, 89.7%}

Statistical Reviewer's notes:

With respect to clinical efficacy in all evaluable patients, Cefdinir is therapeutically equivalent to penicillin, with or without data from Dr. Iravani's site. With respect to microbiologic eradication in all evaluable patients, Cefdinir is statistically superior to penicillin, with or without Dr. Iravani's information. With respect to clinical efficacy in clinically evaluable patients only, Cefdinir is therapeutically equivalent to penicillin, with or without data from Dr. Iravani's site.

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5.1.2. Safety Evaluations

All patients randomized to treatment received study medication and were included in the safety evaluations.

5.2. Efficacy

Medical Officer's Note: Please note that the outcomes for the patients below have been changed:

Outcomes Changed by Medical Officer			
Patient Number	Applicant	FDA	Reason:
1	MICRO: TOC/LTFU (persistence/Not Asse Clin: TOC/LTFU cure/cure	MICRO: TOC/LTFU Not assessable/not assessable Clin: toc/ltfu: not assess/not assessable	This patient had his test of cure visit at 1 day vs. 7 day with a positive culture. If he had a culture further on, it potentially could have been negative.
115	MICRO: TOC/LTFU (Not Asse/Not Asse	MICRO: TOC/LTFU (Erad/Eradication	S. pyogenes was isolated at baseline with a non pathogen(S. Aureus) and was not considered

The response rates and confidence intervals presented in the efficacy results sections are estimates obtained from pooled analyses. Center-adjusted analyses were also performed and results are consistent between the 2 methods in all cases. A side-by-side comparison of all results from the 2 analysis methods can be found in Appendix D.1.

5.2.1. Evaluable Analyses and Qualified Analyses

5.2.1.1. Test-of-Cure Visit (5-10 Days Posttherapy)

5.2.1.1.1. Microbiologic Eradication

The microbiologic eradication rates were 89.7% (201/224) for the cefdinir group and 71.8% (155/216) for the penicillin group. The 95% CI about the difference between cefdinir vs penicillin (cefdinir minus penicillin) was (10.8%, 25.2%), indicating that cefdinir treatment was superior to penicillin because the interval lies above zero. The exploratory CMH test showed that the eradication rate for cefdinir was significantly higher ($p < 0.001$) than that for penicillin.

5.2.1.1.2. Clinical Cure

The clinical response rates were 91.5% (205/224) for the cefdinir group and 90.7% (196/216) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (-4.5%, 6.1%) indicating that cefdinir treatment was equivalent to penicillin based on the fixed criteria for equivalence

CEFDINI4.WPD

(-10%, +10%). The exploratory CMH tests showed no significant difference between the clinical cure rate for cefdinir and penicillin ($p = 0.80$).

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

The response rates were based on the combined investigator/sponsor assessment of clinical cure. Only 1 patient was considered Not Assessable by the investigator and thus was assessed according to the sponsor definition.

5.2.1.1.3. Microbiologic Versus Clinical Response Rates

Most patients (87%) had the same clinical as microbiologic response. Among those who had different responses for clinical and microbiologic assessment, McNemar's test showed no significant pattern to the discordant assessments in the cefdinir group ($p = 0.29$). However, a significant pattern to the discordant results was seen in the penicillin group ($p < 0.001$); 42 of 43 patients with discordant results experienced a clinical cure, yet had a persistent pathogen. Clinical improvement in the penicillin group did not reliably indicate streptococcal eradication.

TABLE 12. Microbiologic Versus Clinical Response at TOC - Evaluable Patients
(Number of Patients)

Microbiologic Response	Clinical Response	
	Cure	Failure
Cefdinir		
Eradication	196	5
Persistence	9	14
Penicillin		
Eradication	154	1
Persistence	42	19

Medical Officer's Note: The pattern of microbiologic and clinical outcomes remains unchanged, with good correlation, but with a relatively large number of penicillin patients with clinical cure but microbiological persistence. Cefdinir still shows superiority microbiologically. Please see table (appendix 12) in appendix P56.

5.2.1.2. Long-Term Follow-Up Visit (Day 25-31)

5.2.1.2.1. Microbiologic Eradication

Of the qualified patients who had *S. pyogenes* eradicated at the TOC visit, 95.9% (164/171) in the cefdinir group and 97.7% (127/130) in the penicillin group also had microbiologic eradication at the LTFU visit.

5.2.1.2.2. Clinical Cure

In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 94.9% (166/175) for the cefdinir group and 96.5% (138/143) for the penicillin group. Clinical cure rates were based on the combined investigator/sponsor determination, which was identical to the investigator determination in this case.

5.2.2. Modified Intent-to-Treat (MITT) Analyses

5.2.2.1. Test-of Cure Visit (5-10 Days Posttherapy)

In the MITT population, the microbiologic eradication rates were 89.8% (211/235) for the cefdinir group and 72.9% (167/229) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (9.9%, 23.8%), indicating that the cefdinir treatment was superior to penicillin because the interval lies above zero. The exploratory CMH test showed that the eradication rate for cefdinir treatment was significantly higher ($p < 0.001$) than that for penicillin treatment.

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

5.2.3. Intent-to-Treat (ITT) Analyses

5.2.3.1. Test-of-Cure Visit (5-10 Days Posttherapy)

5.2.3.1.1. Microbiologic Eradication

The ITT microbiologic eradication rates were 87.9% (211/240) for the cefdinir group, and 69.0% (167/242) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (11.8%, 26.0%), indicating that the cefdinir treatment was superior to penicillin treatment because the interval lies above zero. The exploratory CMH test showed that the eradication rate for cefdinir was significantly higher ($p < 0.001$) than that for penicillin.

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

5.2.3.1.2. Clinical Cure

The ITT clinical response rates were 91.3% (219/240) for the cefdinir group and 90.1% (218/242) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (-4.0%, 6.4%), indicating that cefdinir treatment was equivalent to penicillin treatment based on the fixed criteria for equivalence (-10%, +10%). The exploratory CMH test showed that the clinical response rates were not significantly different ($p = 0.67$) for the 2 treatment groups.

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

5.2.3.2. Long-Term Follow-Up Visit (Day 25-31)

The microbiologic eradication rates for the cefdinir and penicillin groups were 78.3% and 59.1%, respectively. The clinical cure rates for the cefdinir and penicillin treatment groups were 80.8% and 66.9%, respectively.

5.2.4. Other Population Analyses

5.2.4.1. Clinically Evaluable Patients

In the clinically evaluable patient population, the clinical response rate was 91.7% (209/228) for the cefdinir group and 90.9% (200/220) for the penicillin group. According to the sponsor, the 95% CI about the difference between treatment groups was (-4.5%, 6.0%), indicating that cefdinir treatment was equivalent to penicillin treatment based on the fixed criteria for equivalence (-10%, +10%). The exploratory CMH test showed that there was no significant difference ($p = 0.79$) between clinical response rates for cefdinir and penicillin treatment groups.

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

5.2.4.2. Patients Who Took Iron During Treatment

Two cefdinir-treated patients took iron supplements (multivitamin or iron tablets) during treatment. *S. pyogenes* was eradicated at the TOC visit for 1 patient (evaluable) and persisted for the other patient (not evaluable). It is not clear what effect the iron tablets had on this outcome.

5.2.4.3. Patients Who Took Maalox® or Other Aluminum- or Magnesium-Containing Antacids During Treatment

One cefdinir-treated patient took a magnesium-containing antacid (Rolaids™) during treatment. *S. pyogenes* was eradicated at the TOC visit for this evaluable patient.

5.2.5. Summary of Efficacy Results

A summary of the efficacy analyses at the TOC visit is given below (Table 13).

TABLE 13. Summary of Efficacy Analyses at TOC

Efficacy Parameter/Population	Rates (%)		95% CI ^a	Interpretation ^b (Superior, Equivalent, Not Equivalent)	CMH ^c (p-Value)
	Cefdinir	Penicillin			
Microbiologic Eradication					
Evaluable ^d	90	72	(10.8, 25.2)	Superior	<0.001
MITT	90	73	(9.9, 23.8)	Superior	<0.001
ITT	88	69	(11.8, 26.0)	Superior	<0.001
Clinical Response					
Evaluable	92	91	(-4.5, 6.1)	Equivalent	0.80
Clinically Evaluable	92	91	(-4.5, 6.0)	Equivalent	0.79
ITT	91	90	(-4.0, 6.4)	Equivalent	0.67

^a CI about difference between cefdinir vs penicillin (cefdinir minus penicillin)

^b Treatments were equivalent if the 95% CI fell within the fixed criteria for equivalence and contained zero. Cefdinir treatment was superior where indicated.

^c Exploratory CMH; cefdinir vs penicillin

^d Primary efficacy analysis

Medical Officer's Note: The response rates and analysis results for all patient populations are shown in Table 13. Excluding Site 5 had very little effect on response rates. Cefdinir and penicillin are still shown to be equivalent in clinical response rate across patient populations. Cefdinir remains statistically superior to penicillin for microbiological response rate across populations. Please see table 13 in appendix P56.

Statistical Reviewer's notes:

Table 13, as reported by the sponsor, is acceptable.

5.2.6. Appearance of New Pathogens During the Study

5.2.6.1. Superinfections

Two cefdinir-treated patients developed superinfections caused by *S. pyogenes* (different strains than present at baseline); both pathogens were susceptible to cefdinir.

5.2.6.2. Reinfections

Four cefdinir-treated patients developed reinfections with *S. pyogenes* (different strains than present at baseline). All pathogens were susceptible to cefdinir. No penicillin-treated patients developed reinfections.

Medical Officer's Note: I agree with the different outcome responses by the sponsor.

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

5.3. Safety

Medical Officer's Note: When Dr. Irvani's data was not included in the analysis for safety (both the adverse event rates and drug-associated adverse event rates), there was very little effect on the adverse event rates.

Please see

appendix P56 page 4.

5.3.1. Adverse Events

5.3.1.1. Overview

Thirty-eight percent of cefdinir-treated patients and 33% of penicillin-treated patients experienced at least 1 adverse event during the study (Table 14); these rates were not significantly different ($p = 0.212$). Five percent of patients in both treatment groups experienced an adverse event considered associated with study medication. Thirteen percent of cefdinir-treated patients and 14% of penicillin-treated patients experienced an adverse event while receiving study medication.

Statistical Reviewer's notes:

The safety report in this study is based on the sponsor's results. It was felt that the statistical validity of the analysis plan was acceptable, so further reanalysis was not required.

The number of withdrawals after treatment due to adverse events was similar between treatment groups; 2 penicillin-treated patients and no cefdinir-treated patients discontinued treatment due to adverse events. Two serious adverse events occurred during the study; neither was related to study therapy. No deaths occurred during the study.

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TABLE 14. Summary of Adverse Events - All Patients
(Number (%) of Patients)
(Page 1 of 2)

	Cefdinir N = 240	Penicillin N = 242
Adverse Events During Study		
All Adverse Events	92 (38.3)	80 (33.1)
Associated* Adverse Events	13 (5.4)	11 (4.5)
Adverse Events During Treatment		
All Adverse Events	30 (12.5)	33 (13.6)
Adverse Events by Sex^b		
All Adverse Events		
Male	49 (38.3)	40 (32.8)
Female	43 (38.4)	40 (33.3)
Associated Adverse Events		
Male	6 (4.7)	5 (4.1)
Female	7 (6.3)	6 (5.0)
Adverse Events by Race^c		
All Adverse Events		
White	84 (39.3)	73 (34.1)
Hispanic	3 (27.3)	4 (36.4)
Black	1 (12.5)	3 (25.0)
Asian	2 (50.0)	0 (0.0)
Other	2 (66.7)	0 (0.0)
Associated Adverse Events		
White	13 (6.1)	10 (4.7)
Hispanic	0 (0.0)	0 (0.0)
Black	0 (0.0)	1 (8.3)
Asian	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Adverse Events by Age^d		
All Adverse Events		
<2 years	1 (50.0)	1 (100.0)
2 to <6 years	31 (47.7)	24 (38.7)
6 to <13 years	60 (34.7)	55 (31.1)
13 to <18 years	0 (0.0)	0 (0.0)
Associated Adverse Events		
<2 years	0 (0.0)	0 (0.0)
2 to <6 years	4 (6.2)	7 (11.3)
6 to <13 years	9 (5.2)	4 (2.3)
13 to <18 years	0 (0.0)	0 (0.0)

* Considered by the investigator to be possibly, probably, or definitely related to study medication

^b Percentages based on total numbers of males or females in a treatment group

^c Percentages based on total numbers of patients of each race in a treatment group

^d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.

TABLE 14. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 2 of 2)

	Cefdinir N = 240	Penicillin N = 242
Adverse Events by Maximum Intensity*		
All Adverse Events		
Mild	70 (29.2)	67 (27.7)
Moderate	36 (15.0)	24 (9.9)
Severe	1 (0.4)	1 (0.4)
Associated Adverse Events		
Mild	9 (3.8)	8 (3.3)
Moderate	3 (1.3)	4 (1.7)
Severe	1 (0.4)	0 (0.0)
Serious Adverse Events	1 (0.4)	1 (0.4)
Deaths	0 (0.0)	0 (0.0)
Discontinuation of Treatment Due to Adverse Events		
All Adverse Events	0 (0.0)	2 (0.8)
Associated Adverse Events	0 (0.0)	1 (0.4)
Withdrawals After Treatment Due to Adverse Events		
All Adverse Events	6 (2.5)	5 (2.1)
Associated Adverse Events	0 (0.0)	0 (0.0)

* Patients with multiple adverse events were counted once in each applicable category.

Medical Officer's Note: Again, Dr Iravani's site reported a lower incidence of adverse events than the overall reported rates: 21% for cefdinir BID and 11% for penicillin. Because of this, the incidence of all adverse events increased proportionally in both the cefdinir and penicillin groups when data from his site were excluded. As shown below, rates of all-adverse events increased from 38.3% to 40.8% (a factor of 1.07) in the cefdinir group and from 33.1% to 36.0% (a factor of 1.09) in the penicillin group. Likewise, rates of drug-associated adverse events increased from 5.4% to 6.2% (a factor of 1.15) in the cefdinir group and from 4.5% to 5.1% (a factor of 1.13) in the penicillin group. No significant differences in the number of adverse events or drug-associated adverse events reported by patients receiving either cefdinir or penicillin were detected; p values are reported below.

	Cefdinir BID	Penicillin	CMH p-Value
All Adverse Events			
All Sites	38.3% (92/240)	33.1% (80/242)	0.212
Excluding Site 5	40.8% (86/211)	36.0% (77/214)	0.314
Drug-Associated Adverse Events			
All Sites	5.4% (13/240)	4.5% (11/242)	0.678
Excluding Site 5	6.2% (13/211)	5.4% (11/214)	0.678

Similar trends were seen when adverse events and drug-associated adverse events were examined by age, sex, and race.

5.3.1.2. All and Drug-Associated Adverse Events

In general, the adverse event profile of cefdinir was similar to the adverse event profile of penicillin. Adverse events relating to the body as a whole occurred with the highest frequency for both treatment groups. Infection occurred in 10% of cefdinir-treated patients and 5% of penicillin-treated patients; these infections consisted mainly of upper respiratory infections and cold symptoms. Fifteen percent of cefdinir-treated patients and 10% of penicillin-treated patients experienced adverse events related to the respiratory system mainly due to reports of cough and rhinitis commonly associated with upper respiratory infections.

Approximately 10% of patients in each treatment group experienced an adverse event related to the digestive system; the most frequently occurring event in this system was diarrhea which occurred in 5% of cefdinir-treated patients and 4% of penicillin-treated patients (not significantly different, $p = 0.638$). Vomiting occurred in 3% of cefdinir-treated patients and 5% of penicillin-treated patients.

The adverse events most frequently associated with study treatment was diarrhea (2.1%) for cefdinir-treated patients and rash (1.2%) for penicillin-treated patients.

Medical Officer's Note: Small increases were also seen in most individual adverse event rates and drug-associated adverse event rates as a result of a smaller denominator. The largest increase in rates for a particular event was seen in the cefdinir group for infection, where the rate increased by 0.9%, and for increased cough, where the rate increased by 0.8%. Lesser increases in the rates of diarrhea were seen, by 0.1% in the cefdinir group and by 0.6% in the penicillin group. Rates of drug-associated diarrhea increased by 0.3% in the cefdinir group and by 0.1% in the penicillin group. Please see table 15 in appendix P56.

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5.3.1.9. Serious Adverse Events

Two serious adverse events occurred during the study. A cefdinir-treated patient developed possible rheumatic fever after completing treatment and withdrew from the study. The narrative for this patient follows:

Patient 048 (983-056-003), a 7-year-old white girl with GABHS pharyngitis, developed possible rheumatic fever 4 days post treatment with cefdinir. The patient had received cefdinir (7 mg/kg BID) for 5 days for treatment of her pharyngitis, beginning on the first day of her sore throat. Four days after completion of cefdinir, swelling of the left knee appeared and was attributed to trauma. *Streptococcus pyogenes* was eradicated from the pharynx at the TOC culture. The initial swelling resolved, but arthralgia involving the knee and both upper extremities appeared along with a fever of 101.3 and an elevated sedimentation rate, 62 mm/hr. The patient was admitted to the hospital, was treated with aspirin and Penicillin V-K and was discharged 3 days later.

After discharge from the hospital, the patient was sent to a streptococcal infection specialist who felt that the clinical findings were compatible with, but not diagnostic of rheumatic fever. No evidence of cardiac involvement was seen and a bone scan was normal. The possible rheumatic fever resolved on Day 30. Follow-up 4 months poststudy also indicated that there was no cardiac involvement and that the patient had fully recovered. She was also receiving acetaminophen and ibuprofen. The patient had a past history of sinusitis and otitis media. The investigator considered this event moderate in intensity and unlikely to be related to cefdinir.

A penicillin-treated patient was hospitalized for dehydration after 4 days of treatment. Study medication was discontinued and the patient was treated with IV fluids and antibiotics. The event was considered unrelated to therapy.

5.3.1.10. Withdrawals Due to Adverse Events

Two penicillin-treated patients and no cefdinir-treated patients discontinued study medication because of an adverse event (Table 16). This difference was not statistically different ($p = 0.157$). One of these adverse events (stomach cramps, nausea) was considered treatment-associated.

Six cefdinir-treated patients and 5 penicillin-treated patients withdrew from the study after completing treatment. Otitis media was the most common reason patients withdrew from the study. There were no withdrawals due to diarrhea.

Narratives for patients who discontinued treatment or withdrew from the study are in Appendix B.2.

TABLE 16. Withdrawals Due to Adverse Events - All Patients

Center	Patient Number	Age, Sex	Adverse Event	Relationship to Study Medication ^a	Study Day of Onset	Study Day Drug Discontinued	Outcome
Cefdinir							
3	48	7 yr, F ^{cc}	Possible Rheumatic Fever ^{aa}	Unlikely	9	Completed	Recovered
2	29	19 mo, F	Otitis media	Definitely not	12	Completed medication	Unknown
7	14	5 yr, M	Otitis media	Definitely not	18	Completed medication	Recovered
8	7	11 yr, M	Otitis media, sinusitis	Definitely not	17	Completed medication	Recovered
9	36	6 yr, M	Otitis media	Definitely not	7	Completed medication	Recovered
14	3	10 yr, M	Sinusitis	Definitely not	16	Completed medication	Recovered
Penicillin							
5 ^c	33	2 yr, F	Dehydration ^b	Definitely not	4	4	Recovered
3	58	8 yr, F	Stomach cramps, nausea	Possibly	2	2	Recovered
4	21	2 yr, M	Smashed thumb	Definitely not	2	Completed medication	Recovered
10	38	10 yr, F	Urinary tract infection	Definitely not	15	Completed medication	Recovered
10	47	9 yr, F	Otitis media	Definitely not	11	Completed medication	Recovered
11	9	2 yr, F	Sinusitis, conjunctivitis	Unlikely	18	Completed medication	Recovered
12	6	5 yr, M	Impetigo	Definitely not	18	Completed medication	Recovered

^a As assessed by the investigator

^b Serious adverse event

^c Preferred term: infection

Medical Officer's Note: Please see table 16 in Appendix P56. Patient 33 at site 5 (struck out) discontinued penicillin and was hospitalized due to dehydration. This was reported as a serious adverse event. The event was considered by the investigator to be definitely not related to study medication.

5.3.3. Clinical Laboratory Measurements

5.3.3.1. Changes From Baseline

5.3.3.2. Category Shifts

Medical officer's Note. These tables (17 and 18) in the sponsor's study report, which looked at changes from baseline and category shifts have not been revised as this lab data was run on a different set of programs with extensive reworking required to exclude patients in site 5.

5.3.3.3. Markedly Abnormal Clinical Laboratory Values

Medical Officer's Note: The table 19, which shows markedly abnormal clinical laboratory values, from the original NDA has been included, with patients from center 5 lined out. See table 19 in appendix S56.

Medical Officer's Note: The total number of patients experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) decreased from 23 to 20 in the cefdinir treatment group and from 22 to 19 in the penicillin group, but the overall percentages remained relatively constant at 9.5% and 8.9% respectively. The largest change among the individual parameters was seen in polymorphonuclear leukocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal increase, and in lymphocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal decrease. Please see table 20 in appendix P56

6. DISCUSSION

Patients treated with a 5-day course of cefdinir showed a significantly higher microbiologic eradication rate ($p < 0.001$) compared with patients treated with a 10-day course of penicillin. Clinical response rates for the 2 treatment groups were statistically equivalent at the TOC visit.

The higher eradication rate resulting from cefdinir treatment has important implications in the treatment of GABHS pharyngitis in children. The main objective of antimicrobial intervention in this type of infection is the prevention of more serious complications, such as rheumatic fever. Since the reduction of the incidence of rheumatic fever and other nonsuppurative complications of GABHS pharyngitis is not a practical endpoint for a study, the eradication of *S. pyogenes* becomes the accepted surrogate endpoint for efficacy. The superior eradication rate demonstrated by cefdinir may be a result of its stability in the presence of β -lactamases produced by normal flora in the pharynx. The 5-day, BID dosing regimen for cefdinir therapy may also have contributed to the superior microbiological eradication rate by improving treatment compliance; the percent of patients who took the full course of treatment as prescribed was greater (93%) for cefdinir treatment compared with penicillin treatment (76%).

One cefdinir-treated patient developed what was considered "possible" rheumatic fever. It is uncertain whether this patient did indeed have rheumatic fever. The supposed onset was atypically soon after the development of pharyngitis (Study Day 9). The strain of *S. pyogenes* isolated from the pharynx was not a rheumatogenic strain, but was serotyped as T-Type 11 and M- (Opacity Factor) Type 11; this strain was eradicated by cefdinir treatment. It is also not clear that the patient fulfilled all of the modified Jones criteria for polyarthritides; an evaluation of the patient by an internationally recognized infectious disease specialist resulted in this same conclusion (Appendix B.3). If this patient did have rheumatic fever, it was likely due to an antecedent (nonstudy) infection and does not represent the failure of cefdinir.

Cefdinir therapy was well-tolerated by the pediatric patient population in this study. The safety profile of cefdinir was similar to that of penicillin with 38% of cefdinir-treated patients and 33% of penicillin-treated patients experiencing adverse events over the course of the study. Thirteen percent of cefdinir-treated patients and 14% of penicillin-treated patients experienced adverse events during the treatment phase. The most frequently reported adverse events for cefdinir-treated patients were consistent with upper respiratory symptoms (infection 10%, cough, rhinitis 5%). Diarrhea was reported for 5% of cefdinir-treated patients; 2% were

considered associated with treatment. Vomiting (5%) was the most frequently reported adverse event for penicillin-treated patients, which is not unexpected given that stomach upset is commonly associated with penicillin treatment. Withdrawals due to adverse events were similar for both treatments.

Medical Officer's Note: Exclusion of data from Dr Iravani's site did not affect results of the cefdinir capsule studies, as his site enrolled only pediatric patients taking the suspension

*In the study comparing 5 days treatment of BID cefdinir to 10 days treatment with penicillin, cefdinir was again superior to penicillin in eradication of *S. pyogenes* from the pharynx, by both CI and CMH testing. Clinical response for the 2 regimens was equivalent by CI testing.*

As reported adverse event rates were lower at Dr Iravani's site than the overall rate observed in the study, exclusion of data from his site resulted in increased adverse event rates in all treatment groups. Exclusion of data from Dr Iravani's site, however, did not alter analyses, showing that neither adverse event rates nor drug-associated adverse event rates were statistically significantly different between treatment groups at the $p < 0.05$ level, for either study.

7. CONCLUSIONS

- Five days of cefdinir therapy (BID) is more effective microbiologically than 10 days of penicillin therapy (QID) in the treatment of pediatric patients with GABHS pharyngitis. Clinical response rate is equivalent for cefdinir and penicillin therapy.
- Cefdinir therapy is well-tolerated by pediatric patients; adverse event profiles are similar for cefdinir- and penicillin-treated patients.

Medical Officer's Note: The reviewer agrees with the design and conduct of the study

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APPENDIX P56 ,Study 983-56,Pediatric Pharyngitis -5 days

Evaluable Patients

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding site 5 (Iravani).

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.5% (205/224)	90.7% (196/216)	(-4.5%, 6.1%)	0.798
Excluding Site 5	91.3% (179/196)	89.6% (173/193)	(-4.1%, 7.5%)	0.567
Microbiological Response by Patient				
All Sites	89.7% (201/224)	71.8% (155/216)	(10.8%, 25.2%)	<0.001
Excluding Site 5	89.8% (176/196)	69.9% (135/193)	(12.1%, 27.6%)	<0.001

Excluding site 5 had very little effect on the response rates. Cefdinir is still shown to be equivalent to penicillin in clinical response rate, and superior to penicillin for microbiological response by patient, for the evaluable population.

Clinically Evaluable Patients

The table below presents the clinical response rates and analysis results for the clinically evaluable patient population, both including and excluding site 5.

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.7% (209/228)	90.9% (200/220)	(-4.5%, 6.0%)	0.787
Excluding Site 5	91.5% (182/199)	89.7% (175/195)	(-4.1%, 7.5%)	0.552

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
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PROTOCOL 943-56

Excluding site 5 had very little effect on the clinical response rates. Cefdinir and penicillin are still shown to be equivalent for the clinically evaluable population.

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Summary of Microbiologic Response Rates by Patient
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Protocol 983-056

NDA Analysis- All Sites

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Penicillin V	
	N	%	N	%
Patients w/ eradication	201	89.7	155	71.8
Patients w/ persistence	23	10.3	61	28.2
Total	224	100.0	216	100.0

Protocol 983-056 (Subset=56_noinv.txt)
All sites Except Iravani

Pathogen		Number (%) of Pathogens							
		Cefdinir 7 mg/kg BID				Penicillin V			
		Eradication		Persistence		Eradication		Persistence	
		N	%	N	%	N	%	N	%
Gram Positive	Bhsa_mor1	1	100.0	0	0	0	0	0	0
	Bhsa_mor2	1	100.0	0	0	0	0	0	0
	S_pyogen	175	89.8	20	10.3	135	69.9	58	30.0
Total	Pathogens	177	89.8	20	10.2	135	69.9	58	30.1

Protocol 983-056

Center = 983-056-005 Iravani Only

Pathogen		Number (%) of Pathogens							
		Cefdinir 7 mg/kg BID				Penicillin V			
		Eradication		Persistence		Eradication		Persistence	
		N	%	N	%	N	%	N	%
Gram Positive	Bhsa_mor1	0	0	0	0	1	100.0	0	0
	Bhsa_mor2	0	0	0	0	1	100.0	0	0
Total	Pathogens	25	89.3	3	10.7	21	87.5	3	12.5

¹ The preceding page lists the microbiological eradication rates by pathogen/patient according to the NDA analysis (all patients; all sites except Iravani); and Iravani alone.

Adverse Events

The table below presents the adverse event rates and drug-associated adverse event rates, and the analysis results, for patients who took drug both including and excluding site 5.

	Cefdinir BID	Penicillin	CMH p-value
All Adverse Events			
All Sites	38.3% (92/240)	33.1% (80/242)	0.212
Excluding Site 5	40.8% (86/211)	36.0% (77/214)	0.314
Drug-Associated Adverse Events			
All Sites	5.4% (13/240)	4.5% (11/242)	0.678
Excluding Site 5	6.2% (13/211)	5.4% (11/214)	0.678

Excluding site 5 had very little effect on adverse event rates. No significant difference in the number of all adverse events or drug-associated adverse events in patients receiving cefdinir or penicillin was detected.

Dr. Iranvani reported one serious adverse event in this study. A penicillin-treated patient was hospitalized after 4 days of treatment with penicillin. The study medication was discontinued, and the patient treated with IV fluids and antibiotics. The investigator considered the event definitely not related to study therapy.

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Protocol 983-056

Protocol 983-056 was conducted to obtain information on the clinical and microbiological efficacy and safety of 5 days of cefdinir therapy versus 10 days of penicillin therapy in the treatment of streptococcal pharyngitis.

TABLE 1

Eliminating Dr Iravani's site (Center 5) reduced the number of patients randomized to treatment by 12%, the number completing treatment by 11%, and the evaluable population by 12%.

TABLES 6 and 7

Excluding the Iravani data did not substantially change the demographic characteristics of either the total patient population or the evaluable patient population. The number of black patients decreased from 20 to 11, but this was a very small subgroup; white patients constituted 91% of the population.

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TABLE 8

Patient exposure to study medication remained the same, with the majority of cefdinir patients finishing study medication on Day 5 and most penicillin patients finishing medication on Day 11.

TABLE 9

The overall percentages of patients completing the treatment phase, TOC visit phase, and LTFU visit phase of the study remained relatively constant at 96.2%, 89.1%, and 70.6% respectively. The percentage of patients completing the treatment phase increased by 0.6% when patients from Dr Iravani's site were excluded.

TABLE 10

No substantial change was seen in the frequency distribution of reasons for exclusion from evaluable analyses at TOC and reasons for disqualification from qualified analyses at LTFU.

TABLE 11

The revised numbers of patients included in the efficacy summaries are presented.

TABLE 12

The pattern of microbiologic and clinical outcomes remains unchanged, with good correlation, but with a relatively large number of penicillin patients with clinical cure but microbiological persistence. Cefdinir still shows superiority microbiologically.

TABLE 13

The response rates and analysis results for all patient populations are shown in Table 13. Excluding Site 5 had very little effect on response rates. Cefdinir and penicillin are still shown to be equivalent in clinical response rate across patient

populations. Cefdinir remains statistically superior to penicillin for microbiological response rate across populations.

TABLE 14

Again, Dr Iravani's site reported a lower incidence of adverse events than the overall reported rates: 21% for cefdinir BID and 11% for penicillin. Because of this, the incidence of all adverse events increased proportionally in both the cefdinir and penicillin groups when data from his site were excluded. As shown below, rates of all adverse events increased from 38.3% to 40.8% (a factor of 1.07) in the cefdinir group and from 33.1% to 36.0% (a factor of 1.09) in the penicillin group. Likewise, rates of drug-associated adverse events increased from 5.4% to 6.2% (a factor of 1.15) in the cefdinir group and from 4.5% to 5.1% (a factor of 1.13) in the penicillin group. No significant differences in the number of adverse events or drug-associated adverse events reported by patients receiving either cefdinir or penicillin were detected; p values are reported below.

	Cefdinir BID	Penicillin	CMH p-Value
All Adverse Events			
All Sites	38.3% (92/240)	33.1% (80/242)	0.212
Excluding Site 5	40.8% (86/211)	36.0% (77/214)	0.314
Drug-Associated Adverse Events			
All Sites	5.4% (13/240)	4.5% (11/242)	0.678
Excluding Site 5	6.2% (13/211)	5.4% (11/214)	0.678

Similar trends were seen when adverse events and drug-associated adverse events were examined by age, sex, and race.

TABLE 15

For ease of comparison, this revised table includes data from both the NDA study report and the revised data excluding Dr Iravani's site.

Small increases were also seen in most individual adverse event rates and drug-associated adverse event rates as a result of a smaller denominator. The largest increase in rates for a particular event was seen in the cefdinir group for infection, where the rate increased by 0.9%, and for increased cough, where the rate increased by 0.8%. Lesser increases in the rates of diarrhea were seen, by 0.1% in the cefdinir group and by 0.6% in the penicillin group. Rates of drug-associated diarrhea increased by 0.3% in the cefdinir group and by 0.1% in the penicillin group

TABLE 16

Patient 33 at Dr Iravani's site discontinued penicillin and was hospitalized due to dehydration. This was reported as a serious adverse event. The event was considered by the investigator to be definitely not related to study medication.

TABLES 17 and 18

These tables have not been revised; please see the Introduction for an explanation.

TABLE 19

This table is a list of patients with markedly abnormal values at the first posttherapy visit. The table from the original NDA has been included, with patients from Dr Iravani's site (Center 5) lined out.

TABLE 20

The total number of patients experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) decreased from 23 to 20 in the cefdinir treatment group and from 22 to 19 in the penicillin group, but the overall percentages remained relatively constant at 9.5% and 8.9% respectively.

The largest change among the individual parameters was seen in polymorphonuclear leukocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal increase, and in lymphocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal decrease.

DISCUSSION

Exclusion of data from Dr Iravani's site did not affect results of the cefdinir capsule studies, as his site enrolled only pediatric patients taking the suspension.

In the study comparing 10 days treatment of QD and BID cefdinir to penicillin, exclusion of data from Dr Iravani's site did not affect efficacy conclusions. Either cefdinir regimen was superior to penicillin in eradication of *S. pyogenes* from the pharynx, by both CI testing (the confidence interval did not cross zero), and p-value (CMH) testing. Both of the cefdinir regimens were statistically superior to the penicillin regimen in achieving clinical cures as well.

In the study comparing 5 days treatment of BID cefdinir to 10 days treatment with penicillin, cefdinir was again superior to penicillin in eradication of *S. pyogenes* from the pharynx, by both CI and CMH testing. Clinical response for the 2 regimens was equivalent by CI testing.

As reported adverse event rates were lower at Dr Iravani's site than the overall rate observed in the study, exclusion of data from his site resulted in increased adverse event rates in all treatment groups. Exclusion of data from Dr Iravani's site, however, did not alter analyses, showing that neither adverse event rates nor drug-associated adverse event rates were statistically significantly different between treatment groups at the $p < 0.05$ level, for either study.

The primary objective of therapy of streptococcal pharyngitis is eradication of *S. pyogenes* from the pharynx, in order to decrease the risk of complications such as rheumatic fever. The studies included in the cefdinir NDA, with or without data from Dr Iravani's site, demonstrate that cefdinir effectively eradicates streptococci from the pharynx, and does so more reliably than penicillin.

Two of the streptococcal pharyngitis studies were conducted in adolescents/adults, and 2 in children. The efficacy results across all 4 studies are shown in the tables on the following 2 pages. As the pathophysiology of the infection in children and adults is similar, the pathogen identical, and the pharmacokinetics of cefdinir in the populations very similar, study results in adolescents/adults and children can be used

NDA 50-739 (CEFDINIR)
7 MG/KG BIDXSD VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

interchangeably to evaluate the effectiveness of a treatment in either population. The studies included in the cefdinir NDA thus support the use of this compound for the treatment of streptococcal pharyngitis in both children and adults with a treatment duration of 5 or 10 days.

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**Microbiological Response by Patient and Clinical Response Rates - Evaluable Patients
(% of Patients)**

Study	983-7			983-58		983-51			983-51 (Excluding Iravani)			983-56		983-56 (Excluding Iravani)	
Treatment	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef BID	Pen
Microbiological Response by Patient	91.4	91.7	83.4	88.5	82.2	92.5	94.8	70.8	94.3	94.3	70.0	89.7	71.8	89.8	69.9
Clinical Response Rates	93.8	95.9	89.4	89.0	84.6	97.6	96.4	86.8	97.4	96.0	86.3	91.5	90.7	91.3	89.6

Cef = Cefdinir; Pen = Penicillin.

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ON ORIGINAL

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

**Clinical Response Rates - Clinically Evaluable Patients
(% of Patients)**

Study	983-7			983-58		983-51			983-51 (Excluding Iravani)			983-56		983-56 (Excluding Iravani)	
Treatment	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef BID	Pen
Clinical Response Rates	90.9	93.3	85.2	86.7	81.6	97.3	96.5	86.2	97.0	96.1	85.7	91.7	90.9	91.5	89.7

Cef = Cefdinir, Pen = Penicillin.

APPEARS THIS WAY
ON ORIGINAL

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX2D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

TABLE 1. List of Investigators Excluding Site 5

Center 983-56-	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable
1	Gerson Aronovitz, MD	12	12	11
2	W. Manford Gooch III, MD, PC	50	47	44
3	James A. Hodrick, MD	59	56	53
4	Dan Henry, MD	47	45	45
6	Kevin Ludwig, MD*	0	0	0
7	James McCarty, MD	33	31	28
8	Samuel McLinn, MD	30	29	29
9	Michael Pichichero, MD	48	48	46
10	Edward Rothstein, MD	53	53	51
11	Sandra Wiederhold, MD	25	24	24
12	Malcolm Sperling, MD	20	19	19
13	Richard Schwartz, MD	32	32	31
14	Margaret Drebohl, MD	16	13	13
Total		425	409	394

* Investigator received drug but did not enroll patients

APPEARS THIS WAY
 ON ORIGINAL

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients		
		Cefdinir 7 mg/kg BID	Penicillin V	Total
Total	Patients	211	214	425
Sex				
Male	N	112	109	221
	Percent	53.1	50.9	52.0
Female	N	99	105	204
	Percent	46.9	49.1	48.0
Race				
White	N	193	193	386
	Percent	91.5	90.2	90.8
Black	N	3	8	11
	Percent	1.4	3.7	2.6
Asian	N	4	0	4
	Percent	1.9	0	0.9
Other	N	11	13	24
	Percent	5.2	6.1	5.6
Age (Years)				
< 2	N	2	1	3
	Percent	0.9	0.5	0.7
2 to < 6	N	54	48	102

(CONTINUED)

Summary Specification Table 101
(Page 1 of 2)

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14

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Summary of Patient Characteristics
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients		Total
		Cefdinir 7 mg/kg BID	Penicillin V	
Age (Years)				
2 to < 6	Percent	25.6	22.4	24.0
6 to < 13	N	155	163	318
	Percent	73.5	76.2	74.8
13 to < 18	N	0	2	2
	Percent	0	0.9	0.5
Age Range	Max	13	18	18
	Min	1	2	1
Baseline Diagnosis				
Pharyngitis	N	60	63	123
	Percent	28.4	29.4	28.9
Tonsillitis	N	22	15	37
	Percent	10.4	7.0	8.7
Pharyngitis & tonsillitis	N	129	136	265
	Percent	61.1	63.6	62.4

Summary Specification Table 101
(Page 2 of 2)

NDA 58-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX F56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Minimum, Median and Maximum Values
For Demographic and Other Variables
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID			Penicillin V			Total		
	Min	Med	Max	Min	Med	Max	Min	Med	Max
Baseline Parameters									
Age (Years)	1.0	7.5	12.8	1.7	7.8	18.0	1.0	7.8	18.0
Weight (kg)	11.3	25.5	86.6	10.3	26.4	86.4	10.3	26.4	86.6
Height (cm)	78.7	124.5	168.9	82.8	128.3	168.9	78.7	127.0	168.9
Systolic BP (mm Hg)	70.0	100.0	140.0	70.0	98.0	128.0	70.0	98.0	140.0
Diastolic BP (mm Hg)	36.0	60.0	80.0	30.0	60.0	84.0	30.0	60.0	84.0
Temperature (C)	35.4	37.3	40.0	35.3	37.3	39.8	35.3	37.3	40.0

NDA 50-739 (CEFdinir)
7 MG/KG BIDX5D VS
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Summary Specification Table 192
(Page 1 of 1)

dinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

Protocol 983-056 (Subset=56_noinv.txt)

NDA 50-739 (CEFDINIR)
7 MG/KG BID/5D VS.
PEN VK 10MG/KG QID/10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

		Number (%) of Patients		
		Cefdinir 7 mg/kg BID	Penicillin V	Total
Total	Patients	196	193	389
Sex				
Male	N	103	98	201
	Percent	52.6	50.8	51.7
Female	N	93	95	188
	Percent	47.4	49.2	48.3
Race				
White	N	179	176	355
	Percent	91.3	91.2	91.3
Black	N	3	6	9
	Percent	1.5	3.1	2.3
Asian	N	4	0	4
	Percent	2.0	0	1.0
Other	N	10	11	21
	Percent	5.1	5.7	5.4
Age (Years)				
< 2	N	1	1	2
	Percent	0.5	0.5	0.5
2 to < 6	N	48	44	92

(CONTINUED)

Summary Specification Table 102
(Page 1 of 2)

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients		Total
		Cefdinir 7 mg/kg BID	Penicillin V	
Age (Years)				
2 to < 6	Percent	24.5	22.8	23.7
6 to < 13	N	147	147	294
	Percent	75.0	76.2	75.6
13 to < 18	N	0	1	1
	Percent	0	0.5	0.3
Age Range	Max	13	16	16
	Min	2	2	2
Baseline Diagnosis				
Pharyngitis	N	58	54	112
	Percent	29.6	28.0	28.8
Tonsillitis	N	20	15	35
	Percent	10.2	7.8	9.0
Pharyngitis & tonsillitis	N	118	124	242
	Percent	60.2	64.2	62.2

Summary Specification Table 102
(Page 2 of 2)

NDA 50-739 (CEDINIR)
7 MG/KG BIDXSD VS
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Minimum, Median and Maximum Values
For Demographic and Other Variables
Microbiologically-Clinically Evaluable Patients

Protocol 983-056 (Subset=56_noinv.txt)

NDA 50-739 (CEDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

	Cefdinir 7 mg/kg BID			Penicillin V			Total		
	Min	Med	Max	Min	Med	Max	Min	Med	Max
Baseline Parameters									
Age (Years)	1.6	7.7	12.6	1.7	7.8	15.7	1.6	7.8	15.7
Weight (kg)	11.3	26.0	86.6	10.3	26.4	71.8	10.3	26.4	86.6
Height (cm)	82.8	126.5	168.9	82.8	127.0	168.9	82.8	127.0	168.9
Systolic BP (mm Hg)	70.0	100.0	140.0	70.0	98.0	128.0	70.0	98.0	140.0
Diastolic BP (mm Hg)	36.0	60.0	80.0	30.0	60.0	84.0	30.0	60.0	84.0
Temperature (C)	35.4	37.3	40.0	35.3	37.3	39.8	35.3	37.3	40.0

Summary Specification Table 193
(Page 1 of 1)

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Exposure to Study Medication
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

Days on Study Medication	Number (%) of Patients			
	Cefdinir 7 mg/kg BID (Median=5.0)		Penicillin V (Median=11.0)	
	N	%	N	%
1	2	0.9	0	0
2	1	0.5	1	0.5
3	1	0.5	0	0
5	157	74.4	3	1.4
6	50	23.7	1	0.5
7	0	0	2	0.9
9	0	0	1	0.5
10	0	0	68	31.8
11	0	0	132	61.7
12	0	0	3	1.4
Unknown	0	0	3	1.4
Total	211	100.0	214	100.0

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Summary Specification Table 265
(Page 1 of 1)

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Treatment Phase

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicillin V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		207	98.1	202	94.4	409	96.2
Reason for Withdrawal	Lack of Compliance	2	0.9	6	2.8	8	1.9
	Adverse Event	0	0	1	0.5	1	0.2
	Failure at end of therapy	0	0	1	0.5	1	0.2
	No Baseline Pathogen	0	0	1	0.5	1	0.2
	Other/Administrati- ve	2	0.9	3	1.4	5	1.2

NDA 50-739 (CEDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICERS AND STATISTICIAN'S REVIEW
PROTOCOL 983-56Summary Specification Table 269
(Page 1 of 1)

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Short-Term Follow-Up Visit

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicillin in V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		206	97.6	208	97.2	414	97.4
Reason for Withdrawal	Lack of Compliance	2	0.9	3	1.4	5	1.2
	Failure at end of therapy	1	0.5	0	0	1	0.2
	No Baseline Pathogen	0	0	1	0.5	1	0.2
	Other/Administrati- ve	2	0.9	2	0.9	4	0.9

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS
PEN VK 10MG/KG QIDX10D
APPENDIX F56PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56Summary Specification Table 270
(Page 1 of 1)

TABLE 17. All and Associated Adverse Events by Body System: All Patients - Protocol 983-51
[Number (%) of Patients]
(Page 4 of 5)

BODY SYSTEM ^a / Adverse Event	Sites Excluding Iravani					
	Cefdinir				Penicillin	
	14 mg/kg QD N = 264		7 mg/kg BID N = 263		N = 264	
	All	Assoc	All	Assoc	All	Assoc
SKIN AND APPENDAGES (Continued)						
Seborrhea	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Skin Disorder	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)
Dry Skin	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Eczema	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Pruritus	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM						
Lymphadenopathy	4 (1.5)	0 (0.0)	7 (2.7)	0 (0.0)	4 (1.5)	0 (0.0)
Eosinophilia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocytosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
UROGENITAL SYSTEM						
Urinary Tract Infection	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Vaginitis ^b	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)
Hematuria	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Leukorrhea	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dysuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Penis Disorder ^c	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine Abnormality	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vaginal Moniliasis ^b	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM						
Abnormal Dreams	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Emotional Lability	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkinesia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

^a The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

^b The denominators used are for females only: Cefdinir QD, N = 134; Cefdinir BID, N = 135 for all sites and Cefdinir QD, N = 123; Cefdinir BID, N = 131 for sites excluding Iravani.

^c The denominator used is for males only: Cefdinir QD, N = 155 for all sites and Cefdinir QD, N = 141 for sites excluding Iravani.

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Mid-Term Follow-Up Visit

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicillin- in V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		178	84.4	173	80.8	351	82.6
Reason for Withdrawal	Lack of Compliance	4	1.9	3	1.4	7	1.6
	Adverse Event	4	1.9	4	1.9	8	1.9
	Failure at EOT or previous visit	19	9.0	26	12.1	45	10.6
	No Baseline Pathogen	1	0.5	3	1.4	4	0.9
	Other/Administrati- ve	5	2.4	5	2.3	10	2.4

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIANS REVIEW
PROTOCOL 983-56Summary Specification Table 271
(Page 1 of 1)

dfdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Long-Term Follow-Up Visit

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicill- in V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		157	74.4	143	66.8	300	70.6
Reason for Withdrawal	Lack of Compliance	7	3.3	5	2.3	12	2.8
	Adverse Event	6	2.8	6	2.8	12	2.8
	Failure at EOT or previous visit	36	17.1	52	24.3	88	20.7
	No Baseline Pathogen	1	0.5	3	1.4	4	0.9
	Other/Administrati- ve	4	1.9	5	2.3	9	2.1

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Summary Specification Table 272
(Page 1 of 1)

dinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Reasons for Exclusion of Patients from Evaluable Analyses
Test-of-Cure Visit

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients					
		Cefdinir 7 mg/kg BID		Penicillin V		Total	
		N	%	N	%	N	%
Exclusions from Clinical Analyses	*** Total ***	12	5.7	19	8.9	31	7.3
	Clin asmt missed	1	0.5	3	1.4	4	0.9
	Clin out of range	7	3.3	14	6.5	21	4.9
	Concurrent antibac	3	1.4	2	0.9	5	1.2
	Med not as prescrb	7	3.3	10	4.7	17	4.0
Additional Exclusions from Microbiological Analyses	*** Total ***	3	1.4	2	0.9	5	1.2
	Cult out of range	7	3.3	14	6.5	21	4.9
	Culture missed	2	0.9	7	3.3	9	2.1
	No proven pathogn	4	1.9	3	1.4	7	1.6
Total	*** TOTAL ***	15	7.1	21	9.8	36	8.5

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Summary Specification Table 172
(Page 1 of 1)

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Reasons for Disqualification of Microbiologically/Clinically Evaluable Patients from Analysis
Long-Term Follow-Up Visit

Protocol 983-056 (Subset=56_noinv.txt)

Disqualification	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Penicillin V	
	N	%	N	%
*** Total ***	44	22.4	70	36.3
Clin asmt missed	23	11.7	52	26.9
Clin out of range	19	9.7	14	7.3
Concurrent antibac	1	0.5	4	2.1
Cult out of range	19	9.7	13	6.7
Culture missed	25	12.8	54	28.0

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICERS AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Summary Specification Table 175
(Page 1 of 1)

TABLE 11. Patients (With Data) Included in Efficacy
Summaries Excluding Site 5 (Protocol 983-56)
[Number (%) of Patients]

Patient Population	Cefdinir	Penicillin
Intent-to-Treat (ITT)	211	214
Modified Intent-to-Treat (MITT)	207	204
Clinically Evaluable	199	195
Microbiologically-Clinically Evaluable	196	193
Qualified at LTFU	152	123

APPEARS THIS WAY
ON ORIGINAL

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Combined Investigator/Sponsor Determination Response Rates Versus Microbiologic Response Rates

Test-of-Cure Visit

Microbiologically-Clinically Evaluable Patients

Protocol 983-056 (Subset=56_noinv.txt)

Microbiologic Response	Clinical Response							
	Cefdinir 7 mg/kg BID				Penicillin V			
	Cure		Failure		Cure		Failure	
	N	%	N	%	N	%	N	%
Patients w/ eradication	172	87.8	4	2.0	134	69.4	1	0.5
Patients w/ persistence	7	3.6	13	6.6	39	20.2	19	9.8

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

Summary Specification Table 343
(Page 1 of 1)

TABLE 13. Summary of Efficacy Analyses at TOC Excluding Site 5

Efficacy Parameter/ Population	Rates (%)		95% CI ^a	Interpretation ^b (Superior, Equivalent, Not Equivalent)	CMH ^c (p-Value)
	Cefdinir	Penicillin			
Microbiologic Eradication					
Evaluable ^d	90	70	(12.1, 27.6)	Superior	<0.001
MITT	90	72	(10.9, 25.7)	Superior	<0.001
ITT	88	68	(12.3, 27.5)	Superior	<0.001
Clinical Response					
Evaluable	91	90	(-4.1, 7.5)	Equivalent	0.57
Clinically Evaluable	92	90	(-4.1, 7.5)	Equivalent	0.55
ITT	91	89	(-3.9, 7.4)	Equivalent	0.55

^a CI about difference between cefdinir vs penicillin (cefdinir minus penicillin)

^b Treatments were equivalent if the 95% CI fell within the fixed criteria for equivalence and contained zero.
Cefdinir treatment was superior where indicated.

^c Exploratory CMH; cefdinir vs penicillin

^d Primary efficacy analysis

APPEARS THIS WAY
ON ORIGINAL

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patient

Summary of Adverse Events
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID (N=211)		Penicillin V (N=214)	
	N	%	N	%
Number of Patients Reporting AE	86	40.8	77	36.0
Number of Patients Reporting Mild AE	65	30.8	65	30.4
Number of Patients Reporting Moderate AE	33	15.6	22	10.3
Number of Patients Reporting Severe AE	1	0.5	0	0.0
Number of Male Patients Reporting AE	45	40.2	40	36.7
Number of Female Patients Reporting AE	41	41.4	37	35.2
Number of Patients < 2 Years Old Reporting AE	1	50.0	1	100.0
Number of Patients 2 to < 6 Years Old Reporting AE	28	51.9	23	47.9
Number of Patients 6 to < 13 Years Old Reporting AE	57	36.8	53	32.5
Number of Patients 13 to < 18 Years Old Reporting AE	0	0.0	0	0.0
Number of White Patients Reporting AE	80	41.5	70	36.3
Number of Black Patients Reporting AE	0	0.0	3	37.5
Number of Asian Patients Reporting AE	2	50.0	0	0.0
Number of Hispanic Patients Reporting AE	2	25.0	4	40.0
Number of Other Patients Reporting AE	2	66.7	0	0.0

(CONTINUED)

~Patients who did not discontinue treatment due to an AE
Summary Specification Table 148
(Page 1 of 2)

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Strep. Occal Pharyngitis/Tonsillitis Infections in Pediat

Summary of Adverse Events
 All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID (N=211)		Penicillin V (N=214)	
	N	%	N	%
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	0	0.0	1	0.5
Number of Patients Whose Treatment Was Discontinued Due to Non-TESS AE	0	0.0	0	0.0
Number of Patients Withdrawn from Study Due to AE~	6	2.8	5	2.3

-Patients who did not discontinue treatment due to an AE
 Summary Specification Table 148
 (Page 2 of 2)

cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patient

Summary of Associated Adverse Events
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID (N=211)		Penicillin V (N=214)	
	N	%	N	%
Number of Patients Reporting AE	13	6.2	11	5.1
Number of Patients Reporting Mild AE	9	4.3	8	3.7
Number of Patients Reporting Moderate AE	3	1.4	4	1.9
Number of Patients Reporting Severe AE	1	0.5	0	0.0
Number of Male Patients Reporting AE	6	5.4	5	4.6
Number of Female Patients Reporting AE	7	7.1	6	5.7
Number of Patients < 2 Years Old Reporting AE	0	0.0	0	0.0
Number of Patients 2 to < 6 Years Old Reporting AE	4	7.4	7	14.6
Number of Patients 6 to < 13 Years Old Reporting AE	9	5.8	4	2.5
Number of Patients 13 to < 18 Years Old Reporting AE	0	0.0	0	0.0
Number of White Patients Reporting AE	13	6.7	10	5.2
Number of Black Patients Reporting AE	0	0.0	1	12.5
Number of Asian Patients Reporting AE	0	0.0	0	0.0
Number of Hispanic Patients Reporting AE	0	0.0	0	0.0
Number of Other Patients Reporting AE	0	0.0	0	0.0

(CONTINUED)

-Patients who did not discontinue treatment due to an AE
Summary Specification Table 262
(Page 1 of 2)

Summary of Associated Adverse Events
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID (N=211)		Penicillin V (N=214)	
	N	%	N	%
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	0	0.0	1	0.5
Number of Patients Whose Treatment Was Discontinued Due to Non-TESS AE	0	0.0	0	0.0
Number of Patients Withdrawn from Study Due to AE-	0	0.0	0	0.0

NDA 50-739 (CEFDINIR)
7 MG/KG BIDX5D VS.
PEN VK 10MG/KG QIDX10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

-Patients who did not discontinue treatment due to an AE
Summary Specification Table 262
(Page 2 of 2)

TABLE 15. All and Associated Adverse Events: All Patients - Protocol 983-56
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM ^a / Adverse Event	All Sites				Sites Excluding Iravani			
	Cefdinir N = 240		Penicillin N = 242		Cefdinir N = 211		Penicillin N = 214	
	All	Assoc	All	Assoc	All	Assoc	All	Assoc
BODY AS A WHOLE	45 (18.8)	1 (0.4)	33 (13.6)	1 (0.4)	43 (20.4)	1 (0.5)	32 (15.0)	1 (0.5)
Infection	24 (10.0)	0 (0.0)	12 (5.0)	0 (0.0)	23 (10.9)	0 (0.0)	12 (5.6)	0 (0.0)
Abdominal Pain	8 (3.3)	1 (0.4)	6 (2.5)	1 (0.4)	8 (3.8)	1 (0.5)	6 (2.8)	1 (0.5)
Headache	8 (3.3)	0 (0.0)	8 (3.3)	0 (0.0)	8 (3.8)	0 (0.0)	7 (3.3)	0 (0.0)
Accidental Injury	6 (2.5)	0 (0.0)	4 (1.7)	0 (0.0)	6 (2.8)	0 (0.0)	4 (1.9)	0 (0.0)
Allergic Reaction	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)
Flu Syndrome	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Chest Pain	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Fever	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.9)	0 (0.0)
Neck Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Neck Rigidity	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
CARDIOVASCULAR SYSTEM	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.9)	0 (0.0)
Hemorrhage	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular Tachycardia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
DIGESTIVE SYSTEM	26 (10.8)	9 (3.8)	23 (9.5)	7 (2.9)	22 (10.4)	9 (4.3)	23 (10.7)	7 (3.3)
Diarrhea	11 (4.6)	5 (2.1)	9 (3.7)	2 (0.8)	10 (4.7)	5 (2.4)	9 (4.2)	2 (0.9)
Vomiting	8 (3.3)	2 (0.8)	12 (5.0)	2 (0.8)	5 (2.4)	2 (0.9)	12 (5.6)	2 (0.9)
Gastroenteritis	4 (1.7)	0 (0.0)	1 (0.4)	1 (0.4)	4 (1.9)	0 (0.0)	1 (0.5)	1 (0.5)
Glossitis	2 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)
Dyspepsia	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Gingivitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.4)	0 (0.0)	4 (1.7)	2 (0.8)	1 (0.5)	0 (0.0)	4 (1.9)	2 (0.9)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

^a The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

NDA 50-739 (CEFdinir)
7 MG/KG BID/SD VS
PEN VK 10MG/KG QID/SD
APPENDIX P56

PHARYNGITIS/OTITIS-MEDIA
MEDICAL OFFICERS AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

TABLE 15. All and Associated Adverse Events: All Patients - Protocol 983-56
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM*/ Adverse Event	All Sites				Sites Excluding Iravani			
	Cefdinir N = 240		Penicillin N = 242		Cefdinir N = 211		Penicillin N = 214	
	All	Assoc	All	Assoc	All	Assoc	All	Assoc
DIGESTIVE SYSTEM (Continued)								
Flatulence	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Melena	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Mouth Ulceration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Rectal Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Anemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
METABOLIC AND NUTRITIONAL SYSTEM	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Peripheral Edema	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lactic Dehydrogenase Increase	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
MUSCULOSKELETAL SYSTEM	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Leg Cramps	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Convulsion	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
RESPIRATORY SYSTEM	35 (14.6)	0 (0.0)	23 (9.5)	1 (0.4)	35 (16.6)	0 (0.0)	22 (10.3)	1 (0.5)
Cough Increased	13 (5.4)	0 (0.0)	7 (2.9)	0 (0.0)	13 (6.2)	0 (0.0)	7 (3.3)	0 (0.0)
Rhinitis	13 (5.4)	0 (0.0)	10 (4.1)	0 (0.0)	13 (6.2)	0 (0.0)	9 (4.2)	0 (0.0)
Sinusitis	5 (2.1)	0 (0.0)	4 (1.7)	0 (0.0)	5 (2.4)	0 (0.0)	3 (1.4)	0 (0.0)
Pharyngitis	4 (1.7)	0 (0.0)	4 (1.7)	0 (0.0)	4 (1.9)	0 (0.0)	4 (1.9)	0 (0.0)
Epistaxis	2 (0.8)	0 (0.0)	2 (0.8)	1 (0.4)	2 (0.9)	0 (0.0)	2 (0.9)	1 (0.5)
Lung Disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Voice Alteration	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

* The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

NDA 50-739 (CEFdinir)
7 MG/5G BID/5D VS.
PEN VK 10MG/5G QID/10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICERS AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

TABLE 15. All and Associated Adverse Events: All Patients - Protocol 983-56
[Number (%) of Patients]
(Page 3 of 3)

NDA 50-739 (CEFIDINIR)
7 MG/5G BID/5D VS.
PEN VK 10MG/5G QID/10D
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

BODY SYSTEM/ Adverse Event	All Sites				Sites Excluding Iravani			
	Cefdinir N = 240		Penicillin N = 242		Cefdinir N = 211		Penicillin N = 214	
	All	Assoc	All	Assoc	All	Assoc	All	Assoc
SKIN AND APPENDAGES	10 (4.2)	5 (2.1)	15 (6.2)	4 (1.7)	8 (3.8)	5 (2.4)	15 (7.0)	4 (1.9)
Rash	5 (2.1)	4 (1.7)	7 (2.9)	3 (1.2)	5 (2.4)	4 (1.9)	7 (3.3)	3 (1.4)
Alopecia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry Skin	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Fungal Dermatitis	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Maculopapular Rash	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Skin Disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Acne	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Contact Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Erythema Multiforme	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Exfoliative Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Herpes Simplex	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Pustular Rash	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	0 (0.0)
Vesiculobullous Rash	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
SPECIAL SENSES	13 (5.4)	0 (0.0)	18 (7.4)	0 (0.0)	12 (5.7)	0 (0.0)	15 (7.0)	0 (0.0)
Otitis Media	7 (2.9)	0 (0.0)	7 (2.9)	0 (0.0)	6 (2.8)	0 (0.0)	5 (2.3)	0 (0.0)
Ear Pain	4 (1.7)	0 (0.0)	7 (2.9)	0 (0.0)	4 (1.9)	0 (0.0)	6 (2.8)	0 (0.0)
Conjunctivitis	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)
Ear Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Eye Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Eye Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Photophobia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
UROGENITAL SYSTEM	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Dysuria	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hematuria	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

* The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 16. Withdrawals Due to Adverse Events - All Patients

Center	Patient Number	Age, Sex	Adverse Event	Relationship to Study Medication ^a	Study Day of Onset	Study Day Drug Discontinued	Outcome
Cefdinir							
3	48	7 yr, F	Possible Rheumatic Fever ^{b,c}	Unlikely	9	Completed	Recovered
2	29	19 mo, F	Otitis media	Definitely not	12	Completed medication	Unknown
7	14	5 yr, M	Otitis media	Definitely not	18	Completed medication	Recovered
8	7	11 yr, M	Otitis media, sinusitis	Definitely not	17	Completed medication	Recovered
9	36	6 yr, M	Otitis media	Definitely not	7	Completed medication	Recovered
14	3	10 yr, M	Sinusitis	Definitely not	16	Completed medication	Recovered
Penicillin							
5	33	2 yr, F	Dehydration ^b	Definitely not	4	4	Recovered
3	58	8 yr, F	Stomach cramps, nausea	Possibly	2	2	Recovered
4	21	2 yr, M	Smashed thumb	Definitely not	2	Completed medication	Recovered
10	38	10 yr, F	Urinary tract infection	Definitely not	15	Completed medication	Recovered
10	47	9 yr, F	Otitis media	Definitely not	11	Completed medication	Recovered
11	9	2 yr, F	Sinusitis, conjunctivitis	Unlikely	18	Completed medication	Recovered
12	6	5 yr, M	Impetigo	Definitely not	18	Completed medication	Recovered

^a As assessed by the investigator

^b Serious adverse event

^c Preferred term: infection

6.3.1.11. *Clostridium difficile*-Associated Diarrhea

No patients discontinued treatment for diarrhea, therefore, none were tested for *C. difficile*.

6.3.2. Physical Examinations⁽ⁱⁱ⁾

A review of the physical examinations performed at baseline, TOC, and LTFU showed no adverse findings associated with any treatment group.

⁽ⁱⁱ⁾ Appendix C.55, Median Changes in Vital Signs

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit
(Page 1 of 4)

Center	Patient No.	Race	Age (Yr), Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinr									
2	3	White	9, F	39.5	Urine WBC	21-50 /HPF	21-50	1-5	No history noted
2	20	White	12, F	38.6	Alkaline phosphatase	516 U/L	486	25-480	No history noted
2	34	White	12, M	61.0	Urine protein	1+	Negative	Negative	ADD, methylphenidate, diphtheria, hepatitis, MMR vaccines
3	12	White	11, F	48.1	WBC	$26.1 \times 10^9/L$	18.8	4.5-13.5	Failure
3	19	White	6, M	24.0	Lymphocytes	8 %	4	10-49	
					PMNs	80 %	84	20-75	Failure
3	39	White	11, F	45.0	Urine protein	1+	Trace	Negative	AE: stuffy nose, otitis media, beclomethasone, acetaminophen
3	44	White	2, F	13.1	PMNs	76 %	NA	20-75	No history noted
									History otitis media, wheezy bronchitis
3	48	White	7, F	29.0	PMNs	80 %	57	20-75	AE: viral gastroenteritis
									History otitis media, pharyngitis
									AE: possible rheumatic fever, diarrhea, runny nose
									Acetaminophen, ibuprofen
									AE: viral syndrome, vomiting
~~3~~	~~32~~	~~White~~	~~6, F~~	~~20.0~~	~~WBC~~	~~$22.7 \times 10^9/L$~~	~~8.9~~	~~8-14.5~~	
					~~PMNs~~	~~87%~~	~~66~~	~~20-75~~	
					~~Lymphocytes~~	~~7%~~	~~19~~	~~10-66~~	
~~3~~	~~41~~	~~White~~	~~7, M~~	~~21.0~~	~~PMNs~~	~~89%~~	~~81~~	~~20-75~~	Failure
					~~Lymphocytes~~	~~6%~~	~~11~~	~~10-66~~	
~~5~~	~~32~~	~~White~~	~~12, M~~	~~42.7~~	~~Eosinophils~~	~~12%~~	~~10~~	~~0-7~~	ADD, imipramine
7	25	Hispanic	5, M	18.4	PMNs	85 %	70	20-75	No history noted
					Lymphocytes	8 %	17	10-66	
8	10	White	7, F	20.9	PMNs	83 %	77	20-75	Failure
					Lymphocytes	9 %	12	10-66	
8	27	White	8, M	50.9	Alkaline phosphatase	408 U/L	367	25-350	ADD, methylphenidate
									AE: sprain, forearm
9	3	White	8, M	22.7	WBC	$16.4 \times 10^9/L$	15.6	4.5-13.5	Failure
					Lymphocytes	9 %	6	10-49	
9	33	White	10, M	32.7	Bicarbonate	13 mmol/L	22	22-32	Seasonal allergies, recurrent strep throat
									Microbiological failure
					LDH	479 U/L	221	118-273	

WBC = White blood cells; PMN = polymorphonuclear leukocytes; LDH = Lactate dehydrogenase; ADD = Attention deficit disorder; MMR = Measles, mumps, rubella; NA = Not available; AE = Adverse event.

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit
(Page 2 of 4)

Center	Patient No.	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
9	36	White	6, F	19.3	WBC	$3.3 \times 10^9/L$	8.8	5-14.5	AE: otitis media
10	3	White	6, F	19.3	Bicarbonate	11 mmol/L	15	22-32	Failure
					WBC	$20.2 \times 10^9/L$	19.3	5-14.5	
					PMNs	81 %	87	20-75	
10	5	White	6, F	20.3	PMNs	78 %	79	20-75	Microbiological failure
									AE: cough, blood in urine
10	15	White	5, M	22.3	PMNs	88 %	71	20-75	Microbiological failure
									AE: Intercurrent viral illness
					Lymphocytes	7 %	17	10-66	
10	17	White	7, F	30.9	Bilirubin	6.5 mg/dL	0.3	0.2-1.4	Specimen grossly hemolyzed
					AST	367 U/L	18	0-31	
					Potassium	15.9 mEq/L	3.9	3.5-5.1	
					LDH	4591 U/L	225	150-300	
					Sodium	124 mEq/L	136	136-146	
					Phosphorus	9.9 mg/dL	4.5	3.1-6.3	
					Total protein	10.2 g/dL	7.2	5.8-8	
10	20	White	5, F	17.7	LDH	450 U/L	226	150-300	No history noted
10	28	White	4, M	18.2	Platelets	$683 \times 10^9/L$	228	140-450	Sodium fluoride
12	4	White	5, F	25.9	PMNs	77 %	78	20-75	Failure
12	18	White	4, F	15.9	Alkaline phosphatase	1173 U/L	2499	25-350	No history noted
13	6	White	7, M	30.2	LDH	451 U/L	208	150-300	Failure
									Specimen transit time=71 hours
13	15	White	10, F	35.7	Potassium	7.2 mEq/L	4.8	3.5-5.1	No history noted
									Specimen transit time=39 hours
14	16	White	8, M	34.5	Phosphorus	6.7 mg/dL	4.4	3-6	Allergic rhinitis, sinusitis
									Microbiological failure
PENICILLIN									
2	21	White	8, M	24.0	WBC	$15.8 \times 10^9/L$	9.9	4.5-13.5	Microbiological failure
					Lymphocytes	8 %	14	10-49	
2	24	Caucasian/ Black	3, F	16.5	Urine protein	1+	Negative	Negative	No history noted
2	35	White	3, F	18.2	Alkaline phosphatase	451 U/L	331	25-350	No history noted
2	50	White	10, M	35.3	LDH	469 U/L	625	118-273	Elevated AST at baseline

WBC = White blood cells; PMN = polymorphonuclear leukocytes; LDH = Lactate dehydrogenase; AST = aspartate aminotransferase; AE = Adverse event.

NDA 50-739 (CEFDINIR)
7 MG/CG BID/SD VS.
PEN VK 10MG/CG QID/SD
APPENDIX P56

PHARYNGITIS/TONSILLITIS-PEDIATRIC
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
PROTOCOL 983-56

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit
(Page 3 of 4)

Center	Patient No.	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
3	18	White	7, M	22.0	AST	107 U/L	180	0-37	Iron deficiency anemia Elevation of liver enzymes due to viral etiology per site 65 U/L on Day 19
					ALT	134 U/L	225	0-40	75 U/L on Day 19
					LDH	414 U/L	594	150-300	339 U/L on Day 19
3	32	White	7, M	27.5	WBC	22.1 × 10 ⁹ /L	15.2	5-14.5	Earache Microbiological failure
					PMNs	80 %	70	20-75	
3	41	White	6, F	26.4	Alkaline phosphatase	407 U/L	350	25-350	Sinusitis, conjunctivitis
3	52	White	5, F	21.0	PMNs	82 %	77	20-75	AE: contact dermatitis, erythema multiform, prednisolone
4	31	White	7, F	23.9	Urine WBC	21-50 /HPF	1-5	1-5	No history noted
5	16	White	8, F	39.5	Urine WBC	21-50 /HPF	1-5	1-5	No history noted
									1-5 /HPF on Day 19
5	29	White	2, F	12.5	Alkaline phosphatase	438 U/L	217	25-350	No history noted
5	49	White	6, M	20.5	Urine RBC	21-50 /HPF	>50	0	ADD, hematuria, methylphenidate
5	54	Black	4, F	17.5	PMNs	11 %	48	20-75	No history noted
7	29	White	12, F	53.9	Urine specific gravity	1.042	1.025	1.005-1.03	Hay fever
8	1	White	7, F	25.0	LDH	533 U/L	264	150-300	Fifth disease, parvovirus
9	4	White	5, F	18.6	LDH	477 U/L	276	150-300	No history noted
9	8	White	6, M	33.6	Hematocrit	29.9 %	32.2	35-45	Impetigo Microbiological failure AE: URI, impetigo, pseudoephedrine
					LDH	410 U/L	259	150-300	
9	25	White	8, F	27.3	Urine protein	1+	Negative	Negative	URI, pseudoephedrine Microbiological failure
9	39	White	8, M	26.4	Urine protein	1+	Negative	Negative	ADD, methylphenidate
10	11	White	5, M	24.3	PMNs	80 %	78	20-75	Bronchospasm Microbiological failure
10	19	White	7, F	24.3	PMNs	85 %	87	20-75	Allergies Microbiological failure
					Lymphocytes	9 %	4	10-66	
13	3	White	10, F	37.7	Potassium	6.3 mEq/L	5.8	3.5-5.1	No history noted; specimen hemolyzed
					LDH	470 U/L	226	122-220	
13	10	White	7, F	28.2	Potassium	6.5 mEq/L	4.3	3.5-5.1	History of pharyngitis

WBC = White blood cells; PMN = polymorphonuclear leukocytes; LDH = Lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; URI = Upper respiratory infection; ADD = Attention deficit disorder; AE = Adverse event.

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit
(Page 4 of 4)

Center	Patient No.	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
13	13	White	7, M	25.9	WBC	$28.8 \times 10^9/L$	11.6	5-14.5	Failure Specimen transit time=46 hours; extensive leukocyte deterioration
13	16	White	9, F	33.4	Potassium	7.1 mEq/L	4.6	3.5-5.1	No history noted
13	22	White	11, F	47.3	Potassium	6.8 mEq/L	7.1	3.5-5.1	No history noted
13	23	White	9, F	29.1	Urine WBC	21-50 /HPF	1-5	1-5	Specimen transit time=37 hours Microbiological failure

WBC = White blood cells.

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TABLE 20. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline Excluding Site 5^a

[Number (%) of Patients]			
Parameter	Direction of Change	Cefdinir N = 211	Penicillin N = 214
Hematology			
Hematocrit	Decrease	0 (0.0)	1 (0.5)
Platelets	Increase	1 (0.5)	0 (0.0)
White Blood Cells	Decrease	1 (0.5)	0 (0.0)
	Increase	3 (1.4)	3 (1.4)
Polymorphonuclear Leukocytes	Decrease	0 (0.0)	0 (0.0)
	Increase	5 (2.4) ^b	3 (1.4)
Lymphocytes	Decrease	3 (1.4)	1 (0.5)
Eosinophils	Increase	0 (0.0)	0 (0.0)
Blood Chemistry			
Alkaline Phosphatase	Increase	2 (1.0)	2 (0.9)
Bilirubin	Increase	1 (0.5)	0 (0.0)
LDH	Increase	4 (1.9)	4 (1.9)
AST	Increase	1 (0.5)	0 (0.0)
Sodium	Decrease	1 (0.5)	0 (0.0)
Potassium	Increase	2 (1.0)	3 (1.4)
Total Protein	Increase	1 (0.5)	0 (0.0)
Phosphorus	Increase	2 (1.0)	0 (0.0)
Bicarbonate	Decrease	2 (1.0)	0 (0.0)
Urinalysis			
Urine Protein	Increase	2 (1.0)	3 (1.4)
WBCs	Increase	0 (0.0)	2 (0.9)
Specific Gravity	Increase	0 (0.0)	1 (0.5)
Any Parameter^c		20 (9.5)	19 (8.9)

- ^a This table does not include data from patients with markedly abnormal values at the STFU visit that were unchanged or improved relative to the baseline value. Does not include patients listed in Appendix E.22.
- ^b One patient had no baseline value for comparison, but is included in this summary: in the cefdinir BID treatment group, Patient 44, Center 3, for PMNs
- ^c Total number of patients in a treatment group experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) regardless of the laboratory parameter.

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

APPENDIX EP (EFFICACY PHARYNGITIS)

Protocol 51:

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding Site 14 (Iravani) based on the Sponsor's submission:

	Cefdinir QD	Cefdinir BID	Penicillin
Clinical Response Rates			
All Sites	97.6% (246/252)	96.4% (241/250)	86.8% (217/250)
Excluding Site 14	97.4% (222/228)	96.0% (218/227)	86.3% (196/227)
Microbiological Response by Patient			
All Sites	92.5% (233/252)	94.8% (237/250)	70.8% (177/250)
Excluding Site 14	94.3% (215/228)	94.3% (214/227)	70.0% (159/227)

	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	(6.2%, 15.4%)	<0.001	(4.8%, 14.4%)	<0.001
Excluding Site 14	(6.1%, 15.9%)	<0.001	(4.6%, 14.8%)	<0.001
Microbiological Response by Patient				
All Sites	(15.1%, 28.2%)	<0.001	(17.7%, 30.3%)	<0.001
Excluding Site 14	(17.6%, 30.9%)	<0.001	(17.5%, 30.9%)	<0.001

Excluding Site 14 had very little effect on response rates. Both cefdinir QD and cefdinir BID are still shown to be superior to penicillin for both clinical response rate and microbiological response by patient for the evaluable population.

Clinically Evaluable Patients

The table below presents the clinical response rates and analysis results for the clinically evaluable patient population, both including and excluding Site 14.

**PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES**

	Cefdinir QD	Cefdinir BID	Penicillin
Clinical Response Rates			
All Sites	97.3% (251/258)	96.5% (246/255)	86.2% (219/254)
Excluding Site 14	97.0% (226/233)	96.1% (222/231)	85.7% (198/231)
	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin
	Unadjusted	CMH	Unadjusted
	95% CI	p-value	95% CI
All Sites	(6.4%, 15.7%)	<0.001	(5.4%, 15.1%)
Excluding Site 14	(6.3%, 16.3%)	<0.001	(5.2%, 15.5%)
			CMH p-value
			<0.001
			<0.001

Excluding Site 14 had very little effect on the clinical response rates. Both cefdinir QD and cefdinir BID are still shown to be superior to penicillin for the clinically evaluable population.

Protocol 56

Evaluable Patients

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding site 5 (Iravani).

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.5% (205/224)	90.7% (196/216)	(-4.5%, 6.1%)	0.798
Excluding Site 5	91.3% (179/196)	89.6% (173/193)	(-4.1%, 7.5%)	0.567
Microbiological Response by Patient				
All Sites	89.7% (201/224)	71.8% (155/216)	(10.8%, 25.2%)	<0.001
Excluding Site 5	89.8% (176/196)	69.9% (135/193)	(12.1%, 27.6%)	<0.001

Excluding site 5 had very little effect on the response rates. Cefdinir is still shown to be equivalent to penicillin in clinical response rate, and superior to penicillin for microbiological response by patient, for the evaluable population.

PHARYNGITIS / TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
INTEGRATED SUMMARY OF EFFICACY ACROSS PHARYNGITIS STUDIES

Clinically Evaluable Patients

The table below presents the clinical response rates and analysis results for the clinically evaluable patient population, both including and excluding site 5.

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.7% (209/228)	90.9% (200/220)	(-4.5%, 6.0%)	0.787
Excluding Site 5	91.5% (182/199)	89.7% (175/195)	(-4.1%, 7.5%)	0.552

Excluding site 5 had very little effect on the clinical response rates. Cefdinir and penicillin are still shown to be equivalent for the clinically evaluable population.

Statistical Reviewer's Comments: Based on the underlying sample sizes, recalculating confidence intervals, and incorporating Yates' Continuity Correction is not expected to result in considerably different inferences in either protocol 51 or 56.

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PHARYNGITIS STUDIES FINAL CONCLUSIONS AND RECOMMENDATIONS:

The following tables summarize the efficacy findings of the studies evaluated for this pharyngitis NDA submission:

Indication	Study Number	Pathogen Eradication Rates (%) ^a			Clinical Cure Rates (%) ^b		
		Cefdinir QD	Cefdinir BID	Control Drug(s)	Cefdinir QD	Cefdinir BID	Control Drug(s)
Pharyngitis	983-7	91	92	83	95	96	89
	983-58	—	89	82	—	89	85
	983-51	93	95	71	98	96	87
	983-51 excluding Iri- vani	94	94	70	97	96	86
	983-56	—	90	72	—	92	91
	983-56 excluding Iri- vani		90	70		91	90

^a Microbiologically evaluable patients.

^b Microbiologically evaluable patients, except for otitis media and sinusitis studies, in which rates for clinically evaluable patients are used.

**TABLE 52. Microbiologic and Clinical Outcomes - Microbiologically Evaluable Patients
 Pharyngitis Study 983-7**

Parameter	Cefdinir QD		Cefdinir BID		Penicillin	
	n/N	%	n/N	%	n/N	%
<i>S. pyogenes</i> Eradication	192/210	91.4	199/217	91.7	181/217	83.4
Clinical Cure	199/210	94.8	209/217	96.3	193/217	88.9

TABLE 14. Summary of Efficacy Analyses at TOC-per applicant

Pairwise Comparison	Population	Rates (%)	95% CI	Interpretation
Microbiologic Eradication				
QD vs Penicillin	Evaluable ^a	91 vs 83	1.8, 14.3	QD Superior
	MITT	91 vs 84	1.5, 13.3	QD Superior
	ITT	70 vs 64	-2.1, 12.7	Equivalent
BID vs Penicillin	Evaluable ^a	92 vs 83	2.1, 14.5	BID Superior
	MITT	92 vs 84	2.1, 13.8	BID Superior
	ITT	71 vs 64	-0.9, 13.9	Equivalent
QD vs BID	Evaluable	91 vs 92	-5.5, 5.0	Equivalent
	MITT	91 vs 92	-5.5, 4.5	Equivalent
	ITT	70 vs 71	-8.5, 6.1	Equivalent
Clinical Response				
QD vs Penicillin	Evaluable	95 vs 89	0.7, 11.0	QD Superior
	Clinically Evaluable	91 vs 85	0.1, 11.3	QD Superior
	ITT	90 vs 85	-0.2, 10.2	QD at Least Equivalent
BID vs Penicillin	Evaluable	96 vs 89	2.5, 12.2	BID Superior
	Clinically Evaluable	93 vs 85	2.8, 13.5	BID Superior
	ITT	92 vs 85	1.6, 11.6	BID Superior
QD vs BID	Evaluable	95 vs 96	-5.5, 2.4	Equivalent
	Clinically Evaluable	91 vs 93	-7.1, 2.3	Equivalent
	ITT	90 vs 92	-6.2, 2.9	Equivalent

^a Primary efficacy analysis

Table 53. Microbiologic and Clinical Outcomes-Microbiologically Evaluable Patients ,

Pharyngitis

Study 983-58

Parameter	Cefdinir		95%CI	Penicillin	
	n/N	%		n/N	%
<i>S. pyogenes</i> Eradication	193/218	88.5		176/214	82.2
Clinical Cure	194/218	89.0		181/214	84.6
MICRO			-4,12.9		
CLIN			-2,10.8		

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding Site 14 (Iravani) . This is the FDA analysis with continuity correction.

Protocol 51:

Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Clinical Efficacy				
All sites	246/252(97.6%)	241/250(96.4%)	217/250(86.8%)	<u>Cefdinir QD vs Cefdinir BID</u> 252,250(-0.0216, 0.0459) _{97.6%, 96.4%} <u>Cefdinir QD vs Pen</u> 252,250(0.0582, 0.1582) _{97.6%, 86.8%} <u>Cefdinir BID vs Pen</u> 250,250(0.0441, 0.1479) _{96.4%, 86.8%}
Sites 14 excluding Iravani	222/228(97.3%)	218/227(96%)	196/227(86.3%)	<u>Cefdinir QD vs Cefdinir BID</u> 222,227(-0.0238, 0.0505) _{97.3%, 96%} <u>Cefdinir QD vs Pen</u> 222,227(0.0566, 0.1639) _{96%, 86.3%} <u>Cefdinir BID vs Pen</u> 227,227(0.0411, 0.1527) _{96%, 86.3%}
Microbiologic Eradication				
All sites	233/252(92.4%)	237/250(94.8%)	177/250(70.8%)	<u>Cefdinir QD vs Cefdinir BID</u> 252,250(-0.0701, 0.0232) _{92.4%, 94.8%} <u>Cefdinir QD vs pen</u> 252,250(0.1475, 0.2857) _{92.4%, 70.8%} <u>Cefdinir BID vs Pen</u> 250,250(0.1732, 0.3067) _{94.8%, 70.8%}

Criteria	MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW FINAL CONCLUSIONS AND RECOMMENDATIONS			95% Confidence Interval (with continuity correction)
	Cefdinir QD	Cefdinir BID	Penicillin	
Sites 14 excluding Iravani	215/228(94.3%)	214/227(94.3%)	159/227(70%)	<u>Cefdinir OD vs Cefdinir BID</u> 228,227(-0.0468, 0.0473) _{94.3%, 94.3%} <u>Cefdinir OD vs Pen</u> 228,227(0.1713, 0.3137) _{94.3%, 70%} <u>Cefdinir BID vs Pen</u> 227,227(0.1711, 0.3135) _{94.3%, 70%}
Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
protocol 56 -Clinical Efficacy (all evaluable patients)				
All sites		205/224(91.5%)	196/216(90.7%)	224,216(-0.0499, 0.0655) _{91.5%, 90.7%}
Sites excluding Dr Iravani		179/196(91.3%)	173/193(89.6%)	196,193(-0.0465, 0.0804) _{91.3%, 89.6%}
Microbiologic Eradication				
All sites		201/224(89.7%)	155/216(71.7%)	224,216(0.1031, 0.2563) _{89.7%, 71.7%}
Sites excluding Dr. Iravani		176/196(89.7%)	135/193(69.9%)	196,193(0.1160, 0.2809) _{89.7%, 69.9%}
Clinical Efficacy (clinically evaluable patients)				
All sites		209/228(91.6%)	200/220(90.9%)	228,220(-0.0491, 0.0642) _{91.6%, 90.9%}
Sites excluding Dr Iravani		182/199(91.4%)	175/195(89.7%)	199,195(-0.0455, 0.0798) _{91.4%, 89.7%}

PROTOCOL 7

TABLE 17. Summary of Adverse Events - All Patients-Applicant
 [Number (%) of Patients]
 (Page 1 of 2)

	Cefdinir		Penicillin N = 310
	QD N = 305	BID N = 304	
Adverse Events During Study			
All Adverse Events	169 (55.4)	157 (51.6)	140 (45.2)
Associated* Adverse Events	102 (33.4)	91 (29.9)	57 (18.4)

PROTOCOL 58

TABLE 13. Summary of Adverse Events - All Patients
 [Number (%) of Patients]

	Cefdinir N = 278	Penicillin N = 280
Adverse Events During Study		
All Adverse Events	161 (57.9)	143 (51.1)
Associated* Adverse Events	61 (21.9)	47 (16.8)

PROTOCOL 51

adverse event rates and
 drug-associated adverse
 event rates, both
 including and excluding
 site 5

Cef. QD vs
 Penicillin
 CMH
 p-value

Cef. BID vs
 Penicillin
 CMH
 p-value

	Cefdinir QD	Cefdinir BID	Penicillin		
All Adverse Events					
All Sites	41.2% (119/289)	44.6% (129/289)	37.9% (110/290)	0.393	0.087
Excluding Site 14	44.3% (117/264)	47.5% (125/263)	40.2% (106/264)	0.295	0.078
Drug-Associated Adverse Events					
All Sites	8.3% (24/289)	9.3% (27/289)	7.2% (21/290)	0.620	0.612
Excluding Site 14	8.7% (23/264)	10.3% (27/263)	8.0% (21/264)	0.727	0.364

PROTOCOL 56

The table below presents the adverse event rates and drug-associated adverse event rates, and the analysis results, for patients who took drug both including and excluding site 5.

	Cefdinir BID	Penicillin	CMH p-value
All Adverse Events			
All Sites	38.3% (92/240)	33.1% (80/242)	0.212
Excluding Site 5	40.8% (86/211)	36.0% (77/214)	0.314
Drug-Associated Adverse Events			
All Sites	5.4% (13/240)	4.5% (11/242)	0.678
Excluding Site 5	6.2% (13/211)	5.4% (11/214)	0.678

Medical Officer's Note: As reported adverse event rates were lower at Dr Iravani's site than the overall rate observed in the study, exclusion of data from his site resulted in increased adverse event rates in all treatment groups. Exclusion of data from Dr Iravani's site, however, did not alter analyses, showing that neither adverse event rates nor drug-associated adverse event rates were statistically significantly different between treatment groups at the $p < 0.05$ level, for either study.

Medical Officer's Final Conclusions on Efficacy:

1. Cefdinir, given as a 5-day (BID) capsule is equivalent to penicillin in the eradication of GABHS from the throats of patients with streptococcal pharyngitis.
- 5 day suspension or 10-day (QD or BID) regimen (capsule or suspension), more effective than penicillin in the eradication of GABHS from the throats of patients with streptococcal pharyngitis.
2. Cefdinir, given as a 5-day (BID) regimen, is equivalent to penicillin in symptomatic relief in streptococcal pharyngitis
- 10-day (QD or BID) regimen is more effective than penicillin in symptomatic relief in streptococcal pharyngitis.
3. The 5-day regimen appears to give somewhat lower eradication rates than the 10-day regimen.
4. Cefdinir has not been studied for effectiveness in the prevention of rheumatic fever.
5. When Dr. Irivani's data was not included in the analysis for microbiologic and clinical efficacy, there was little effect on the outcome.

Medical Officer's Final Conclusions on Safety:

1. Cefdinir is well-tolerated.
2. Cefdinir appears to have a safety profile within the ranges reported for other recently approved

PHARYNGITIS/TONSILLITIS
MEDICAL OFFICER'S AND STATISTICIAN'S REVIEW
FINAL CONCLUSIONS AND RECOMMENDATIONS

cephalosporins. Overall, the risk of adverse events during treatment with cefdinir is balanced by its clinical benefits.

3. When Dr. Irivani's data was not included in the analysis for safety (both the adverse event rates and drug-associated adverse event rates), there was very little effect on the adverse event rates).

Concur:

/S/

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/S/

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Original NDA 50-739
Original NDA 50-749
HFD-520/Division Files
HFD-520/MO/R. Viraraghavan
HFD-40/DDMAC/J. Spearmon

**NDA 50-739: Clinical and Statistical Review, Omnicef® (cefdinir axetil)
for the treatment of acute otitis media**

Reviewers' note: The following review was performed, whenever possible, with the removal of data gathered by Dr. Robert Fiddes' and Dr. Abdollah Irvani's study sites. The data gathered by these study sites is believed to be unreliable.

Indication: Acute Otitis Media (AOM)

Title and Study Number: Investigator-blinded, randomized, comparative, multicenter study of cefdinir versus amoxicillin/clavulanate in the treatment of AOM with effusion in pediatric patients (Protocol 983-10)

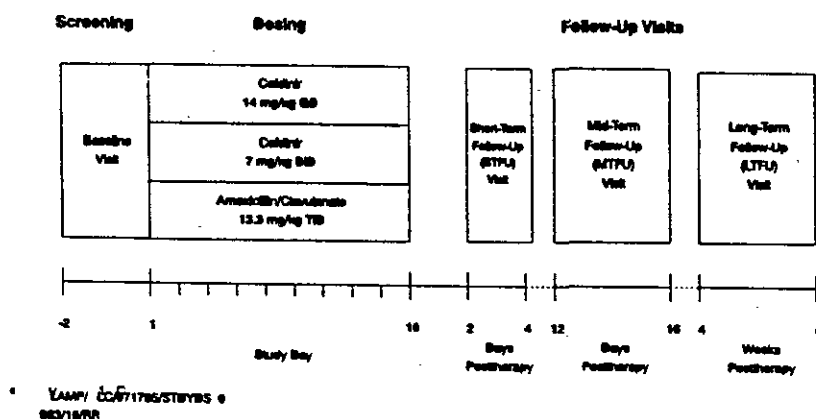
Objective: To compare the efficacy and safety of two 10-day dosage regimens of cefdinir suspension (14 mg/kg QD and 7 mg/kg BID) and one 10-day regimen of amoxicillin/clavulanate (Augmentin® at 13.3 mg/kg TID) in the treatment of pediatric patients with acute suppurative otitis media with effusion.

Reviewers' note: This selection of Augmentin as a comparator agent is an excellent choice -- this agent is widely used in the treatment of AOM because of successful use in this infection. It is well-recognized as having excellent activity against the primary agents of AOM, Streptococcus pneumoniae, Haemophilus influenzae (including beta-lactamase producing strains) and Moraxella catarrhalis.

Study Design: This was an investigator-blinded, randomized, comparative, multicenter study with 3 parallel-treatment groups. An ear examination and clinical assessment were performed during the Days 3 to 5 interval of therapy. Patients who had not improved at this time discontinued treatment.

The protocol and case report forms specified that the mid-term follow-up (MTFU) visit be made 12 to 16 days posttherapy. However, many sites performed the MTFU visit beginning on Day 22. This was actually 11 days posttherapy for patients who started BID or TID treatment midday on Day 1 and therefore ended treatment on Day 11 instead of Day 10. For analysis purposes, the TOC window was widened to 11 to 16 days posttherapy and the long-term follow-up (LTFU) window to 27 to 42 days posttherapy to include these patient data.

Figure 1: Study Design



Procedure/Observation	Baseline ^a	Day 1	Days 3-5	Day 10 (End of Therapy)	Posttherapy		
					2-4 Days ^b	12-16 Days ^c	4-6 Weeks ^d
Medical History	X						
Physical Examination ^e	X				X	X	
Otoscopic Examination ^e	X		X		X	X	X
Tympanometry ^e	X		X		X	X	X
Tympanocentesis, Culture, and Susceptibility Testing ^f	X				X ^g	X ^g	X ^g
Clinical Assessment of Signs and Symptoms ^e	X		X		X	X	X
Adverse Event Monitoring ^h		X					X
Clinical Laboratory Tests ^e	X				X	X ^g	X ^g
Study Drug Dosing		X		X			

^a Prior to treatment (within 48 hours)

^b Short-term follow-up (STFU) visit

^c Mid-term follow-up (MTFU) visit

^d Long-term follow-up (LTFU) visit

^e Also to be performed whenever therapy is discontinued early

^f Performed only at selected study sites through January 14, 1993. Required for all study participants as of January 15, 1993 (see Amendment 2).

^g For patients with baseline culture who do not show satisfactory clinical improvement

^h Only if abnormalities were detected 2 to 4 days posttherapy

ⁱ Only if abnormalities were detected 12 to 16 days posttherapy

Table 1: Schedule of Clinical Observations and Laboratory Measurements

Methodology: After baseline screening, patients were randomized to receive cefdinir QD, cefdinir BID, or amoxicillin/clavulanate for 10 days. Patients returned for a short-term follow-up visit 2 to 4 days posttherapy, a mid-term follow-up visit 12 to 16 days posttherapy which served as the test-of-cure (TOC), and a long-term follow-up (LTFU) visit 4 to 6 weeks posttherapy. Results from ear examinations, tympanocentesis cultures, and clinical assessments were used to compare the efficacy of the treatments. Results from adverse event reporting, physical examinations, and clinical laboratory tests were used to compare the safety.

Reviewers' note: This study provided the microbiologic evidence required to support the indication of acute otitis media as required by DAIDP's Points-to-Consider Guidance document.

Patients and Inclusion/Exclusion Criteria: Patients were boys and girls aged from 6 months to 12 years, who had acute suppurative otitis media with effusion for less than one week. Patients needed to have erythema of the tympanic membrane and middle ear effusion, supported by tympanometry, in at least one ear. Postmenarch girls were required to have a negative pregnancy test prior to drug administration.

Medical officer's note: The inclusion criteria are not particularly stringent and are really minimal clinical findings for a diagnosis of AOM. For this study to provide sufficient evidence in support of the indication of AOM, it must demonstrate that subjects enrolled must, on average, possess signs and symptoms enough to support a diagnosis of AOM consistent with a bacterial etiology. Multiple other signs and symptoms were recorded and followed among those enrolled, but did not constitute entry criteria. Some of these were incorporated into assessment which determined outcome.

Patients were to be excluded from participating in the study for any of the following reasons:

- Subacute or chronic otitis media, acute exacerbations of chronic otitis media, or chronic middle ear effusion;
- A ventilation tube or perforated tympanic membrane in either ear at baseline;
- Diseases, complicating factors (eg, mastoiditis), or structural abnormalities that would confound evaluation of the therapeutic response;
- Hepatic disease, obstruction of the biliary tract, or baseline bilirubin or hepatic enzyme levels (AST, ALT) >2 times the upper limit of normal;
- Baseline serum creatinine >1.5 times the upper limit of normal;

- Hypersensitivity to β -lactams (including penicillins and cephalosporins);
- Receipt of another systemic antibacterial agent within 7 days of study start;
- Use of a topical aural antibacterial within 2 days of study start;
- A baseline pathogen known to be resistant to cefdinir or amox/clav prior to randomization;
- Concomitant infections requiring systemic antibacterial therapy;
- Receipt of any other investigational compound within 4 weeks of study entry;
- Prior participation in this or any other cefdinir study;
- Iron supplements, including iron-containing multivitamins, required. Patients were allowed to participate in this study if they abstained from iron-containing products for the duration of therapy;
- Concomitant decongestant therapy required. Patients receiving decongestants at baseline were allowed to enter the study provided that they did not receive decongestants at any time during the study, including the follow-up period.

Reviewers' note: The first 3 exclusion criteria are unique to this indication. Current DAIDP's current Evaluability Criteria do not require that patients with "perforated eardrums..., recurrent episodes or chronic episodes" but that such patients should be enrolled with subset analysis planned. Almost no patients with such conditions were enrolled and little can be said about anything but those with fairly uncomplicated AOM. This will be considered later in this review. This application only seeks approval for AOM and does not seek approval for related conditions or highly resistant organisms such as penicillin resistant *Streptococcus pneumoniae*. Any labeling applied to this indication must reflect this.

The last 11 exclusion criteria are common to other indications in the application and some are generated by concerns relevant to cefdinir and some to cephalosporins as a class. Labeling will reflect any issues generated by these findings in its safety subsections.

Withdrawal from the study was allowed if: (1) a baseline pathogen resistant to both study drugs was isolated, (2) the patient had spontaneous perforation of the tympanic membrane, or (3) they required additional/other antibacterials for their otitis media. At the investigator's discretion, patients also could be withdrawn because of insufficient efficacy, an adverse event, a laboratory abnormality, or lack of cooperation.

Reviewers' note: If patients required additional antimicrobial therapy or condition worsened or did not cure on therapy causing the investigator to withdraw the patient, the patient was carried through as a failure. Patients who had assessments done early or had insufficient treatment duration became failures.

Evaluability Criteria: Four populations were analyzed: (1) clinically evaluable, (2) microbiologically-clinically (strictly evaluable), (3) an intent-to-treat (ITT) and (4) a modified intent-to-treat (MITT).

Evaluable populations for these analyses are had the following criteria:

Clinically evaluable

- ◆ clinical assessment of at least minimal required signs and symptoms complete and within predetermined range
- ◆ study medication taken as prescribed (80% of course completed)
- ◆ susceptible baseline pathogen
- ◆ no concurrent systemic antibacterial therapy and no systemic antibacterial within 7 days prior to the first dose of study medication
- ◆ did not have an intentional randomization violation

Strictly evaluable

- ◆ being clinically evaluable plus having a proven baseline pathogen
- ◆ off-schedule cultures

Reviewers' note: The criteria are acceptable provided (as stated elsewhere in the Sponsor's report and supported by review of data) that all early failures who required other antimicrobial therapy or had an off-schedule culture because of early failure are carried forward to TOC as failures.

MITT

- ◆ patients who had the correct indication
- ◆ received study medication
- ◆ had at least 1 baseline pathogen, and had a follow-up culture or a follow-up clinical assessment of signs and symptoms.

ITT

- ◆ all patients who were randomized to treatment

Included in the ITT population are patients who had no baseline tympanocentesis, no baseline pathogen, or no follow-up culture and no follow-up clinical assessment. These patients were considered to have microbiologic persistence in the ITT summaries and analyses. Patients who had no follow-up clinical assessment were categorized as clinical failures in the ITT summaries and analyses.

Reviewers' note: Such a stringent analysis of the ITT population allows for a worst case scenario and is appropriate. Unfortunately, it is not particularly sensitive given that the outcome is demonstration of therapeutic equivalence.

Endpoints: The measures of efficacy were clinical cure rate by patient and microbiologic eradication rate by patient and pathogen in the clinically evaluable, microbiologically-clinically (i.e., strictly) evaluable, modified intent-to-treat, and intent-to-treat populations.

The primary outcome measure was the clinical cure rate in clinically evaluable patients at the test-of-cure (TOC) visit which occurred 11 to 16 days posttherapy. See figure one above. Secondary outcome measures were the microbiologic eradication rate by pathogen and the microbiologic eradication rate by patient. The primary end point was the TOC visit; the LTFU visit was a secondary end point. Data from the LTFU visit were summarized and presented as supporting information. No statistical analyses of LTFU data were done.

Most microbiologic eradication rates were presumed from clinical responses. Superinfection and reinfection also were examined.

The measures of safety were adverse event data (occurrence, intensity, relationship to study drug, frequency, duration, management of study medication, and patient outcome), and the results from physical examinations and clinical laboratory tests (hematology, chemistry, urinalysis) in all patients randomized to treatment who received drug. Assessments of clinical and microbiologic responses at the TOC visit, 11 to 16 days posttherapy, were used to evaluate the efficacy of cefdinir QD, cefdinir BID, and amox/clav. The LTFU visit, 27 to 42 days posttherapy, provided information on recurrence of infection.

The patient clinical signs and symptoms used in determining clinical response in this study were: otalgia, irritability, anorexia, lethargy, decreased hearing, vertigo, and fever. In infants and young children, in whom some signs and symptoms were difficult to assess, otalgia could be expressed as ear pulling, decreased hearing could be based on the guardian's report, and vertigo could be expressed by stumbling, falling, or clumsiness. Based on the judgment of the investigator, the severity of all these signs and symptoms, except fever, were graded as Absent, Mild, Moderate, or Severe (0, 1, 2, or 3, respectively). Body temperature was recorded by the investigator and the presence of fever was determined by the Sponsor using an objective temperature guideline (see table below); the absence of fever was graded as 0 and the presence as 1.

Table 2. Determination of Presence of Fever

Method of Measurement	Fever	
	°F	°C
Oral	≥100.4	≥38.0
Axillary	≥99.1	≥37.3
Rectal	≥102.0	≥38.9
Aural	≥100.0	≥37.8

A total patient clinical signs and symptoms score for use by the Sponsor was obtained by the following method. Symptom severity scores for otalgia, irritability, anorexia, lethargy, decreased hearing, vertigo, and fever were each weighted (ie, multiplied) by a factor of 1. The resulting values were summed across all symptoms to provide a total patient clinical score which could range from 0 through 19 at baseline, TOC, or LTFU.

Reviewers' note: *The scoring system appears to be a fair method by which to summarize outcomes, but the medical officer will review each category to assure that resolution occurred, patients were adequately symptomatic and that any single finding did not carry the entire weight of the score. It is unfortunate that temperature was treated as a binary finding with a low score: though not specific it is an excellent marker of illness in the subjects of interest. In addition, the sponsor makes no mention of reporting use of antipyretics prior to evaluation for entry. Valuable information which would be useful in validating the study has been lost.*

The otoscopic examination of each ear assessed the following: erythema of the tympanic membrane, evidence of middle ear effusion, loss of landmarks (opacity of tympanic membrane), loss of light reflex of tympanic membrane, bulging of tympanic membrane, drainage, perforation of tympanic membrane, and tympanic membrane movement. Tympanometry was done on each ear to confirm the presence or absence of middle ear effusion.

The ear signs and symptoms used in determining clinical response in this study were: erythema of the tympanic membrane, loss of landmarks, loss of light reflex of tympanic membrane, bulging of the tympanic membrane, and drainage. Based on the judgment of the investigator, erythema of the tympanic membrane was graded as Absent, Mild, Moderate, or Severe (0, 1, 2, or 3, respectively); loss of landmarks and loss of light reflex as No or Yes (0 or 1, respectively); and bulging of tympanic membrane and drainage as Absent or Present (0 or 1, respectively).

For each ear, a total ear clinical signs and symptoms score for use by the Sponsor was obtained by the following method. The symptom severity score for erythema of the tympanic membrane was weighted by a factor of 1; all of the other ear symptom severity scores were weighted by a factor of 2. The resulting values were summed across all ear symptoms to provide a total ear clinical score for each ear which could range from 0 through 11 at baseline and 0 through 11 at TOC and LTFU. The total ear clinical score was expected to equal at least 1 in either the left or right ear at baseline because erythema of the tympanic membrane in at least 1 ear was an inclusion criterion.

The calculated total patient and ear scores were used in determining the Sponsor assessment of clinical response.

Reviewers' note: *The scoring system may be a fair method by which to summarize findings at enrollment and outcomes, but the medical officer will review each category to assure that resolution occurred and was satisfactory. A cure should be document resolution of signs, symptoms and findings. A residual finding of effusion is allowable. All outcomes but erythema are binary (ie, either present or absent). Erythema is graded as mild, moderate or severe — it is not clear to this reviewer how investigators interpreted erythema for assignment.*

Sponsor's Assessment of Clinical Response at TOC:

- **Cure:** ($\geq 50\%$ decrease in patient clinical score at TOC relative to baseline) and ($\geq 50\%$ decrease in left ear clinical score at TOC relative to baseline [if baseline left ear score >0]) and ($\geq 50\%$ decrease in right ear clinical score at TOC relative to baseline [if baseline right ear score >0]);
- **Failure:** $<50\%$ decrease in the patient clinical score or either ear clinical score at TOC relative to baseline; or
- **Not Assessable:** No baseline signs and symptoms or no follow-up data.

Sponsor's Assessment of Clinical Response at LTFU:

- **Cure:** (Cure at TOC) and ($\geq 50\%$ decrease in patient clinical score at LTFU relative to baseline) and ($\geq 50\%$ decrease in left ear clinical score at LTFU relative to baseline [if baseline left ear score >0]) and ($\geq 50\%$ decrease in right ear clinical score at LTFU relative to baseline [if baseline right ear score >0]) and (no increase of more than 1 point in any clinical score at LTFU relative to TOC);
- **Recurrence:** (Cure at TOC) and (≥ 2 -point increase in patient clinical score or either ear clinical score at LTFU relative to TOC) or [$<50\%$ decrease in the patient clinical score or either ear clinical score at LTFU relative to baseline]);
- **Failure:** Clinical failure at TOC; or
- **Not Assessable:** No baseline signs and symptoms or no follow-up data.

Reviewers' note: *There are limitations to this system as outlined. It will be reviewed and acceptable provided that the final score represents a cure: resolution of signs and symptoms with allowable residual effusion.*

Investigator's Assessment of Clinical Response at TOC:

- **Cure:** Absence of all patient/ear clinical signs and symptoms (excluding presence of residual effusion);
- **Improvement:** Satisfactory remission but not complete absence of patient/ear clinical signs and symptoms;
- **Failure:** No significant remission of patient/ear clinical signs and symptoms; or
- **Not Assessable:** Unable to assess patient (no data).

Investigator's Assessment of Clinical Response at LTFU:

- **Cure:** Absence of all patient/ear clinical signs and symptoms (excluding presence of residual effusion);
- **Improvement:** Satisfactory remission but not complete absence of patient/ear clinical signs and symptoms;
- **Recurrence:** Worsening of patient/ear clinical signs and symptoms since previous visit; or
- **Not Assessable:** Unable to assess patient (no data).

Reviewers' note: *The category of improvement is problematic. It is not clear whether this should be assigned cure or failure at TOC. Other aspects of the patient's course may be more valid in assigning such patients to an outcome category (for instance, did the patient require additional antimicrobial therapy at a later date, etc.)*

Because the investigator assessment had been intended as the primary clinical response measure, it became necessary to devise a set of rules by which the investigator assessment of Improvement could be reclassified. This was accomplished by generating a Combined Investigator/Sponsor Clinical Assessment (Table 4). For the TOC visit, investigator assessments of Improvement were reclassified as either Cure, Failure, or Not Assessable in agreement with the Sponsor assessment. If the investigator clinical assessment at TOC was Not Assessable and quantitative clinical signs and symptoms data had been collected, the patient also was reclassified according to the Sponsor assessment. Investigator assessments of Cure and Failure were retained regardless of Sponsor assessment.

The combined assessment at the LTFU visit depended not only on the individual assessments at LTFU, but also on the combined assessment at the TOC visit. For patients with a combined assessment of Cure at TOC, the rules for the combined assessment at LTFU were analogous to those at the TOC visit: the investigator assessments of Cure and Recurrence took precedence over the Sponsor assessment, whereas investigator assessments of Improvement or Not Assessable were reclassified according to the Sponsor assessment (see table below). In contrast, patients with a combined assessment of Failure at the TOC visit were considered failures on the combined assessment scale at the LTFU visit, regardless of investigator determination. (Patients assessed as failures by the Sponsor at the TOC visit were automatically failures on the Sponsor assessment scale at the LTFU visit.).

Table 3. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU^{a,b}

Sponsor Assessment at TOC	Investigator Assessment at TOC			
	Cure	Improvement	Failure	Not Assessable
Cure	Cure	Cure	Failure	Cure
Failure	Cure	Failure	Failure	Failure
Not Assessable	Cure	Not Assessable	Failure	Not Assessable

Sponsor Assessment at LTFU	Investigator Assessment at LTFU			
	Cure	Improvement	Recurrence	Not Assessable
Cure	Cure	Cure	Recurrence	Cure
Failure	Cure	Failure	Recurrence	Failure
Recurrence	Cure	Recurrence	Recurrence	Recurrence
Not Assessable	Cure	Not Assessable	Recurrence	Not Assessable

^a The combined assessments are shown in bold typeface.

^b Note: If a patient had a combined clinical assessment of Failure at the TOC visit, the patient was automatically a Failure on the combined assessment scale at the LTFU visit.

The resulting combined clinical assessment was selected as the primary measure of clinical response in this study. The clinical cure rate was the percentage of patients rated as cured on the combined assessment scale. Each patient provided one observation. Clinical cure rates were calculated separately for the TOC and LTFU visit data.

Reviewers' note: This begs an analysis of worse possible scenario: all improved by investigator become failures, and all not assessable also become failures. If this analysis holds up and demonstrates equivalence, it suggests a certain robustness to the equivalence findings despite problems discussed above.

Microbiologic Response by Pathogen: If a middle ear effusion specimen was collected at baseline, the microbiologic response of each baseline pathogen was determined at the TOC and LTFU visits based on the results of follow-up culture(s) from the same ear or, if no follow-up cultures were done, from the results of patient and ear clinical assessments.

If a patient's ear showed erythema of the tympanic membrane, loss of landmarks, loss of light reflex, bulging of the tympanic membrane, effusion/fluid, drainage, perforation, or tympanic membrane movement at baseline, the Sponsor considered that ear to be affected. At the TOC and LTFU visits, the clinical response of each ear was classified as:

- **Ear Cure:** (Ear affected at baseline) and (Patient is a Cure at the follow-up visit) or (Patient is not cured but ear is not affected at the follow-up visit);
- **Ear Failure:** (Ear affected at baseline) and (Patient is not cured and ear is still affected at the follow-up visit); or
- **Ear Not Assessable:** (Ear not affected at baseline) or (Ear affected at baseline and no follow-up clinical assessment data).

The microbiologic response of each baseline pathogen was then classified at the TOC and LTFU visits as:

- **Eradication:** (Pathogen not present in follow-up culture from baseline ear) or (No follow-up culture performed from baseline ear and Ear Cure at the follow-up visit—presumed eradication);
- **Persistence:** (Pathogen present in follow-up culture from baseline ear) or (No follow-up culture performed from baseline ear and Ear Failure at the follow-up visit—presumed persistence); or
- **Not Assessable:** (No proven baseline pathogen) or (Ear not assessable).

The microbiologic eradication rate by pathogen was the percentage of eradicated baseline pathogens. Patients with multiple pathogens (including the isolation of the same species from both ears) provided multiple observations in the analyses of microbiologic efficacy on a per pathogen basis. The microbiologic eradication rate by pathogen was calculated separately for the TOC and LTFU visit data. Patients without baseline pathogens could become superinfected or reinfect.

Reviewers' note: *This reviewer agrees with the above assignments provided that patients with multiple pathogens were graded as such: (1) Same organism in both ears counts as only one pathogen; and (2) Different pathogens, whether in the same ear or different ears, counted as distinct pathogens.*

Microbiologic Response by Patient: If a patient had a positive baseline culture, the patient was classified by his/her overall microbiologic response at the TOC visit as:

- **Patient With Eradication:** (TOC culture shows absence of all baseline pathogens) or (No TOC culture performed and all baseline pathogens have presumed eradication at TOC);
- **Patient With Persistence:** (TOC culture shows presence of at least 1 baseline pathogen) or (No TOC culture performed and at least 1 baseline pathogen has presumed persistence at TOC); or
- **Not Assessable:** (No proven baseline pathogen) or (No baseline signs/symptoms) or (No follow-up clinical data).

If a patient had a positive baseline culture, the patient was classified by his/her overall microbiologic response at the LTFU visit as:

- **No Relapse:** (Patient With Eradication at TOC) and (Continued eradication or presumed eradication of all baseline pathogens at LTFU)
- **Relapse:** (Patient With Eradication at TOC) and (Persistence or presumed persistence of at least 1 baseline pathogen at LTFU)
- **Patient With Persistence:** Patient With Persistence at TOC; or
- **Not Assessable:** (No proven baseline pathogen) or (No baseline signs/symptoms) or (No follow-up clinical data).

The microbiologic eradication rate by patient was the percentage of patients with eradication of all baseline pathogens. Each patient provided only 1 observation. The microbiologic eradication rate by patient was calculated separately for the TOC and LTFU visit data.

Reviewers' note: *This is acceptable and very similar to clinical cure outcome.*

Appearance of New Pathogens: For patients with a baseline culture, the appearance of a new pathogen (causing infection) during and following therapy was classified as:

- **Superinfection:** (Appearance of a nonbaseline pathogen in any culture up to completion of study drug, defined for practical purposes as up to and including TOC) and (<50% decrease in the patient clinical score or either ear clinical score at the corresponding clinical assessment of signs and symptoms relative to baseline). In addition, all superinfections were reviewed by the Sponsor. Appearance of a new pathogen in any culture through TOC and a worsening of the clinical score relative to the previous visit also denoted superinfection; or
- **Reinfection:** (Appearance of a new pathogen—not appearing at any prior visit—in the LTFU culture) + (Classified clinically as Recurrence at LTFU).

If a patient had a new organism(s) isolated in any postbaseline culture, but had no corresponding clinical assessment of signs and symptoms, the determination of pathogenicity was made by the Sponsor.

Reviewers' note: *Although not possible to statistically analyze these outcomes, the appearance of new pathogens is of critical importance and one would not expect to see differences in treatment arms.*

Statistical Methods: Two methods were used to estimate clinical cure rates and their standard errors. The first method used pooled estimates, giving equal weight to each patient in the analysis. The second method used a categorical modeling procedure to obtain center-adjusted estimates, giving equal weight to each study center in the analysis. Two-tailed 95% confidence intervals were constructed from pairwise differences in these parameter estimates (cefdinir QD minus amox/clav, cefdinir BID minus amox/clav, and cefdinir QD minus cefdinir BID) using a standard normal approximation. The resulting confidence interval for each pairwise difference was compared to previously defined fixed criteria for evaluating treatment equivalence at TOC. A Cochran-Mantel-Haenszel (CMH) analysis compared clinical cure rates between treatments and the Breslow-Day method checked for treatment-by-center interaction. Descriptive statistics were calculated for microbiological data at TOC and for all efficacy data at LTFU; no statistical testing was performed on these data. Safety data were summarized for all patients who received study medications. A CMH analysis, adjusting for center, was used to compare treatment discontinuation rates due to adverse events, overall adverse event and associated adverse event rates, and incidence of diarrhea.

Reviewers' note: Pooled estimates, not center-adjusted estimates, are the method of analysis preferred by us. Two-tailed 95% confidence intervals about the difference in treatment arms are the main measure of interest. CMH analysis will carry no weight here; it may show equivalence among treatment arms when the two-tailed 95% CI does not. Descriptive statistics are of critical for outcomes that are not powered for statistical significance. Unfortunately, one can do little more for these than get a sense of the data.

Table 4. List of Investigators

Center	Investigator(s)	Number of Patients			
		Randomized to Treatment	Completed Treatment	Clinically Evaluable	Strictly Evaluable
1	R. Paster	21	21	19	0
2	C. Khurana	60	59	57	0
3	A. Iravani	131	117	120	42
4	J. Hedrick	95	85	79	48
5	W. Gooch	25	21	20	0
6	S. Wiederhold	49	45	44	13
7	S. Chartrand	28	27	22	15
8	J. McCarty	170	143	140	57
9	E. Rothstein, H. Bernstein	34	33	32	0
10	J. Haddad	65	50	41	15
11	R. Fiddes	60	55	50	8
12	S. McLinn	81	78	63	35
13	G. Aronovitz	33	33	25	14
Total		852	767	712	247

Reviewers' note: *The Table above demonstrates significant problems given the large numbers, particularly those microbiologically ("strictly") evaluable enrolled by a few investigators. It is also extremely unfortunate that data obtained from the two investigators above appearing in boldface had to be removed from analysis based on a recommendation from the FDA's Office of Compliance. After investigation, it was believed the data was not reliable. Thus, 50 strictly evaluable patients out of a total of 247 were lost for efficacy and safety analysis and 120 clinically evaluable patients out of 712 were lost to efficacy and safety analysis. This is an enormous loss. Quantitatively, the number of organisms available for evaluation is reduced by about 20%. The loss of 17% of the clinical sample is worrisome for the loss of power — the confidence interval will no doubt be wider. However, because subsets as specific and small as particular microorganisms are not a feature of clinical outcome analysis, it may still be possible to demonstrate equivalence.*

Safety: The safety of cefdinir was assessed using adverse event data and the results from physical examinations and clinical laboratory tests. All patients randomized to treatment who received drug were evaluated for safety.

Reviewers' note: *For a summary of how adverse events were recorded and analyzed, see Medical officer's review of CAP.*

Sample Size: This investigator-blinded, comparative study of cefdinir versus amox/clav was designed with a planned sample size of 190 clinically evaluable patients per randomized group. The sample size was designed to provide at least 80% probability (power) of having a "successful" study assuming an overall response rate of 90% and an equivalence threshold of $\pm 10\%$.

Reviewers' note: *Unfortunately, the observed response rate was less than anticipated by this optimistic estimate. However, review of other Medical officer reviews provides that the response rates found in this study is not unlike those found in previous studies. The IDSA Guidelines on Acute Otitis Media states only the following:*

"It is expected that an effective agent will sterilize middle-ear fluid of bacterial pathogens in >80% of infected ears within 72 hours" and that a Phase II study should demonstrate a favorable response with a "clinical and microbiologic response rate of $\geq 80\%$ " to support launching a phase III study (pp. S70 and S71). In addition, the Division's Points to Consider (p. 39) does not provide any guidance on this issue; it merely states that the indication of AOM suggests one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved agent.

Thus, no absolute level is predetermined. The IDSA Guidelines do state, however, "The control drug chosen for a clinical trial should be among the most effective and safe agents available for treatment" (p. S70). Amoxicillin-clavulanate is a widely endorsed and accepted as a highly effective treatment for AOM. Thus, this reviewer believes demonstration of equivalence or superiority to the comparator arm is the most important criteria in this clinical trial and not a predetermined cure rate.

The following table delineates the confidence intervals necessary to demonstrate equivalence given different maximum estimated response rates:

Table 5: Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Treatments are Equivalent if 95% Confidence Interval for Treatment Difference Is Within Bounds
90% or greater	-10%, +10%
80%-89%	-15%, +15%
70%-79%	-20%, +20%

Results

Demographic Information: Demographic information for all patients randomized to treatment (N = 852), the clinically evaluable patient population (N = 712), and the strictly evaluable patient population (N = 247) is presented, by treatment group in the following tables. Patients were similarly distributed across the 3 treatment groups by sex, race, and age in all populations studied with the following exceptions. In the all patient and clinically evaluable patient populations, greater percentages of patients <2 years received cefdinir QD or BID than received amox/clav and greater percentages of patients 2 to <6 years received amox/clav than received either cefdinir regimen. In the strictly evaluable population, greater percentages of patients <2 years received cefdinir QD than received either cefdinir BID or amox/clav and greater percentages of patients 2 to <6 years received amox/clav than received either cefdinir regimen.

The baseline characteristics of the clinically evaluable patients were similar to those of all patients randomized to treatment. The baseline characteristics of the strictly evaluable patients were similar to those of all patients randomized to treatment, except that in the strictly evaluable population a greater percentage of patients were white and the median age was lower for the total of all treatment groups combined.

Table 6. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav N = 222	Total N = 661
	QD N = 218	BID N = 221		
Sex				
Male	119 (54.6)	123 (55.7)	118 (53.2)	360 (54.5)
Female	99 (45.4)	98 (44.3)	104 (46.8)	301 (45.5)
Race				
White	127 (58.3)	130 (58.8)	146 (65.8)	403 (61.0)
Black	27 (12.4)	20 (9.0)	16 (7.2)	63 (9.5)
Asian	1 (0.5)	5 (2.3)	5 (2.3)	11 (1.7)
Other	63 (28.9)	66 (29.9)	55 (24.8)	184 (27.8)
Age, yr				
Median	2.3	2.2	2.9	
Range	<1-13	1-13	1-13	<1-13
Distribution				
<2	101 (46.3)	104 (47.1)	86 (38.7)	291 (44.0)
2 to <6	77 (35.3)	71 (32.1)	83 (37.4)	231 (34.9)
6 to <13	40 (18.3)	46 (20.8)	53 (23.9)	208 (24.4)
Temperature, °C				
Median	37.3	37.3	37.3	37.3

Table 7. Patient Characteristics - Clinically Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav		Total	
	QD N = 181	BID N = 183	N = 178		N = 542	
Sex						
Male	99 54.7	106 57.9	99 55.6		304 56.1	
Female	82 45.3	77 42.1	79 44.4		238 43.9	
Race						
White	108 59.7	111 60.7	122 68.5		341 62.9	
Black	19 10.5	17 9.3	14 7.9		50 9.2	
Asian	1 0.6	5 2.7	5 2.8		11 2.0	
Other	53 29.3	50 27.3	37 20.8		140 25.8	
Age, yr						
Median	2.6	2.4	3.2		2.7	
Range	<1 - 13	1 - 12	1 - 13		<1 - 13	
Distribution						
<2	77 42.5	82 44.8	61 34.3		220 40.6	
2 to <6	67 37.0	61 33.3	74 41.6		202 37.3	
6 to <13	37 20.4	40 21.9	43 24.2		120 22.1	
Temperature, °C						
Median	37.3	37.3	37.3		37.3	

Table 8. Patient Characteristics - Strictly Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav		Total	
	QD N = 65	BID N = 66	N = 66		N = 197	
Sex						
Male	33 (50.8)	42 (63.6)	34 (51.5)		109 (55.3)	
Female	32 (49.2)	24 (36.4)	32 (48.5)		88 (44.7)	
Race						
White	44 (67.7)	45 (68.2)	50 (75.8)		139 (70.6)	
Black	7 (10.8)	5 (7.6)	3 (4.5)		15 (7.6)	
Other	14 (21.5)	16 (24.2)	13 (19.7)		43 (21.8)	
Age, yr						
Median	1.4	1.9	2.3		1.9	
Range	0.4-11.0	0.6-11.3	0.5-10.7		0.4-11.3	
Distribution						
<2	40 (61.5)	33 (50.0)	30 (45.5)		103 (52.3)	
2 to <6	17 (26.2)	24 (36.4)	24 (36.4)		65 (33.0)	
6 to <13	8 (12.3)	9 (13.6)	12 (18.2)		29 (14.7)	
Temperature, °C						
Median	37.3	37.4	37.2		37.4	

Reviewers' note: It is unfortunate that treatment arms are not balanced better respect to age. However, nothing can be done to correct this finding post hoc.

Clinical Signs and Symptoms, Distribution at Enrollment: This data includes patients from Fiddes' and Iravani's sites.

Table 9. Mean Patient Clinical Scores at Baseline - All, Clinically Evaluable, and Strictly Evaluable Patients (includes Fiddes' and Iravani's sites)

Patient Population	Cefdinir		Amox/Clav
	QD	BID	
All Patients	5.4	5.3	5.1
Clinically Evaluable Patients	5.4	5.2	5.1
Strictly Evaluable Patients	6.3	5.7	5.5

Reviewers' note: The scores are close, but the reviewers have two comments (1) the enrolled subjects are not particularly symptomatic or ill; and (2) this distribution is slightly unfavorable for cefdinir, especially the QD regimen.

Ear: The ear clinical signs and symptoms used in the sponsor assessment of clinical cure were erythema of tympanic membrane, loss of light reflex, loss of landmarks, bulging of the tympanic membrane, and drainage. The other ear clinical signs and symptoms assessed (ie, effusion/fluid, perforation, tympanic membrane movement) contributed only to the assessment of microbiologic eradication for patients with baseline tympanocentesis who did not have follow-up cultures. In general, the presence and severity of ear clinical signs and symptoms at baseline were similar among the 3 treatment groups in all populations studied.

Table 10. Mean Ear Clinical Scores at Baseline - All, Clinically Evaluable, and Strictly Evaluable Patients (includes Fiddes' and Iravani's site)

Ear/Patient Population	Cefdinir		Amox/Clav
	QD	BID	
Left Ear			
All Patients	5.5	5.1	5.2
Clinically Evaluable Patients	5.4	5.1	5.3
Strictly Evaluable Patients	5.9	5.6	5.3
Right Ear			
All Patients	5.3	5.4	5.2
Clinically Evaluable Patients	5.3	5.3	5.2
Strictly Evaluable Patients	5.5	5.9	6.0

Reviewers' note: This distribution is fairly evenly distributed by treatment arms. Once again, this population does not appear to be particularly ill.

Duration of therapy:

Table 11. Patient Exposure to Study Medication - All Patients, including those from Fiddes' and Iravani's sites

Days on Study Medication ^a	Cefdinir		Amox/Clav N = 287
	QD	BID	
	N = 280	N = 285	
1	5	1	1
2	2	2	3
3	2	0	1
4	1	3	2
5	6	0	4
6	2	0	0
7	0	1	1
8	1	2	3
9	3	8	3
10	212	166	88
11	30	91	160
12	5	5	6
13	2	1	5
14	1	1	0
15	0	0	3
16	0	0	1
Median	10	10	11
Unknown	8	4	6

^a In this table, days on study medication were determined from the dates of first and last dose recorded on the Medication Record (Case Report Form 13).

Reviewers' note: This distribution is as expected.

Table 12. Patient Disposition - All Patients, includes patients from Fiddes' and Iravani's sites
[Number-(%) of Patients]

Patient Disposition	Cefdinir		Amox/Clav	Total
	QD	BID		
Randomized to Treatment	280	285	287	852
Discontinued Treatment				
Lack of Compliance With the Protocol	8 (2.9)	7 (2.5)	11 (3.8)	26 (3.1)
Adverse Event	8 (2.9)	6 (2.1)	7 (2.4)	21 (2.5)
Other/Administrative	6 (2.1)	7 (2.5)	6 (2.1)	19 (2.2)
Failure at End of Therapy	8 (2.9)	5 (1.8)	6 (2.1)	19 (2.2)
Completed Treatment	250 (89.3)	260 (91.2)	257 (89.5)	767 (90.0)

Reviewers' note: Only a small number of patients discontinued treatment, even if one created a worst case scenario with those enrolled by Fiddes and Iravani. Thus, the therapies were well tolerated in all treatment arms.

Results

Exclusions: See table below. Patients who were excluded from the clinically evaluable analyses were automatically also excluded from the strictly evaluable analyses.

**Table 13 . Reasons Patients Were Excluded From Clinically Evaluable and Strictly Evaluable Analyses at TOC, including those enrolled by Fiddes and Iravani
(Number of Patients)**

	Cefdinir		Amox/Clav
	QD	BID	
Reasons Patients Were Excluded From Clinically Evaluable Analyses^a			
Clinical Assessment of Signs and Symptoms Missed	10	4	7
Clinical Assessment of Signs and Symptoms Out of Time Range ^b	23	27	33
Concurrent Antibacterial ^b	2	1	1
Medication Not As Prescribed ^b	19	9	16
Prior Antibacterial	1	2	1
Resistant Baseline Pathogen(s)	8	6	9
Total Not Clinically Evaluable	44	42	54
Additional Reasons Patients Were Excluded From Strictly Evaluable Analyses^a			
Culture Out of Time Range ^b	1	1	0
No Baseline Susceptibility Tests	0	1	4
No Proven Baseline Pathogen	74	65	64
Optional Microbiology Test Not Done	108	111	111
Total Not Strictly Evaluable	199	200	206

^a Patients who had multiple reasons for being excluded from efficacy analyses were counted for each reason that applied.

^b Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early failures were not removed from the clinically evaluable or strictly evaluable analyses for these reasons but were carried forward as failures. Also, patients who had a culture done early because they were early failures were carried forward as failures in the strictly evaluable analyses.

Patients who were disqualified from the clinically qualified analyses at long term follow-up were automatically also disqualified from the strictly qualified analyses at long term follow-up.

Table 14. Reasons Patients Were Disqualified From the Clinically Qualified and Strictly Qualified Analyses at LTFU, includes patients enrolled by Fiddes and Iravani (Number of Patients)

	Cefdinir		Amox/Clav
	QD	BID	
Reasons Clinically Evaluable Patients Were Disqualified From Clinically Qualified Analyses^a			
Clinical Assessment of Signs and Symptoms Missed	82	69	66
Clinical Assessment of Signs and Symptoms Out of Time Range ^b	6	5	6
Concurrent Antibacterial ^b	2	4	1
Total Not Clinically Qualified	89	77	73
Reasons Strictly Evaluable Patients Were Disqualified From Strictly Qualified Analyses^a			
Clinical Assessment of Signs and Symptoms Missed	33	28	32
Clinical Assessment of Signs and Symptoms Out of Time Range ^b	2	3	1
Concurrent Antibacterial ^b	1	3	1
Culture Out of Time Range ^b	0	1	0
Total Not Strictly Qualified	36	34	34

- ^a Patients who had multiple reasons for being disqualified were counted for each reason that applied.
^b Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early recurrences were not removed from the clinically qualified or strictly qualified analyses for these reasons. Also, patients who had a culture done early because they were early recurrences were not removed from the strictly qualified analyses for this reason.

Reviewers' note: The reviewers agree that the exclusions tallied in the tables above are reasonable. In addition, carrying forward failures as described in footnotes a and b was appropriate. The reasons for nonevaluability are plausible and distribution fairly even. It is very unfortunate that the microbiology was not better -- many cases were lost.

The table below shows the number of patients with data included in the clinically evaluable, clinically qualified, strictly evaluable, strictly qualified, MITT, and ITT populations.

Table 15. Patients With Data Included in Efficacy Summaries excluding those enrolled by Fiddes and Iravani [Number (%) of Patients^a]

Patient Population	Cefdinir		Amox/Clav
	QD	BID	
Clinically Evaluable	181 (83.0)	183 (82.8)	178 (80.2)
Clinically Qualified	117 (53.7)	124 (56.1)	125 (56.3)
Strictly Evaluable	65 (29.8)	66 (29.9)	66 (29.7)
Strictly Qualified	37 (17.0)	37 (16.7)	38 (17.1)
Modified Intent-to-Treat (MITT)	77 (35.3)	87 (39.4)	83 (37.4)
Intent-to-Treat (ITT)	218 (100.0)	221 (100.0)	287 (100.0)

- ^a Percentages are based on the number of patients randomized to treatment.

Reviewers' note: Note that the clinically evaluable population falls short of the 190 clinically evaluable patients per treatment arm required by sample size calculation. Thus, the primary clinical outcome has a power less than 80%.

Clinically Evaluable and Clinically Qualified Analyses

TOC Visit (11-16 Days Posttherapy)

Clinical Cure by Patient

**Table 16. Clinical Cure Rate by Patient at TOC Clinically Evaluable Patients
Investigator/Sponsor Determination**

Clinically Evaluable Patients	Cefdinir				Amox/Clav	
	QD		BID		n/N	%
	n/N	%	n/N	%		
All	128/181	70.7	127/183	69.4	129/178	72.5
With Baseline Tympanocentesis	69/102	67.6	64/101	63.4	69/100	69.0
No Baseline Tympanocentesis	59/79	74.7	63/82	76.8	60/78	69.0

n/N = Number of patients with combined determination of cure/total number of patients.

95% confidence intervals about the difference in proportion

All

cefdinir QD versus amox/clav (-11.64, 8.13)

cefdinir BID versus amox/clav (-12.99, 6.84)

cefdinir QD versus cefdinir BID (-8.64, 11.28)

With baseline tympanocentesis

cefdinir QD versus amox/clav (-15.17, 12.47)

cefdinir BID versus amox/clav (-9.77, 18.33)

cefdinir QD versus cefdinir BID (-9.77, 18.33)

The clinical cure rates shown above are based on the combined investigator/sponsor assessments (see this review page 7 for discussion).

Reviewers' note: The cures rates are disappointing, but very close by treatment arm. Consequently, the 95% confidence intervals superficially meet the $\pm 15\%$ fixed criteria for a maximum cure rate of 70%. However, the sample size estimate was based on having 190 clinically evaluable patients per arm. The study appears to demonstrate equivalence, but is really underpowered. This is a great deficiency in a primary endpoint.

Tympanometry Results: The presence of middle ear effusion, determined by tympanometry, was used as an ancillary measure of clinical efficacy. The investigator's tympanometric assessment of the left or right ear was considered Satisfactory by the Sponsor if the specified ear was reported as Abnormal at baseline and Normal by TOC. The investigator's tympanometric assessment of the patient (ie, both ears) was considered Satisfactory by the Sponsor if both ears were reported as Normal at TOC.

Table. 17 Satisfactory Tympanometry Assessments at TOC Clinically Evaluable Patients excluding Fiddes and Iravani

	Left Ear		Right Ear		Patient	
	n/N ^a	%	n/N ^a	%	n/N ^b	%
Cefdinir QD	61/129	47.3	43/119	36.1	60/167	35.9
Cefdinir BID	51/128	39.8	50/131	38.2	57/167	34.1
Amox/Clav	47/135	34.8	41/129	31.8	58/167	34.7

^a n/N = Number of patients with normal tympanometry assessment of specified ear at TOC/total number of patients with abnormal tympanometry assessment of specified ear at baseline.

^b n/N = Number of patients with normal tympanometry assessment of both ears at TOC/total number of patients who had tympanometry at TOC.

Reviewers' note: This is not a primary outcome measure. However, the tympanometry assessments by patient are very close.

LTFU Visit (27-42 Days Posttherapy)

Clinical Cure by Patient: Clinically evaluable patients who continued to satisfy necessary protocol requirements between the TOC and LTFU visits were considered clinically qualified at LTFU.

Table 18. Clinical Cure Rate by Patient at LTFU - Clinically Qualified Patients Who Were Classified as Cures at TOC excluding Fiddes and Iravani

	Cefdinir				Amox/Clav	
	QD		BID		n/N	%
	n/N	%	n/N	%		
Cure Rate	103/117	88.0	104/124	83.9	101/125	80.8

n/N = Number of patients with combined determination of continued cure at LTFU (ie, no clinical recurrence)/total number of patients.

The clinical cure rates shown in above are based on the combined investigator/Sponsor assessments (see page 7).

95% confidence intervals about the difference in proportion

cefdinir QD versus amox/clav (-2.66, 17.13)

cefdinir BID versus amox/clav (-7.20, 13.34)

cefdinir QD versus cefdinir BID (-5.41, 13.74)

Reviewers' note: This is not a primary outcome measure, and there are many patients lost to follow-up that could skew the endpoint. Nonetheless, the outcome measures are close and suggest that cefdinir is not worse than amoxicillin/clavulanate in the treatment of AOM.

Tympanometry Results: In general, results from ear and patient tympanometry assessments in clinically evaluable patients were similar among the 3 treatment groups at the LTFU visit.

Table 19. Satisfactory Tympanometry Assessments at LTFU - Clinically Evaluable Patients excluding Fiddes and Iravani

	Left Ear		Right Ear		Patient	
	n/N ^a	%	n/N ^a	%	n/N ^b	%
Cefdinir QD	50/88	56.8	33/76	43.4	57/114	50.0
Cefdinir BID	49/87	56.3	54/91	59.3	65/118	55.1
Amox/Clav	53/99	53.5	46/90	51.1	68/124	54.8

^a n/N = Number of patients with normal tympanometry assessment of specified ear at LTFU/total number of patients with abnormal tympanometry assessment of specified ear at baseline.

^b n/N = Number of patients with normal tympanometry assessment of both ears at LTFU/total number of patients who had tympanometry at LTFU.

Reviewers' note: This is not a primary outcome measure. Nonetheless, by patient the rates are again quite close.

Strictly Evaluable and Strictly Qualified Analyses

TOC Visit (11-16 Days Posttherapy)

Clinical Cure by Patient

Table 20. Clinical Cure Rate by Patient (According to Baseline Pathogen) at TOC - Strictly Evaluable Patients excluding Fiddes and Iravani

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	1/1	100.0	0/0	0	0/0	0
<i>Streptococcus pneumoniae</i>	13/19	68.4	11/21	52.4	17/27	63.0
<i>Streptococcus pyogenes</i>	6/6	100.0	2/3	66.7	2/3	66.7
<i>Haemophilus influenzae</i>	11/16	68.8	17/22	77.3	14/18	77.8
<i>Moraxella catarrhalis</i>	3/5	60.0	6/7	85.7	3/6	50.0
Multiple						
<i>Streptococcus pneumoniae</i>	6/8	75.0	2/3	66.7	6/7	85.7
<i>Haemophilus influenzae</i>	7/10	70.0	5/10	50.0	5/6	83.3
<i>Moraxella catarrhalis</i>	2/6	33.3	0/0	0	1/3	33.3

n/N = Number of patients with combined determination of cure/total number of patients.

The clinical cure rates shown above are based on the combined investigator/Sponsor assessments (see page 7).

*Reviewers' note: The cure rates are disappointing overall, but the cure rates are comparable across treatment arms. Amoxicillin/clavulanate did not outperform the two cefdinir arms. Because the only organisms that can be evaluated for labeling based on these numbers are *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, these were the only organisms evaluated for cure with multiple pathogens. It appears that the cefdinir regimens are therapeutically comparable to amoxicillin/clavulanate against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Nonetheless, the reviewers are disappointed because the rates are low overall-- quite dismal, but similar rates have been seen in other submissions.*

Microbiologic Eradication by Pathogen:

Table 21. Microbiologic Eradication Rate by Baseline Pathogen at TOC - Pathogens From Strictly Evaluable Patients, excluding Fiddes and Iravani

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	2/3	66.7	1/1	100.0	0/3	—
<i>Streptococcus pneumoniae</i>	22/30	73.3	13/29	44.8	28/38	73.7
<i>Streptococcus pyogenes</i>	7/7	100.0	2/4	50.0	2/5	40.0
<i>Haemophilus influenzae</i>	22/32	68.8	25/39	64.1	20/25	80.0
<i>Haemophilus parainfluenzae</i>	0/0	—	1/1	100.0	0/0	—
<i>Moraxella catarrhalis</i>	6/12	50.0	6/7	85.7	5/10	50.0
Total	59/84	70.2	48/81	59.3	55/81	67.9

n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

Reviewers' note: The numbers are too small to detect statistical significance, but eradication rates are similar overall. What the reviewers find peculiar and are entirely unable to explain is why cefdinir BID appears to lag here with respect to *Streptococcus pneumoniae*. This makes entirely no sense given other clinical, biopharmaceutical and microbiologic data submitted in this application.

In general, the microbiologic eradication rates by pathogen achieved by cefdinir QD, cefdinir BID, and amox/clav were not decreased by the presence of β -lactamase for *Haemophilus influenzae* and *Moraxella catarrhalis*.

Table 22. Microbiologic Eradication Rate by β -lactamase + *H. influenzae* & *M. catarrhalis* at TOC —Pathogens From Strictly Evaluable Patients, excluding Fiddes & Iravani

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
<i>H. influenzae</i> , β L+	8/15-10/14	53-71%	9/11-14/15	82-93%	18/23-20/22	78-91%
<i>M. catarrhalis</i> , β L+	4/8-5/9	50-55%	6/7	86%	4/9-5/9	44-56%

β L = β -Lactamase.

n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

Reviewers' note: The Sponsor did not provide a breakup of the beta-lactamase status of the isolates once the Fiddes and Iravani sites were excluded. The above table presents the best and worst case scenario. Although numbers were lost, percentages were little changed. For *Haemophilus influenzae*, the original % eradication rate was 59%, 88%, and 85% for cefdinir QD, cefdinir BID and amoxicillin/clavulanate, respectively. For *Moraxella catarrhalis*, the original % eradication rate was 47%, 88%, and 60% for cefdinir QD, cefdinir BID and amoxicillin/clavulanate, respectively. Large numbers of organisms were not lost. Although not the most compelling data, when considered with the entire application, the evidence supports efficacy against beta-lactamase producing strains in this application.

Microbiologic Eradication by Patient: This analysis will not be undertaken because the results are virtually the same as clinical cure rate at TOC by pathogen.

Intent-to-Treat Analyses

Test-of-Cure Visit (11-16 Days Posttherapy):

Table 23. Clinical and Microbiologic Efficacy Results at TOC - All Patients

	Clinical Cure Rate by Patient		Microbiologic Eradication Rate by Pathogen	
	n/N ^a	%	n/N ^b	%
Cefdinir QD	183/280	65.4	83/126	65.9
Cefdinir BID	199/285	69.8	83/129	64.3
Amox/Clav	205/287	71.4	92/138	66.7

^a n/N = Number of patients with combined determination of cure/total number of patients.

^b n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

95% confidence intervals about the difference in proportion

Clinical cure rate by patient

cefdinir QD versus amox/clav (-14.06, 1.92)

cefdinir BID versus amox/clav (-9.42, 6.21)

cefdinir QD versus cefdinir BID (-12.18, 3.24)

Reviewers note: Although underpowered, this analysis suggests therapeutic equivalence because the outcome measures are fairly close.

Long-Term Follow-Up Visit (27-42 Days Posttherapy):

Table 24. Clinical and Microbiologic Efficacy Results at LTFU - All Patients

	Clinical Cure Rate by Patient		Microbiologic Eradication Rate by Pathogen	
	n/N ^a	%	n/N ^b	%
Cefdinir QD	146/280	52.1	55/126	43.7
Cefdinir BID	167/285	58.6	73/129	56.6
Amox/Clav	161/287	56.1	63/138	45.7

^a n/N = Number of patients with combined determination of cure at LTFU (ie, no clinical recurrence)/total number of patients.

^b n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

Reviewers' note: Although the cure rates are fairly close, the efficacy is low. It is impossible to draw convincing conclusions from such analysis.

Safety

All and Associated Adverse Events: Adverse events that occurred during this study primarily affected the digestive system and diarrhea was the most frequently reported adverse event and associated adverse event in all treatment groups.

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients
excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir								Amox/Clav N = 222			
	QD N = 218				BID N = 221							
	All		Assoc		All		Assoc		All		Assoc	
BODY AS A WHOLE	32 ^a	(14.7)	2	(0.9)	40 ^a	(18.1)	1	(0.5)	31 ^a	(14.0)	4 ^a	(1.8)
Infection	20	(9.2)	0	(0.0)	28	(12.7)	0	(0.0)	19	(8.6)	0	(0.0)
Accidental Injury	6	(2.8)	0	(0.0)	5	(2.3)	0	(0.0)	6	(2.7)	1	(0.3)
Fever	2	(0.9)	0	(0.0)	4	(1.8)	1	(0.5)	4	(1.8)	0	(0.0)
Headache	2	(0.9)	0	(0.0)	3	(1.4)	0	(0.0)	2	(0.9)	2	(0.9)
Abdominal Pain	2	(0.9)	2	(0.9)	2	(0.9)	0	(0.0)	4	(1.8)	3	(1.4)
Flu Syndrome	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	2	(0.9)	0	(0.0)
Sepsis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
DIGESTIVE SYSTEM	41 ^a	(18.8)	32 ^a	(14.7)	52 ^a	(23.5)	39 ^a	(17.6)	84 ^a	(37.8)	70 ^a	(31.5)
Diarrhea	33	(15.1)	29	(13.3)	36	(16.3)	28	(12.7)	71	(32.0)	66	(29.7)
Vomiting	9	(4.1)	5	(2.3)	10	(4.5)	4	(1.8)	20	(9.0)	12	(5.4)
Gastroenteritis	1	(0.5)	0	(0.0)	4	(1.8)	2	(0.9)	6	(2.7)	3	(1.4)
Abnormal Stools	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	0	(0.0)	2	(0.9)	1	(0.5)	1	(0.5)	0	(0.0)
Constipation	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Dyspepsia	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	2	(0.9)	1	(0.5)
Glossitis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Mouth Ulceration	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Flatulence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
Gastrointestinal Disorder	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal Hemorrhage	2	(0.9)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients
excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Event DIGESTIVE SYSTEM (cont'd)	Cefdinir								Amox/Clav N = 287			
	QD N = 218				BID N = 2							
	All		Assoc		All		Assoc		All		Assoc	
Liver Function Tests Abnormal	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral Moniliasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)	1	(0.3)
Rectal Hemorrhage	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HEMIC AND LYMPHATIC SYSTEM	4	(1.8)	1	(0.5)	5	(2.3)	0	(0.0)	2	(0.9)	0	(0.0)
Lymphadenopathy	2	(0.9)	0	(0.0)	4	(1.8)	0	(0.0)	1	(0.5)	0	(0.0)
Anemia	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Leukopenia	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL	2*	(0.9)	1	(0.5)	3*	(1.4)	2*	(0.9)	3*	(1.4)	2*	(0.9)
SGOT Increased	2	(0.9)	1	(0.5)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
SGPT Increased	1	(0.5)	0	(0.0)	2	(0.9)	2	(0.7)	2	(0.7)	2	(0.7)
Dehydration	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Lactic Dehydrogenase Increased	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	2	(0.9)	1	(0.5)
NERVOUS SYSTEM	1	(0.5)	0	(0.0)	4	(1.8)	0	(0.0)	1	(0.5)	1	(0.5)
Convulsion	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Dizziness	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vertigo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients
excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir								Amox/Clav N = 287			
	QD N = 280				BID N = 285							
	All		Assoc		All		Assoc		All		Assoc	
RESPIRATORY SYSTEM	30*	(13.8)	0	(0.0)	25*	(11.3)	0	(0.0)	21*	(9.5)	0	(0.0)
Cough Increased	7	(3.2)	0	(0.0)	7	(3.2)	0	(0.0)	3	(1.4)	0	(0.0)
Pharyngitis	7	(3.2)	0	(0.0)	6	(2.7)	0	(0.0)	8	(3.6)	0	(0.0)
Rhinitis	7	(3.2)	0	(0.0)	6	(2.7)	0	(0.0)	2	(0.9)	0	(0.0)
Sinusitis	5	(1.8)	0	(0.0)	4	(1.4)	0	(0.0)	3	(1.0)	0	(0.0)
Asthma	4	(1.8)	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.9)	0	(0.0)
Laryngitis	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	1	(0.5)	0	(0.0)
Lung Disorder	2	(0.9)	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Bronchiolitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
Bronchitis	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Pneumonia	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)
SKIN AND APPENDAGES	24*	(11.0)	19	(8.7)	32*	(14.5)	20	(9.0)	33*	(14.9)	26	(11.7)
Rash	14	(6.4)	13	(6.0)	20	(9.0)	13	(5.9)	23	(10.4)	19	(8.6)
Cutaneous Moniliasis	5	(2.3)	5	(2.3)	7	(3.2)	6	(2.7)	7	(3.2)	6	(2.7)
Alopecia	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Contact Dermatitis	2	(0.9)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Dry Skin	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	3	(1.4)	0	(0.0)
Maculopapular Rash	1	(0.5)	1	(0.5)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Pustular Rash	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Vesiculobullous Rash	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)	1	(0.5)

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients
excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir								Amox/Clav N = 287			
	QD N = 280				BID N = 285							
	All		Assoc		All		Assoc		All		Assoc	
SPECIAL SENSES	3	(1.4)	0	(0.0)	7	(3.2)	0	(0.0)	11	(4.1)	0	(0.0)
Conjunctivitis	2	(0.9)	0	(0.0)	4	(1.8)	0	(0.0)	3	(1.4)	0	(0.0)
Otitis Media	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis Externa	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	2	(0.9)	0	(0.0)
Corneal Lesion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
Ear Disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	3	(1.4)	0	(0.0)
Eye Disorder	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
UROGENITAL SYSTEM ^b	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(0.0)	1	(0.0)
Vaginal Moniliasis ^b	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)

Reviewers' note: The adverse events recorded, both all and associated, are consistent with other cephalosporins and penicillins. The numbers above represent only one trial; the integrated review of the suspension evaluates the adverse event profile with the perspective of greater numbers exposed.

Deaths: One patient who completed treatment with cefdinir QD died due to intussusception 51 days after completing study medication. This adverse event was considered definitely not related to study medication by the investigator.

Table 26. Deaths - All Patients

Treatment	Age, Sex	Study Day of Death	Study Day Drug Discontinued	Cause of Death	Relationship to Study Medication	Study Day of Onset of Adverse Event
Cefdinir QD	12 mo, M	61	Completed Medication	Intussusception (Gastrointestinal Disorder)	Definitely Not	58

Reviewers' note: After review of the narrative, the reviewers agree that the death was not related to study medication.

Withdrawals Due to Adverse Events: Patients were considered withdrawn due to an adverse event if because of an adverse event they did not complete therapy or did not complete a follow-up visit. Twenty-one (2%) patients discontinued study medication because of adverse events: 8 (3%) treated with cefdinir QD, 6 (2%) with cefdinir BID, and 7 (2%) with amox/clav. In all groups, most treatment discontinuations were due to diarrhea and/or rash considered related to study medication by the investigators.

Twenty-one additional patients (10 treated with cefdinir QD, 3 with cefdinir BID, and 8 with amox/clav) were withdrawn due to adverse events after completing treatment but before the LTFU visit; none for adverse events considered related to study medication. Most (18) of these patients developed bacterial infections requiring systemic antibiotic therapy and therefore were not eligible to continue in the study; 3 of these patients had accidental injury.

Table 27. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients
includes data from Fiddes and Iravani
(Page 1 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir QD	9 yr, M	Sore Throat (Pharyngitis)	Unlikely	24	Completed Medication	Not Yet Recovered
	6 yr, F	Pharyngitis	Definitely Not	20	Completed Medication	Recovered
	14 mo, M	Scabies (Infection)	Unlikely	24	Completed Medication	Not Yet Recovered
	17 mo, M	Sinusitis	Definitely Not	13	Completed Medication	Unknown
	13 mo, F	Sinusitis	Unlikely	12	Completed Medication	Not Yet Recovered
	12 mo, M	Sinusitis	Definitely Not	8	9	Not Yet Recovered
	15 mo, M	Macular Rash (Maculopapular Rash)	Probably	3	3	Recovered
	10 mo, F	Diarrhea	Definitely	1	5	Recovered
	9 mo, F	Neck Laceration (Accidental Injury)	Definitely Not	9	Completed Medication	Recovered
	8 yr, M	Vomiting	Probably	1	1	Recovered
	7 mo, M	Diarrhea	Definitely	2	2	Recovered
	18 mo, M	Diaper Dermatitis (Rash)	Probably	2	3	Unknown
	10 mo, M	Diarrhea	Probably	2	2	Recovered
	9 mo, F	Generalized Rash (Rash)	Possibly	4	4	Recovered

Table 27. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients
includes data from Fiddes and Iravani
(Page 2 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir QD (cont'd)	9 yr, F	Otitis Externa	Definitely Not	20	Completed Medication	Not Yet Recovered
	7 yr, M	Pharyngitis	Definitely Not	24	Completed Medication	Not Yet Recovered
	11 mo, M	Nasopharyngitis (Pharyngitis)	Definitely Not	25	Completed Medication	Recovered
	6 yr, F	Upper Respiratory Infection (Infection)	Definitely Not	24	Completed Medication	Not Yet Recovered
	12 yr, M	Acute Sinusitis (Sinusitis)	Definitely Not	19	Completed Medication	Not Yet Recovered
	16 mo, F	Sinusitis	Definitely Not	26	Completed Medication	Unknown
	5 yr, F	Sinusitis	Definitely Not	32	Completed Medication	Unknown
	14 mo, M	Vomiting	Probably	1	4	Recovered
		Loose Stools (Diarrhea)	Probably	3		Recovered
	6 mo, F	Diarrhea	Probably	1	1	Recovered
	6 yr, F	Diarrhea	Possibly	1	2	Unknown
		Nonpruritic Rash (Rash)	Probably	2		Not Yet Recovered
	13 mo, F	Febrile Seizure (Convulsion)	Unlikely	1	2	Recovered
		Dehydration	Unlikely	2		Recovered
	13 mo, F	Generalized Macular Rash - Face, Neck, Trunk (Maculopapular Rash)	Possibly	8	10	Not Yet Recovered
Amox/Clav	9 mo, M	Diarrhea	Probably	6	9	Not Yet Recovered
	3 yr, M	Diarrhea	Probably	3	4	Unknown
	2 yr, M	Anorexia	Possibly	1	5	Recovered
		Diarrhea	Definitely	2		Recovered
		Dehydration	Probably	4		Recovered

Table 27. Withdrawals Due to Adverse Events - All Patients

(Page 3 of 4)

Treatment	Age,* Sex	Adverse Event ^b	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/Clav (cont'd)	7 mo, F	Diarrhea	Probably	1	5	Recovered
		Vomited (Vomiting)	Probably	2		Recovered
		Diaper Rash (Rash)	Probably	5		Recovered
	7 mo, F	Bronchiolitis	Definitely Not	21	Completed Medication	Not Yet Recovered
		Pneumonia	Definitely Not	21		Not Yet Recovered
	2 yr, M	Diarrhea	Definitely	2	7	Recovered
		Gastroenteritis	Definitely	2		Recovered
		Vomiting	Definitely	2		Recovered
	21 mo, M	URI (Infection)	Definitely Not	19	Completed Medication	Not Yet Recovered
	10 mo, F	Liquid Stools (Diarrhea)	Probably	2	2	Recovered
		Rash	Probably	2		Recovered
	6 yr, F	Exacerbation of Pre-existing Wound on Scalp (Accidental Injury)	Definitely Not	15	Completed Medication	Recovered
	15 mo, F	Loose Stools (Diarrhea)	Probably	2	8	Recovered
		Vomiting	Probably	8		Recovered
		Yeast Infection - Perineal Area (Cutaneous Moniliasis)	Probably	9		Unknown
	18 mo, M	URI (Infection)	Definitely Not	36	Completed Medication	Recovered
		Pneumonitis (Pneumonia)	Definitely Not	36		Recovered
	3 yr, M	Laceration Abdomen (Accidental Injury)	Definitely Not	19	Completed Medication	Recovered
	12 mo, F	Diarrhea	Possibly	1	2	Recovered

Table 27. Withdrawals Due to Adverse Events - All Patients
(Page 4 of 4)

Treatment	Age, ^a Sex	Adverse Event ^b	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/Clav (cont'd)	11 yr, F	Otitis Externa	Definitely Not	20	Completed Medication	Not Yet Recovered
	14 mo, F	Nasopharyngitis (Pharyngitis)	Definitely Not	14	Completed Medication	Not Yet Recovered
	21 mo, M	Nasopharyngitis (Pharyngitis)	Definitely Not	13	Completed Medication	Recovered

Reviewers' note: Review of the narratives suggests that the investigators assigned relationships are appropriate. The most common events that are related to discontinuation of therapy are skin rashes and events related to the gastrointestinal tract. This is consistent with other cephalosporins and penicillins.

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***Clostridium difficile*-Associated Diarrhea:** Fourteen patients (3 in the cefdinir QD group, 4 in the cefdinir BID group, and 7 in the amox/clav group) discontinued treatment due to diarrhea; 2 of these patients in the cefdinir BID group and 5 in the amox/clav group had other adverse events (eg, vomiting, rash) that also contributed to treatment being discontinued.

In November 1992, the Sponsor requested that all patients discontinuing treatment due to diarrhea be tested for *Clostridium difficile* toxin. Of the 9 patients who had diarrhea and discontinued treatment after that date none were tested. Seven of these patients (3 treated with cefdinir QD, 1 with cefdinir BID, and 3 with amox/clav) recovered from the diarrhea by study completion. For 1 patient treated with cefdinir BID (Patient 208, Center 983-10-10) and 1 treated with amox/clav (Patient 45, Center 983-10-3) the outcome was reported as unknown.

One patient who had diarrhea during treatment, but did not discontinue medication, was tested for *Clostridium difficile* toxin. Patient 225 (983-10-5), a 15-month-old girl who completed a 10-day course of cefdinir QD, had moderate diarrhea on Day 5, mild vomiting on Day 6, mild diaper rash on Day 8, and mild elevated liver function tests on Day 10. The vomiting and diarrhea were thought to be due to concomitant viral gastroenteritis. A fecal sample collected on Day 12 was negative for *Clostridium difficile* toxin. The diarrhea ended on Day 13, the vomiting on Day 10, and the elevated liver function values on Day 48. The diaper rash was continuing at the end of the study. The diarrhea was considered probably, the vomiting unlikely, and the diaper rash and elevated liver function tests possibly related to treatment.

Reviewers' note: It is unfortunate more patients were not tested for C. difficile-associated diarrhea. However, adverse event rates appear to be fairly evenly distributed by treatment arm and thus the diarrhea profile of cefdinir in pediatric patients is similar to that of amox/clav.

Clinical Laboratory Measurements: In all 3 treatment groups, the most frequent markedly abnormal laboratory changes were increases in lymphocytes and lactate dehydrogenase (LDH) levels and decreases in bicarbonate levels. The increases in lymphocytes were most likely due to development of other infectious processes and the decreases in bicarbonate were most likely due to crying and expected to be transient. The increases in LDH are unexplained.

Table 28. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline^a

excluding Fiddes and Iravani
[Number (%) of Patients]

Parameter	Direction of Change	Cefdinir		Amox/Clav N = 222
		QD N = 218	BID N = 221	
Hematology				
Hemoglobin	Decrease	2 (0.9)	1 (0.4)	
Hematocrit	Decrease	2 (0.9)		
Erythrocytes	Decrease	1 (0.5)		
White Blood Cells	Increase			1 (0.4)
	Decrease	1 (0.5)	3 (1.4)	2 (0.9)
Lymphocytes	Increase	5 (2.3)	6 (2.7)	6 (2.7)
Eosinophils	Increase		2 (0.9)	2 (0.9)
Platelets	Increase	3 (1.4)	3 (1.4)	1 (0.5)
	Decrease	1 (0.5)		
Polymorphonuclear leukocytes	Increase			2 (0.9)
	Decrease	4 (1.8)	8 (3.6)	5 (2.3)
Blood Chemistry				
Alkaline Phosphatase	Increase	3 (1.4)	2 (0.9)	2 (0.9)
Aspartate Aminotransferase	Increase		2 (0.9)	
Alanine Aminotransferase	Increase		2 (0.9)	
Potassium	Increase	1 (0.5)	1 (0.4)	
Calcium	Decrease	2 (0.9)	4 (1.8)	1 (0.5)
Phosphorus	Increase	3 (1.4)	4 (1.8)	5 (2.3)
	Decrease	2 (0.9)		1 (0.5)
Bicarbonate	Decrease	4 (1.8)	6 (2.7)	3 (1.4)
Lactate Dehydrogenase	Increase	8 (2.9)	19 (6.6)	14 (4.9)
Urinalysis				
Protein	Increase	1 (0.5)		
Urine pH	Increase	4 (1.8)	3 (1.4)	1 (0.5)
Red Blood Cells	Increase		1 (0.4)	
Any Parameter ^b		36 (16.5)	40 (18.1)	27 (12.2)

^a The first posttherapy visit was typically the STFU visit.

^b Total number of patients in a treatment group experiencing a markedly abnormal laboratory value (more abnormal than at baseline) regardless of the laboratory parameter.

Reviewers' note: These laboratory abnormalities appear to be evenly distributed by treatment arm. The numbers are small, but the reviewers find nothing worrisome. Laboratory abnormalities will be reviewed in the integrated safety analysis of the suspension formulation. This review will have the benefit of greater numbers.

Conclusions: This application suffers (1) from losing a significant amount of data due to unreliable investigators and (2) low eradication rates. However, the data is not significantly worse than that found in other successful applications. It is impossible to explain the performance of cefdinir BID against *Streptococcus pneumoniae* given the performance of cefdinir QD and the similar clinical cures rates of the treatment arms. It follows that if cefdinir QD is approved, cefdinir BID must be approved. See the following chart:

Table 29. Microbiologic Eradication Rates by Pathogen Achieved by Cefdinir, Amox/Clav, Cefprozil, and Loracarbef Against the Most Common Pathogens in AOME—data from this NDA and other NDA reviewed by FDA.

Baseline Pathogen	Cefdinir ^a		Amox/Clav ^a	Cefprozil ^b	Loracarbef ^b
	QD	BID			
<i>Streptococcus pneumoniae</i>	73%	45%	74%	83%	68%
<i>Haemophilus influenzae</i>	69%	64%	80%	50%	65%
<i>Moraxella catarrhalis</i>	50%	86%	50%	60%	71%

^a Data from this study, strictly evaluable patients at TOC

^b Data from Medical Officers' Reviews

A strong comparator arm that is widely recommended for the treatment of AOM was utilized in this study. Equivalence was supported by multiple analyses, but cannot be irrefutably proved because of deficiencies in statistical power. It is very unfortunate that the second study submitted in support of this application has no microbiologic data. However, it is a strong clinical study with design nearly identical to this one and could pivotally swing evidence in favor of efficacy.

In AOM, DAIDP has not required trials to be powered at the level of statistical significance by pathogen. This would be a large burden that would clearly provide much more compelling data. There is enough microbiologic data in this application to support activity against the three major pathogens of AOM. Only one microbiologic study is required, and no absolute eradication rates are preset. The data submitted in this application meets that found in other successful submissions. In addition, the critical numbers of three pathogens recommended is also met. Thus, although the reviewer found much of the submission disappointing, it appears to meet at least minimal requirements to support the application.

Finally, this study provides no concerns with respect to safety that have not been seen before with other cephalosporins. In fact, its safety profile is almost identical to other extended spectrum cephalosporins.

Indication: Acute Otitis Media (AOM)

Title and Study Number: Investigator-blinded, randomized, comparative, multicenter study of cefdinir versus amoxicillin/clavulanate in the treatment of AOM with effusion in pediatric patients (Protocol 983-11)

Reviewers' note: This study is almost identical to protocol 983-10 but for two features: (1) the study is designed to be clinical only, with microbiologic evaluation performed at the investigator's discretion; and (2) protocol 983-10 was a domestic study whereas protocol 983-11 only utilized study sites in Europe, South Africa and Australia.

Objective, Study Design: Same as Study 983-10, but this is a study designed only for clinical evaluation. Therefore, no tympanocentesis was undertaken unless the investigator deemed it necessary. In addition, clinical laboratory tests were not performed on posttherapy visit 4 to 6 weeks after end of therapy.

Methodology: The design is identical to protocol 983-11.

Patients and Inclusion/Exclusion Criteria: The inclusion criteria are the same as protocol 983-10 with the following changes:

- Pneumotoscopy could be substituted for tympanometry to document middle ear effusion, but tympanometry was preferred.
- There is no requirement for a negative pregnancy test in postmenarchal girls.

Reviewers' note: As mentioned in the medical officer's note in the review of 983-10, the inclusion criteria are not particularly stringent and are really minimal clinical findings for a diagnosis of AOM.

The exclusion criteria were identical to those for protocol 983-10 with the following addition:

- Significant history or clinical evidence of significant cardiovascular, renal hepatic, hematological, gastrointestinal, neurological (including seizures), psychiatric, or other chronic disease;

Reviewers' note: This is certainly a reasonable addition to the exclusion criteria.

Permissible reasons for patient withdrawal were the same as allowed in protocol 983-10.

Evaluability Criteria: Three populations were analyzed: (1) clinically evaluable, (2) an intent-to-treat (ITT), and (3) all patients who received study medication.

Reviewers' note: The difference between protocol 983-10 and this protocol is that this is not designed to be a microbiologically evaluable study. Therefore, there are no patient populations evaluable for microbiologic outcomes.

The clinically evaluable patients differed from those in protocol 983-10 by the following reasons:

- Patients in 983-10 were required to have a susceptible baseline pathogen. Because this protocol had no microbiologic requirement, it could not be an issue.
- This protocol specified that the clinical evaluations had to be performed within the range of days specified in the protocol.

A population of clinically qualified patients was examined at LTFU. These were clinically evaluable patients who did not have any additional protocol violations between TOC and LTFU (same as protocol 983-10).

The ITT population was all those randomized to treatment at both TOC and LTFU (same as protocol 983-10).

Endpoints: Assessment of clinical response at the TOC visit, 11 to 16 days posttherapy, was used to evaluate clinical efficacy. The primary measure of efficacy used in this study was clinical cure rate. The presence or absence of middle ear effusion determined by tympanometry (preferable) or pneumotoscopy at the TOC visit was an ancillary measure of clinical efficacy.

NDA 50-739: Clinical & Statistical Review, Omnicef® (cefdinir axetil) for the treatment of acute otitis media

Patient clinical signs and symptoms and scoring system used in determining clinical response were the same as those used in protocol 983-10.

The otoscopic examination of each ear and the scoring system was assessed in the same manner as those in 983-10. However, this study allowed pneumotoscopy in addition to tympanometry (preferred) to confirm the presence or absence of middle ear effusion.

The calculated total patient and ear scores were used in determining the Sponsor assessment of clinical response. The investigator's global impression of clinical response was based on professional opinion after the evaluation done above.

Sponsor's Assessment of Clinical Response at TOC:

Same as that used in protocol 983-10.

Sponsor's Assessment of Clinical Response at LTFU:

Same as that used in protocol 983-10.

Investigator's Assessment of Clinical Response at TOC:

Same as that used in protocol 983-10.

Investigator's Assessment of Clinical Response at LTFU:

Same as that used in protocol 983-10.

As in protocol 983-10, a Combined Investigator/Sponsor Clinical Assessment was devised to reassign investigator assessments of Improvement to either Cure, Failure, or Not Assessable.

Statistical Methods and Sample Size Requirements:—Statistical methods and sample size requirements are the same as those employed in protocol 983-10. Sample size estimates (190 patients randomized per treatment arm for a total of 570 clinically evaluable patients) are the same as protocol 983-10.

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The following is the list of investigators.

Table 30. List of Investigators

Center	Investigator(s)	Number of Patients		
		Randomized to Treatment	Completed Treatment	Clinically Evaluable
1	S. Fradd/R. Martin	18	17	19
2	D. Miller	37	35	32
3	D. Moran	40	36	35
5	I. Patchett	51	51	46
7	M. Adler	96	76	78
9	P. David	40	37	37
10	L. Christiaen	56	54	53
12	S. Furman	80	78	68
13	F. Ascensi	8	4	2
14	C. Rodrigo	4	4	3
16	M. I. de José	3	2	2
18	A. Berger	50	31	39
19	C. von Sydow	21	17	1
20	A. Joensson	18	14	14
21	P. Rigné	12	10	9
22	P. MacDonald	32	28	28
23	A.M. Fasher/ S. Young	50	45	31
24	M. Fischer	13	13	1
25	R. Haas	19	18	15
26	E. Neumann	64	61	59
31	A. Ottaviani	1	1	0
32	D. Bassetti	4	4	2
37	D. Dutchman	34	28	27
38	H. Schumacher	1	1	1
Total		752	665	595

Reviewers' note: Protocol 983-10 is a domestic study that only included US study sites. Protocol 983-11, while almost identical to protocol 983-10, had two major differences: (1) a clinical only (microbiologic evaluation optional at investigator's discretion); and (2) study centers were located in Europe, South Africa, and Australia.

Safety: The safety evaluation for this protocol is the same as in protocol 983-10.

Results**Demographic Information:****Table 33. Patient Characteristics - All Patients**
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav N = 251	Total N = 752
	QD N = 247	BID N = 254		
Sex				
Male	127 (51.4)	128 (50.4)	129 (51.4)	384 (51.1)
Female	120 (48.6)	126 (49.6)	122 (48.6)	368 (48.9)
Race				
White	224 (90.7)	233 (91.7)	222 (88.4)	679 (90.3)
Black	3 (1.2)	5 (2.0)	1 (0.4)	9 (1.2)
Asian	12 (4.9)	12 (4.7)	19 (7.6)	43 (5.7)
Other	8 (3.2)	4 (1.6)	9 (3.6)	21 (2.8)
Age, yr				
Median	4.5	4.5	4.7	4.5
Range	0.4-12.9	0.5-13.0	0.5-12.9	0.4-13.0
Distribution				
<2	47 (19.0)	41 (16.1)	42 (16.7)	130 (17.3)
2 to <6	108 (43.7)	126 (49.6)	119 (47.4)	353 (46.6)
6 to <13	92 (37.2)	86 (33.9)	90 (35.9)	268 (35.6)

Table 34. Patient Characteristics - Clinically Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav N = 197	Total N = 595
	QD N = 195	BID N = 203		
Sex				
Male	99 (50.8)	101 (49.8)	103 (52.3)	303 (50.9)
Female	96 (49.2)	102 (50.2)	94 (47.7)	292 (49.1)
Race				
White	178 (91.3)	186 (91.6)	172 (87.3)	536 (90.1)
Black	3 (1.5)	3 (1.5)	1 (0.5)	7 (1.2)
Asian	11 (5.6)	10 (4.9)	16 (8.1)	37 (6.2)
Other	3 (1.5)	4 (2.0)	8 (4.1)	15 (2.5)
Age, yr				
Median	4.5	4.7	4.7	4.6
Range	0.4 - 12.9	0.5 - 12.7	0.5 - 12.9	0.4 - 12.9
Distribution				
<2	34 (17.4)	28 (13.8)	28 (14.2)	90 (15.1)
2 to <6	91 (46.7)	108 (53.2)	98 (49.7)	297 (49.9)
6 to <13	70 (35.9)	67 (33.0)	71 (36.0)	208 (35.0)

Reviewers' note: The differences between the population here and that in protocol 983-10 is that there are far fewer minorities enrolled here and that the patients tend to be older, with a median age two years older than that of 983-10. However, treatment arms are fairly well balanced with respect to demographic variables evaluated here.

Clinical Signs and Symptoms, Distribution at Enrollment:

Table 35. Mean Patient Clinical Scores at Baseline - All and Clinically Evaluable Patients

Patient Population	Cefdinir		Amox/Clav
	QD	BID	
All Patients	8.4	8.5	8.7
Clinically Evaluable Patients	8.6	8.5	8.7

Reviewers' note: The scores in protocol 983-10 varied from 5.1 to 5.4. Here the scores are higher, supporting a more symptomatic population. With the same protocol, differences in populations emerge. Scores here are fairly well balanced by treatment arm.

Ear:

Table 36. Mean Ear Clinical Scores at Baseline - All, Clinically Evaluable, and Strictly Evaluable Patients (includes Fiddes' and Iravani's site)

Ear/Patient Population	Cefdinir		Amox/Clav
	QD	BID	
Left Ear			
All Patients	5.2	5.0	5.5
Clinically Evaluable Patients	5.4	5.0	5.6
Right Ear			
All Patients	5.2	5.3	5.0
Clinically Evaluable Patients	5.1	5.4	5.0

Reviewers' note: This distribution is fairly evenly distributed by treatment arms. Once again, this population does not appear to be particularly ill. These scores are very similar to those derived in protocol 983-10.

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Duration of therapy:

Table 37. Patient Exposure to Study Medication - All Patients

Days on Study Medication	Cefdinir		Amox/Clav N = 251
	QD N = 247	BID N = 254	
1	2	1	2
2	1	1	9
3	4	4	5
4	2	5	2
5	1	1	0
6	1	1	0
7	1	0	8
8	3	2	2
9	1	2	3
10	203	130	102
11	15	89	105
12	4	5	2
13	1	1	1
15	0	1	0
Median	10	10	10
Unknown	8	11	10

Reviewers' note: This distribution is as expected.

Table 38. Patient Disposition - All Patients
[Number (%) of Patients]

Patient Disposition	Cefdinir		Amox/Clav	Total
	QD	BID		
Randomized to Treatment	247	254	251	752
Discontinued Treatment				
Adverse Event	10 (4.0)	15 (5.9)	24 (9.6)	49 (6.5)
Lack of Compliance	3 (1.2)	4 (1.6)	13 (5.2)	20 (2.7)
Lack of Efficacy (Treatment Failure)	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.7)
Spontaneous Perforation	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Other/Administrative Reasons	6 (2.4)	4 (1.6)	2 (0.8)	12 (1.6)
Completed Treatment	226 (91.5)	229 (90.2)	210 (83.7)	665 (88.4)

Reviewers' note: Only a small number of patients discontinued treatment. Thus, the therapies were well tolerated in all treatment arms.

Results

Exclusions: See table below. Patients who were excluded from the clinically evaluable analyses were automatically also excluded from the strictly evaluable analyses.

Table 39. Reasons Patients Were Not Clinically Evaluable at TOC or Disqualified at LTFU
(Number of Patients)

	Cefdinir		Amox/Clav
	QD	BID	
Randomized to Treatment	247	254	251
Reasons Patients Were Not Clinically Evaluable at TOC Analyses			
Clinical Assessment Missed	10	11	12
Clinical Assessment Out of Time Range ^b	13	24	22
Concurrent Antibacterial ^b	3	5	2
Condition Prevented Assessment	1	2	2
Medication Not As Prescribed ^b	17	16	29
No Baseline Signs and Symptoms	20	17	17
Prior Antibacterial	2	0	1
Randomization Violation	1	0	0
Total Not Clinically Evaluable	52	51	54
Clinically Evaluable Patients at TOC	195	203	197
Reasons Patients Were Disqualified From LTFU Analyses			
Clinical Assessment Missed	22	27	22
Clinical Assessment Out of Time Range	5	9	9
Concurrent Antibacterial	15	16	12
Total Disqualified	31	42	33
Qualified Patients at LTFU	164	161	164

^a Patients who had multiple reasons for being excluded from efficacy analyses were counted for each reason that applied.

^b Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early failures were not removed from the clinically evaluable or strictly evaluable analyses for these reasons but were carried forward as failures. Also, patients who had a culture done early because they were early failures were carried forward as failures in the strictly evaluable analyses.

Reviewers' note: The reviewers agree that the exclusions tallied in the tables above are reasonable. In addition, carrying forward failures as described in footnote b is appropriate. The reasons for nonevaluability are plausible and distribution fairly even.

The table below shows the number of patients with data included in the clinically evaluable, clinically qualified, and ITT populations.

Table 40. Patients With Data Included in Efficacy Summaries
[Number (%) of Patients*]

Patient Population	Cefdinir				Amox/Clav	
	QD		BID			
Clinically Evaluable	195	(78.9)	203	(79.9)	197	(78.5)
Clinically Qualified	164	(84.1)	161	(79.3)	164	(83.2)
Intent-to-Treat (ITT)	247	(100.0)	254	(100.0)	251	(100.0)

* Percentages are based on the number of patients randomized to treatment.

Reviewers' note: Fortunately, this study is not underpowered. There are at least 190 clinically evaluable patients in each treatment arm yielding a power of 80%

Clinically Evaluable and Clinically Qualified Analyses

TOC Visit (11-16 Days Posttherapy)

Clinical Cure by Patient

Table 41. Clinical Cure Rate by Patient at TOC, Clinically Evaluable Patients

Clinically Evaluable Patients	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Investigator determination	171/195	87.7	173/203	85.2	171/197	86.8
Combined Sponsor/Investigator determination	166/195	85.1	169/203	83.2	155/197	78.7

n/N = Number of patients with combined determination of cure/total number of patients.

95% confidence intervals about the difference in proportion

Investigator determination

cefdinir QD versus amox/clav (-6.22, 8.00)

cefdinir BID versus amox/clav (-8.88, 5.71)

cefdinir QD versus cefdinir BID (-4.75, 9.69)

Combined Sponsor/Investigator determination

cefdinir QD versus amox/clav (-1.66, 14.55)

cefdinir BID versus amox/clav (-3.62, 12.76)

cefdinir QD versus cefdinir BID (-5.79, 9.04)

Reviewers' note: Both analyses demonstrate therapeutic equivalence with acceptable cure rates..

LTFU Visit (27-42 Days Posttherapy)

Clinical Cure by Patient

Table 42. Clinical Cure Rate by Patient at LTFU, Clinically Evaluable Patients

Clinically Evaluable Patients	Cefdinir				Amox/Clav	
	QD		BID		n/N	%
	n/N	%	n/N	%		
Investigator determination	149/164	90.8	148/161	91.9	140/164	85.4
Combined Sponsor/Investigator determination	153/164	93.3	145/161	90.0	143/164	87.2

n/N = Number of patients with combined determination of cure/total number of patients.

95% confidence intervals about the difference in proportion

Investigator determination

cefdinir QD versus amox/clav (-2.10, 13.08)

cefdinir BID versus amox/clav (-0.91, 14.03)

cefdinir QD versus cefdinir BID (-7.78, 5.64)

Combined Sponsor/Investigator determination

cefdinir QD versus amox/clav (-0.90, 13.10)

cefdinir BID versus amox/clav (-4.64, 10.38)

cefdinir QD versus cefdinir BID (-7.78, 5.64)

Reviewers' note: This is not a primary outcome measure, but once again both analyses demonstrate at least therapeutic equivalence of cefdinir to itself and amoxicillin/clavulanate.

ITT Analysis

Table 43. Clinical Cure Rate by Patient at TOC

	Cefdinir				Amox/Clav	
	QD		BID		n/N	%
	n/N	%	n/N	%		
All patients enrolled, TOC	211/247	85.4	212/254	83.5	204/251	81.3
All patients enrolled, LTFU	183/247	74.1	190/254	74.8	171/251	68.1

n/N = Number of patients with combined determination of cure/total number of patients.

95% confidence intervals about the difference in proportion, ITT analysis at TOC

cefdinir QD versus amox/clav (-2.78, 11.08)

cefdinir BID versus amox/clav (-4.85, 9.23)

cefdinir QD versus cefdinir BID (-4.78, 8.70)

95% confidence intervals about the difference in proportion, ITT analysis at LTFU

cefdinir QD versus amox/clav (-2.38, 14.31)

cefdinir BID versus amox/clav (-1.58, 14.93)

cefdinir QD versus cefdinir BID (-8.75, 7.32)

Reviewers' note: This analysis supports the therapeutic equivalence of cefdinir to itself and to amoxicillin/clavulanate.

Table 44. All and Associated* Adverse Events by Body System and Treatment Group - All Patients Receiving Study Medication

[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir				Amox/Clav N = 248			
	QD N = 246		BID N = 251					
	All	Associated	All ^b	Associated	All	Associated	All	Associated
BODY AS A WHOLE	9 ^c (3.7)	2 ^c (0.8)	18 ^c (7.2)	4 (1.6)	22 ^c (8.9)	4 (1.6)		
Abdominal Pain	2 (0.8)	2 (0.8)	4 (1.6)	1 (0.4)	3 (1.2)	1 (0.4)		
Infection	5 (2.0)	0 (0.0)	4 (1.6)	0 (0.0)	5 (2.0)	0 (0.0)		
Flu Syndrome	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.4)	2 (0.8)	0 (0.0)		
Headache	1 (0.4)	1 (0.4)	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)		
Mucous Membrane Disorder	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	3 (1.2)	0 (0.0)		
Overdose	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)		
Accidental Injury	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)		
Face Edema	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)		
Fever	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)		
Lab Test Abnormal	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)		
Neck Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)		
Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)		
SKIN AND APPENDAGES	5 (2.0)	2 (0.8)	8 (3.2)	7 (2.8)	11 (4.4)	7 (2.8)		
Rash	3 (1.2)	2 (0.8)	6 (2.4)	6 (2.4)	9 (3.6)	6 (2.4)		
Eczema	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)		
Fungal Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)		
Angioedema	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Maculopapular Rash	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Pustular Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)		
SPECIAL SENSES	10 (4.1)	1 (0.4)	8 (3.2)	0 (0.0)	6 (2.4)	0 (0.0)		
Ear Disorder	5 (2.0)	0 (0.0)	6 (2.4)	0 (0.0)	3 (1.2)	0 (0.0)		
Conjunctivitis	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)		
Otitis Externa	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)		
Otitis Media	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Taste Perversion	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		

Table 44. All and Associated^a Adverse Events by Body System and Treatment Group - All Patients Receiving Study Medication[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir						Amox/Clav N = 248	
	QD N = 246			BID N = 251				
	All	Associated		All ^b	Associated		All	Associated
NERVOUS SYSTEM	1 (0.4)	0 (0.0)		3 (1.2)	1 (0.4)		2 (0.8)	0 (0.0)
CNS Stimulation	0 (0.0)	0 (0.0)		1 (0.4)	1 (0.4)		0 (0.0)	0 (0.0)
Nervousness	0 (0.0)	0 (0.0)		1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)		1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.4)	0 (0.0)
Somnolence	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.4)	0 (0.0)
Torticollis	1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
UROGENITAL SYSTEM	0 (0.0)	0 (0.0)		3 (1.2)	0 (0.0)		1 (0.4)	0 (0.0)
Urinary Tract Infection	0 (0.0)	0 (0.0)		2 (0.8)	0 (0.0)		1 (0.4)	0 (0.0)
Balanitis	0 (0.0)	0 (0.0)		1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)
CARDIOVASCULAR SYSTEM	2 (0.8)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Palpitation	1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Syncope	1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
HEMIC & LYMPHATIC SYSTEM	1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.8)	0 (0.0)
Anemia	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.8)	0 (0.0)
Thrombocytopenic Purpura	1 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
METABOLIC & NUTRITIONAL DISORDERS	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.4)	1 (0.4)
Bilirubinemia	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.4)	1 (0.4)

^a Considered by the investigator to be possibly, probably, or definitely related to treatment.^b All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir BID treatment.^c The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have ≥ 1 adverse event per system.*Medical officer's note: The adverse event profile is typical of cephalosporins. Gastrointestinal events, particularly diarrhea are prominent.*

Table 45. Serious Nonfatal Adverse Events - All Patients Receiving Study Medication

Treatment	Age ^a , Sex	Serious Adverse Event ^b	Intensity	Relationship to Study Medication ^c	Study Day of Onset of Adverse Event	Management of Study Drug	Outcome
Cefdinir QD	15 mo, F	Salmonella infection colon (Colitis)	Severe	Definitely Not	4	Interrupted	Recovered
	15 mo, F	Amigdalitis viral (Pharyngitis)	Moderate	Definitely Not	34	None	Recovered
	3 yr, M	Recurrence of otitis media (Otitis media)	Severe	Definitely Not	59 ^d	None	Unknown
Cefdinir BID	4 yr, M	Abdominal pain	Moderate	Definitely Not	4	None	Recovered
		Constipation	Moderate	Definitely Not	4	None	Recovered
	19 mo, F	Streptococcus angina (Pharyngitis)	Severe	Definitely Not	43	None	Recovered
	4 yr, M	Sinusitis	Severe	Definitely Not	15	None	Recovered
	9 yr, F	Diarrhoea (Diarrhea)	Severe	Probably	2	Discontinued	Recovered/Sequelae
Amox/Clav	7 yr, F	Acute appendicitis (Gastrointestinal disorder)	Severe	Definitely Not	1	Discontinued	Recovered
	4 yr, M	Diarrhea	Severe	Definitely	3	Discontinued	Recovered
		Vomiting	Severe	Definitely	3	Discontinued	Recovered
		Intense persistent cough (Cough increased)	Severe	Definitely Not	3	None	Recovered
		Cough (Cough increased)	Mild	Definitely Not	6	None	Recovered
	7 mo, M	Asthma,	Moderate	Definitely Not	21	None	Recovered
		Croup (Laryngitis)	Moderate	Definitely Not	21	None	Recovered

^a Age at baseline^b When the investigator term and COSTART IV term differ, the COSTART IV adverse event term appears in parentheses.^c As determined by the investigator^d Day 49 was the last follow-up visit.

Medical officer's note: Review of narratives supports investigator assignment of relationship to study drug. Once again gastrointestinal events are prominent. However, cefdinir does not appear to be worse than amoxicillin/clavulanate on this count. This issue will be addressed in the integrated summary of safety for the suspension formulation.

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication
(Page 1 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir QD	10 yr, F	Diarrhea	Probably	2	6	Not Yet Recovered
	4 yr, M	Diarrhea	Definitely	2	3	Recovered
	2 yr, M	Diarrhea	Probably	2	2	Recovered
	6 yr, M	Upper Respiratory Tract Infection (Pharyngitis)	Definitely Not	22	10	Recovered
	7 mo, M	Diarrhea	Probably	1	Unknown	Recovered
	16 mo, F	Tonsillitis (Pharyngitis)	Definitely Not	19	10	Recovered
	11 yr, F	Vaso-Vagal Attack (Syncope)	Unlikely	1	1	Recovered
	14 mo, M	Diarrhea	Probably	4	3	Recovered
	5 yr, F	Left Bronchopneumonia (Pneumonia)	Definitely Not	20	10	Not Yet Recovered
	21 mo, F	Diarrhea	Probably	2	3	Recovered
	4 yr, M	Diarrhea	Probably	4	7	Recovered
	2 yr, F	Pneumonia	Unlikely	5	5	Recovered
	15 mo, F	Diarrhea	Definitely	4	4	Recovered
	9 yr, F	Abdominal Pain	Probably	9	9	Recovered
	11 yr, M	Diarrhea	Definitely	3	3	Recovered
Cefdinir BID	15 mo, F	Diarrhea	Probably	2	2	Recovered
	8 yr, M	Vomiting	Probably	1	1	Recovered
	8 mo, M	Tonsillitis (Pharyngitis)	Definitely Not	15	11	Not Yet Recovered
	2 yr, F	Diarrhea	Probably	2	Not Available	Recovered
	7 mo, F	Diarrhea	Definitely	1	Not Available	Recovered
		Vomiting	Definitely	1	1	Recovered

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication

(Page 2 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir BID	9 mo, F	Diarrhea	Possibly	3	4	Not Yet Recovered
	11 yr, F	Diarrhea	Probably	3	3	Not Yet Recovered
	19 mo, M	Diarrhea	Probably	2	6	Not Yet Recovered
	4 yr, F	Hyperexcitability (CNS Stimulation)	Possibly	3	4	Recovered
	7 yr, M	Diarrhea	Probably	4	4	Recovered
		Vomiting	Probably	4		Recovered
	14 mo, F	Rash	Probably	3	4	Recovered
	9 yr, F	Diarrhea	Probably	2	3	Recovered/ Sequelae ^c
	11 yr, F	Gastric Flu (Flu Syndrome)	Possibly	7	8	Recovered
	20 mo, M	Diarrhea	Definitely	2	3	Recovered
Amox/Clav	5 yr, M	Overdose	Definitely	1	4	Recovered
		Nausea	Definitely	2		Recovered/ Sequelae ^c
	8 yr, F	Vomiting	Possibly	7	7	Recovered
	6 yr, F	Urinary Tract Infection	Definitely Not	14	10	Unknown
	5 yr, M		Definitely Not	19	11	Recovered
	12 yr, F	Allergic Rash (Rash)	Probably	2	2	Recovered
	2 yr, F	Vomiting	Definitely	1	1	Recovered
	7 yr, F	Diarrhea	Probably	2	2	Recovered
	2 yr, F	Pharyngitis	Definitely Not	34	11	Recovered
	7 yr, F	Vomiting	Possibly	1	2	Recovered
	6 yr, F	Vomiting	Probably	1	2	Recovered

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication

(Page 3 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/clav	18 mo, M	Diarrhea	Definitely	7	7	Recovered
	2 yr, M	Vomiting	Definitely	1	2	Recovered
	7 yr, F	Vomiting	Probably	1	2	Recovered
	3 yr, M	Vomiting	Possibly	6	7	Recovered
	22 mo, F	Diarrhea	Definitely	2	2	Recovered
	6 yr, M	Vomiting	Definitely	1	2	Recovered
	2 yr, F	Colitis	Possibly	7	7	Recovered
		Itching Erythema (Rash)	Unlikely	7		Recovered
	7 yr, F	Acute Appendicitis (Gastrointestinal Disorder)	Definitely Not	1	1	Recovered
	4 yr, M	Diarrhea	Definitely	3	3	Recovered
		Vomiting	Definitely	3		Recovered
	21 mo, F	Diarrhea	Definitely	2	3	Recovered
	10 mo, M	Diarrhea	Definitely	3	Not Available	Not Yet Recovered
	8 mo, M	Rash	Possibly	9	9	Recovered
	9 mo, M	Diarrhea	Probably	2	3	Recovered
	2 yr, F	Diarrhea	Possibly	5	9	Recovered
	19 mo, F	Allergic Erythema (Rash)	Probably	2	2	Recovered
	7 mo, F	Allergic Skin Rash (Rash)	Probably	3	3	Recovered

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication

(Page 4 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/clav	19 mo, M	Acute Right Otitis Externa (Otitis Externa)	Unlikely	9	10	Not Yet Recovered
	19 mo, F	Diarrhea	Probably	1	4	Recovered
	10 yr, F	Tonsillitis (Pharyngitis)	Definitely Not	22	10	Not Yet Recovered
		Congested Nose (Rhinitis)	Definitely Not	22		Not Yet Recovered

Reviewers' note: The reviewers agree with the relationship of event to study medication assigned by the investigator. There are no surprising findings with respect to this chart.

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Table 47 . Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients

BODY SYSTEM/ Adverse Event	Cefdinir		Amox/Clav N = 248
	QD N = 246	BID N = 251	
BODY AS A WHOLE	0	2	1
Abdominal Pain	0	1	0
Flu Syndrome	0	1	0
Overdose	0	0	1
CARDIOVASCULAR SYSTEM	1	0	0
Syncope	1	0	0
DIGESTIVE SYSTEM	8	11 ^a	20 ^a
Diarrhea	8	10	9
Vomiting	0	3	9
Colitis	0	0	1
Gastrointestinal Disorder	0	0	1
Nausea	0	0	1
NERVOUS SYSTEM	0	1	0
CNS Stimulation	0	1	0
RESPIRATORY SYSTEM	4	1	3 ^a
Pharyngitis	2	1	3
Pneumonia	2	0	0
Rhinitis	0	0	1
SKIN AND APPENDAGES	0	1	5
Rash	0	1	5
SPECIAL SENSES	0	0	1
Otitis Externa	0	0	1
UROGENITAL SYSTEM	0	0	1
Urinary Tract Infection	0	0	1

^a The total number for each body system may be less than the number of patients in that body system total because a patient can have ≥ 1 adverse event per system.

Reviewers' note: There are no surprises in this list. It appears that cefdinir has adverse events similar in profile to other cephalosporins. Diarrhea is prominent; this is not unexpected.

Deaths: There were no deaths in this study.

Clostridium difficile-Associated Diarrhea: Twenty-seven patients (8 in the cefdinir QD group, 10 in the cefdinir BID group, and 9 in the amox/clav group) discontinued treatment due to diarrhea. None of the investigators considered an episode of diarrhea to be indicative of pseudomembranous colitis. Therefore, only 2 of these patients were tested for *C. difficile* and neither was positive. All 27 patients recovered from their diarrhea by study completion.

Reviewers' note: It is unfortunate that more patients were not tested. However, cefdinir appears to have a diarrhea profile comparable, and not worse, than the amoxicillin clavulanate arm.

Table 48. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline*

[Number (%) of Patients]					
Parameter	Direction of Change	Cefdinir		Amox/Clav	
		QD N = 246	BID N = 251	N = 248	
Hematology					
Hemoglobin	Decrease	3 (1.2)	0 (0.0)	0 (0.0)	
Hematocrit	Decrease	4 (1.6)	2 (0.8)	0 (0.0)	
Erythrocytes	Decrease	0 (0.0)	1 (0.4)	0 (0.0)	
White Blood Cells	Increase	2 (0.8)	2 (0.8)	2 (0.8)	
	Decrease	2 (0.8)	0 (0.0)	4 (1.6)	
Polymorphonuclear Neutrophils	Increase	2 (0.8)	2 (0.8)	1 (0.4)	
	Decrease	2 (0.8)	2 (0.8)	1 (0.4)	
Lymphocytes	Increase	4 (1.6)	2 (0.8)	4 (1.6)	
	Decrease	2 (0.8)	1 (0.4)	1 (0.4)	
Eosinophils	Increase	5 (2.0)	7 (2.8)	4 (1.6)	
Basophils	Increase	1 (0.4)	0 (0.0)	0 (0.0)	
Platelets	Increase	3 (1.2)	6 (2.4)	3 (1.2)	
Blood Chemistry					
Glucose, Random	Decrease	9 (3.7)	4 (1.6)	9 (3.6)	
Blood Urea	Increase	1 (0.4)	0 (0.0)	0 (0.0)	
Alkaline Phosphatase	Increase	9 (3.7)	12 (4.8)	10 (4.0)	
Bilirubin	Increase	0 (0.0)	0 (0.0)	1 (0.4)	
Lactate Dehydrogenase	Increase	40 (16.3)	33 (13.1)	36 (14.5)	
Aspartate Aminotransferase	Increase	1 (0.4)	0 (0.0)	0 (0.0)	
Alanine Aminotransferase	Increase	2 (0.8)	0 (0.0)	0 (0.0)	
Gamma Glutamyl Transferase	Increase	0 (0.0)	2 (0.8)	1 (0.4)	
Sodium	Increase	1 (0.4)	0 (0.0)	1 (0.4)	
	Decrease	0 (0.0)	1 (0.4)	0 (0.0)	
Potassium	Increase	7 (2.9)	9 (3.6)	10 (4.0)	
	Decrease	0 (0.0)	0 (0.0)	1 (0.4)	
Phosphorus	Increase	14 (5.7)	12 (4.8)	14 (5.7)	
	Decrease	3 (1.2)	4 (1.6)	4 (1.6)	
Chloride	Increase	0 (0.0)	0 (0.0)	1 (0.4)	
Bicarbonate	Increase	0 (0.0)	0 (0.0)	1 (0.4)	
	Decrease	2 (0.8)	0 (0.0)	3 (1.2)	
Urinalysis					
Protein	Increase	1 (0.4)	1 (0.4)	1 (0.4)	
Glucose	Increase	0 (0.0)	0 (0.0)	2 (0.8)	
White Blood Cells	Increase	2 (0.8)	2 (0.8)	2 (0.8)	
Red Blood Cells	Increase	1 (0.4)	2 (0.8)	0 (0.0)	
Urine pH	Increase	2 (0.8)	1 (0.4)	0 (0.0)	
Urine Specific Gravity	Increase	5 (2.0)	5 (2.0)	7 (2.8)	
	Decrease	0 (0.0)	2 (0.8)	0 (0.0)	
Any Parameter^b		81 (32.9)	81 (32.3)	91 (36.7)	

* The first posttherapy visit was typically the STFU visit.

^b Total number of patients in a treatment group experiencing a markedly abnormal laboratory value (more abnormal than at baseline) regardless of the laboratory parameter.

Reviewers' note: The changes in laboratory parameters are comparable by treatment arm. The lactate dehydrogenase increase appears unusual, but nothing else is remarkable. This can be more fully evaluated in the integrated safety summary.

Conclusions for studies 983-10 and 983-11:

The data from study 983-10 is problematic: the sample size is smaller than calculated for and the study does not meet 80% power. The cure rates overall are disappointingly low, but other applications have demonstrated similar dismal cure rates. However, the data, when analyzed several ways, suggests that response rates, both microbiologic and clinical, are therapeutically equivalent among the cefdinir QD, cefdinir BID and amoxicillin/clavulanate arms. There is enough isolates to demonstrate efficacy against *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta-lactamase producing strains) and *Moraxella catarrhalis*.

The data from study 983-11 involves clinical cure only. This adequately powered study supports the therapeutic equivalence of the three treatment arms with good cure rates.

Studies 983-10 and 983-11 revealed no surprises with respect to adverse events. The profile of cefdinir is similar to other cephalosporins with diarrhea being prominent. The integrated safety review for the suspension formulation will determine the adequacy of the Sponsor's label with respect to adverse events.

Recommendations: That cefdinir suspension be labeled for efficacy against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the treatment of AOM at the dose of 14 mg/kg QD for 10 days and 7 mg/kg BID for 10 days.

That the Sponsor's labeling with respect to safety be accepted; this will be determined by the integrated safety review of the suspension formulation.

/S/

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Concurrence:

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cc: Orig NDAs 50-739 & 50-740

HFD-520/Division File
HFD-520/CSO BDuvall-Miller
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague
HFD-520/Pharm/FPelsor
HFD-520/MO/HHamilton
HFD-520/TL/JSoreth
HFD-725/Stat/AChakravarty
HFD-725/Stat/TL/DLin

**Medical Officer's Review of New Drug Application
for Acute Maxillary Sinusitis**

NDA: 50-739, 50-749

SPONSOR: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company

Date of Submission: 3 September 1997

CDER Stamp Date: 4 September 1997

Date of Assignment: 1 November 1996

Date of First Draft: 1 June 1997

Date of Final Draft: 1 July 1997; 30 June 1999

Materials submitted with application:

1. Parke-Davis CANDA for Cefdinir
2. NDA 50-739, Vols. No. 197-232
3. Diskette with file sinusitis2.doc, study 983-006, acute maxillary sinusitis
4. Diskette with file sinusitis reanalysis summary

Proposed INDICATION AND USAGE section (pertinent to sinusitis):

Acute Maxillary Sinusitis caused by susceptible strains of *Haemophilus influenzae* (including β -lactamase producing strains), *Haemophilus parainfluenzae* (including β -lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains), *Staphylococcus aureus* (methicillin-susceptible strains), *Moraxella catarrhalis* (including β -lactamase producing strains), *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pyogenes*.

Proposed DOSAGE AND ADMINISTRATION section (pertinent to sinusitis):

Capsules

The recommended dosage and duration of treatment for various infections in adults and adolescents are described in the following chart; the total daily dose for all infections is 600 mg. OMNICEF may be taken without regard to meals.

Adults and Adolescents (Age 13 Years and Older)

Type of Infection	Dosage	Duration
Acute Maxillary Sinusitis	300 mg q12h	10 days
	or 600 mg q24h	10 days

INTRODUCTION

The following is excerpted from the sponsor's introductory comments:

Sinusitis is a common disorder of both adults and children and can lead to potentially life-threatening complications such as epidural or subdural empyema, brain abscess, or cavernous sinus thrombosis. Therefore, early diagnosis and effective antimicrobial therapy are crucial. The bacterial etiology of sinusitis can only be determined by sinus aspiration, a procedure considered invasive and not routinely performed. Therapy is usually empirically selected based on the most likely pathogen(s) involved. Because the incidence of β -lactamase-producing strains among respiratory pathogens is rising, commonly used agents such as ampicillin and amoxicillin are becoming increasingly ineffective. Unfortunately, agents that are resistant to β -lactamase activity are often associated with unpleasant side effects. Thus, the development of drugs that are stable in the presence of β -lactamase and are well-tolerated is of considerable importance.

Cefdinir (CI-983, PD 134393, FK 482) is a semisynthetic, extended-spectrum cephalosporin antibiotic intended for use in the treatment of mild to moderate bacterial infections. Cefdinir acts by inhibiting cell-wall synthesis and is highly stable in the presence of β -lactamase enzymes. As a result, many β -lactamase-producing organisms that confer resistance to penicillins and to some cephalosporins are susceptible to cefdinir.

Cefdinir is active in vitro against organisms commonly associated with sinus infections, including *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, *Streptococcus pyogenes*, anaerobic gram-positive cocci, and many other gram-negative bacteria. Phase 2/3 studies have shown clinical efficacy of cefdinir and other cephalosporins in the treatment of patients with acute and chronic sinusitis.

The sponsor has conducted two active-controlled trials (#983-36 and 983-37) comparing cefdinir (600mg daily) to amoxicillin/clavulanate (Augmentin®) (500/125 mg TID) in the treatment of adults with acute maxillary sinusitis. The trials were identical in rationale, design, and objectives with one important difference: in #983-36, some patients consented to sinus puncture, while others did not; in #983-37, it was required of all patients to undergo sinus puncture at study entry.

TRIAL # 983-6**OBJECTIVE/RATIONALE**

The objective of this study was to evaluate the efficacy and safety of two 10-day dosage regimens of cefdinir (600 mg QD or 300 mg BID) versus a 10-day regimen of amoxicillin/clavulanate (amox/clav; Augmentin®) (500/125 mg TID) in the treatment of adult patients with acute maxillary sinusitis.

STUDY DESIGN

This was an investigator-blinded, randomized, comparative, multi center study with 3 parallel-treatment groups. Patients with acute maxillary sinusitis were randomly assigned to receive either cefdinir QD, cefdinir BID, or amox/clav TID for 10 days. The protocol specified a treatment group ratio of 1:1:1. The protocol and Case Report Forms (CRFs) specified that the test-of-cure (TOC) visit was to occur during the 7- to 14-day post-therapy interval and the long-term follow-up (LTFU) visit during the 21- to 35-day post-therapy interval. However, patients who began BID or TID treatment in the afternoon or evening of Day 1 did not complete therapy until Day 11. Therefore, a TOC visit scheduled for Study Day 17 corresponded to Day 6 post-therapy. For purposes of analysis, the TOC window was widened to 6 to 15 days post-therapy to include these patients.

The study was designed to enroll both patients who did, and patients who did not, consent to undergo a sinus puncture at baseline (for the purpose of pathogen isolation). Patients who did not have a sinus puncture were potentially clinically evaluable only, whereas, patients who *did* have a baseline sinus puncture were potentially microbiologically and clinically evaluable. When adequate enrollment of clinically evaluable patients was achieved (i.e., met and surpassed the required number designated in the protocol), study centers were provided written notification that, beginning January 15, 1993, only patients who consented to a baseline sinus puncture were to be enrolled.

STUDY MANAGEMENT

Forty-two centers in the United States participated in this study, which was monitored by Parke-Davis Pharmaceutical Research. Investigators met to review the protocol on April 5, 1992. Identical protocols and case report forms were used by all centers. The study was conducted under the Good Clinical Practice Guidelines. Institutional review board approvals and written informed patient consents were obtained from each center prior to patient enrollment.

Amendment 1 required that magnesium- or aluminum-containing antacids should be withheld for 2 hours before and after study drug dosing. This amendment applied to all active centers. Addendum A was implemented to further characterize the pharmacokinetics of cefdinir in

patients with acute maxillary sinusitis. This addendum applied only to Centers 5, 20, 26, and 33. The pharmacokinetic results are reported separately in RR-MEMO 764-02163.

There were no intentional code breaks in this study. Center 30 inadvertently used the investigator's copy of the randomization code card for dispensing drug. However, this did not constitute a true code break, and the investigator blinding was not compromised. The blind was broken on March 16, 1995.

A total of 1229 patients entered the study and 1109 patients (90%) completed treatment (Table 1). The first patient began treatment on May 21, 1992, and the last patient completed the last follow-up visit on August 4, 1994. Clinical laboratory and microbiologic data were measured by a central laboratory.

Medical Officer's Comments:

The medical officer agreed with the design and management of the study as appropriate for testing cefdinir against standard comparator therapy for acute maxillary sinusitis.

TABLE 1. List of Investigators

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Clinically Evaluable ^a
1	J. Applegate	13	9	8
2	C. Banov	27	25	26
3	S. Barton	4	4	3
4	S. Chartrand	4	4	4
5	R. Chiulli	35	28	28
6	M. Dennington	79	73	62
7	R. Slavin	9	9	7
8	D. Dvorin	11	10	6
9	S. Goldstein	6	5	4
10	W. Gooch III	59	58	51
11	G. Handley	18	11	11
12	H. Harris	18	14	16
13	J. Hedrick	36	35	33
14	S. Hirsch	61	57	50
15	J. Johnson	1	1	1
16	J. Klimas	4	2	1
17	M. Lawrence	12	11	9
18	T. Littlejohn III	42	39	37
19	H. Loveless	21	18	13

Table 1
(continued)

20	J. McCarty	63	59	54
21	D. McCluskey	22	18	18
23	R. Nielsen	68	64	60
24	D. Pearlman	1	0	0
25	A. Puopolo	33	27	23
26	J. Scott	39	36	35
27	J. Salisbury	48	45	39
28	W. Schoenwetter	12	12	10
29	G. Shapiro	35	35	31
30	S. Wiederhold	43	34	32
33	S. Weakley	17	17	16

* Included in clinically evaluable patient analyses at TOC

TABLE 1. List of Investigators
(Continued)

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Clinically Evaluable*
34	S. Weisberg	2	2	2
35	A. Shah	12	11	9
36	J. Gwaltney	75	72	63
38	R. Fiddes	116	94	81
39	R. Gore	2	2	1
41	N. Garrison	48	43	37
42	R. Ziering	23	20	19
43	A. Goforth	36	35	35
46	P. Obert	6	5	4
48	K. Gien-Gia Hoang	18	18	13
50	R. Schwartz	29	28	16
Total		1229	1109	982

- * Included in clinically evaluable patient analyses at TOC

Materials

Cefdinir capsules and amox/clav tablets were packaged and provided by Parke-Davis Pharmaceutical Research (Table 2).

TABLE 2. Study Medication

	Lot	Formulation
Cefdinir 300-mg Capsules	CM 080051 9	134393-25
	CM 086051 9	134393-25
	CM 106061 9	134393-25
	CM 1781292 9	134393-25
Amox/Clav '500' mg Tablets	TB2616 9	Marketed
	TM2947 9	Marketed
	TS0111 9	Marketed
	WR0924 9	Marketed

Drug Administration

Study medications were administered orally on a QD, BID, or TID schedule and were taken without regard to meals (Table 3). To maintain investigator blinding, medications were dispensed by a third party and all records concerning medication information were kept in a separate location. Additionally, patients were instructed not to reveal the dose regimen or formulation of study medication to the investigator.

TABLE 3. Dosing Schedule

Treatment Group	Dose (Number of Capsules or Tablets)		
	Morning	Afternoon	Evening
Cefdinir QD	2 × 300 mg	None	None
Cefdinir BID	1 × 300 mg	None	1 × 300 mg
Amox/Clav TID	1 × 500 mg	1 × 500 mg	1 × 500 mg

Methods of Assigning Patients to Treatment

An independent randomization schedule was prepared for each center. A block size of 6 patients was used, with 2 treatment replicates per block, consistent with the protocol-specified 1:1:1 treatment group ratio.

At each center, patients who met the entry criteria at screening were assigned the next consecutive patient number according to the randomization schedule and were dispensed the corresponding study medication. The patient number and dose regimen were preprinted on each package of study medication; the treatment group and total daily dose were recorded on the appropriate case report form by the third party who dispensed the medication (not the investigator).

Inclusion Criteria

Eligible patients were:

- at least 13 years of age,
- either males or nonpregnant, nonlactating females who were unable or unlikely to become pregnant during treatment (postmenopausal, surgically sterilized, sexually inactive, or using barrier or hormonal method of birth control),
- were to be diagnosed with acute maxillary sinusitis (current episode ≤ 4 weeks duration) confirmed by x-ray, and present with purulent nasal discharge and localized facial pain.

Exclusion Criteria

Patients were excluded from the study if they had:

- Chronic maxillary sinusitis or a primary diagnosis of acute or chronic frontal or ethmoid sinusitis;
- Complicating factors or diseases that precluded evaluation of response to study medication;
- Indwelling nasogastric tubes or drains;
- Hepatic disease, obstruction of the biliary tract, or hepatic enzyme levels >2 times the upper limit of normal;
- Serum creatinine >1.5 times the upper limit of normal or creatinine clearance <30 mL/min;
- Hypersensitivity to β -lactam drugs;
- A concomitant infection requiring systemic antimicrobial therapy or local intranasal antibiotics;
- Received any other investigational drug within the 4 weeks prior to this study;
- Received cefdinir at any previous time; or
- Received another systemic or intranasal antibiotic within 48 hours or <5 of the prior antibiotic's half-lives before the first dose of study medication.

Medical Officer's Comments

The medical officer agreed with the inclusion and exclusion criteria established for the study.

Prohibited Medications or Precautions

Concurrent treatment with other systemic antibiotics, local intranasal antibiotics, or probenecid was not allowed during the study. Probenecid has been reported to inhibit renal tubular secretion of concomitantly administered cefdinir, resulting in a 50% increase in the elimination half-life.⁽¹⁵⁾

Concurrent dietary iron supplements, including iron-containing multivitamins, were also not allowed. This was because of concerns that the bioavailability of cefdinir may be decreased following formation of a nonabsorbable cefdinir-iron complex in the gastrointestinal tract.⁽¹⁶⁾

Magnesium- or aluminum-containing antacids were to be withheld 2 hours before and after study-drug dosing.

Antihistamines, oral and topical steroids, and nasal decongestants were discouraged but not prohibited.

Guidelines for Patient Withdrawal

Treatment could be discontinued early because of lack of efficacy, an adverse event, a laboratory abnormality, lack of compliance, or patient request. Patients could also be withdrawn from the study after completing treatment but before the LTFU visit. All patients who received at least 3 days of therapy were to have a complete physical examination, clinical assessment, clinical laboratory tests, and x-ray assessment at the time of withdrawal. These patients were also evaluated at the TOC and LTFU visits, provided they had received no additional antibacterial therapy in the interim.

Criteria for Evaluation**Efficacy**

Efficacy assessments were based on clinical and microbiologic responses at the TOC visit: clinical cure rate summarized by patient, microbiologic eradication rate summarized by pathogen, and microbiologic eradication rate summarized by patient. The LTFU visit provided information on recurrence of infection.

TABLE 4. Clinical Observations and Laboratory Measurements

	Baseline ^a	Day 1	Days 3 to 5	Day 10	Posttherapy Visits	
					Days 6-15 ^b	Days 21-35 ^c
Medical History	X					
Physical Examination ^d	X				X	X
Clinical Assessment of Disease ^d	X		X		X	X
Clinical Laboratory Tests ^{d,e}	X				X	X ^f
Efficacy Assessment ^d					X	X
Sinus X-Ray ^d	X				X	X
Sinus Aspiration	X ^g				X ^h	X ^h
Adverse Events		X				X
Dosing		X		X		

^a Forty-eight hours prior to start of therapy

^b Test-of-cure (TOC) visit

^c Long-term follow-up (LTFU) visit

^d Perform also after early withdrawal

^e Hematology, blood chemistry, urinalysis, and a baseline pregnancy test for women of childbearing potential

^f If abnormalities detected at the TOC or early termination visits

^g Optional prior to January 15, 1993.

^h Only 1 posttherapy aspiration was requested for those patients who had a culture-positive baseline aspirate and who were not showing satisfactory (or continuing satisfactory for LTFU) clinical improvement.

Clinical Response

The clinical signs and symptoms in this study were purulent nasal discharge, localized facial pain, localized tenderness, nasal obstruction, headache, alteration of smell, and fever ($>100.4^{\circ}\text{F}$ or $>38^{\circ}\text{C}$). The clinical response for each patient was assessed separately by the investigator and the sponsor. The investigator assessment of clinical response rate was defined as the percentage of patients cured or improved based on the investigator's opinion as to clinical outcome. The sponsor assessment of clinical response rate was defined as the percentage of patients cured and was based on a quantitative analysis of signs and symptoms, or clinical score (see Appendix A.4). In the original protocol, the sponsor assessment also included an Improved category, but in subsequent discussions with FDA Parke-Davis agreed to delete this category and response criteria were redefined to accommodate this change (Table 5).

TABLE 5. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU^{a,b}

Sponsor Assessment at TOC	Investigator Assessment at TOC			
	Cure	Improvement	Failure	Not Assessable
Cure	Cure	Cure	Failure	Cure
Failure	Cure	Failure	Failure	Failure
Not Assessable	Cure	Not Assessable	Failure	Not Assessable

Sponsor Assessment at LTFU	Investigator Assessment at LTFU			
	Cure	Improvement	Recurrence	Not Assessable
Cure	Cure	Cure	Recurrence	Cure
Failure	Cure	Failure	Recurrence	Failure
Recurrence	Cure	Recurrence	Recurrence	Recurrence
Not Assessable	Cure	Not Assessable	Recurrence	Not Assessable

^a The combined assessments are shown in bold typeface.

^b If a patient had a combined clinical assessment of failure at TOC, the patient was automatically a failure on both the sponsor and combined assessment scales at LTFU, regardless of any subsequent assessments.

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Microbiological Response

The microbiologic eradication rate by pathogen was defined as the percentage of eradicated baseline pathogens. Patients with multiple pathogens provided multiple observations in the analyses of microbiologic efficacy on a per pathogen basis. The microbiologic eradication rate by pathogen was calculated separately for the TOC and LTFU visit data. Pathogens could be cultured from 1 or both sinuses. The sinus side (right or left) from which each pathogen was obtained was recorded. If the same pathogen was isolated from both sinuses, they were counted as multiple pathogens.

For patients who underwent antral puncture for the culture of a baseline pathogen, the microbiologic response of each baseline pathogen was defined as:

- **Eradication:** Pathogen not present in follow-up culture from baseline side *or* no follow-up culture performed from baseline side but patient assessed as a clinical cure on baseline side (presumed eradication);
- **Persistence:** Pathogen present in follow-up culture from baseline side *or* no follow-up culture performed from baseline side but patient assessed as a clinical failure/recurrence on baseline side (presumed persistence); *or*
- **Not Assessable:** No proven baseline pathogen *or* no follow-up data on baseline side.

Microbiologic Response by Patient

The microbiologic eradication rate by patient was defined as the percentage of patients with eradication of all baseline pathogens. Each patient provided only 1 observation. The microbiologic eradication rate was calculated separately for the TOC and LTFU visits.

At the TOC visit, patients with a positive baseline culture were classified according to their overall microbiologic response based on baseline and 6- to 15-days posttherapy results:

- **Eradication:** All baseline pathogens eradicated at TOC *or* no TOC culture performed and presumed eradication;
- **Persistence:** Persistence of at least 1 baseline pathogen at TOC *or* no TOC culture performed and presumed persistence; *or*
- **Not Assessable:** No proven baseline pathogen *or* no baseline signs/symptoms *or* no follow-up clinical data.

At the LTFU visit, patients with a positive baseline culture were classified according to their overall microbiologic results based on baseline, 6- to 15-days posttherapy, and 21- to 35-days posttherapy results.

- **No Relapse:** Patients with eradication or presumed eradication of all baseline pathogens at TOC *and* continued eradication or presumed eradication of all baseline pathogens at LTFU;
- **Relapse:** Patients with eradication or presumed eradication at TOC *and* persistence *or*

- presumed persistence of at least 1 baseline pathogen at LTFU;
- **Persistence:** ~~All patients with persistence at TOC or no TOC culture and presumed persistence; or~~
 - **Not Assessable:** No proven baseline pathogen *or* no baseline signs/symptoms/ *or* no follow-up clinical data.

Summaries and analysis populations examined in this report are: a clinically evaluable population, a population of patients who were both microbiologically and clinically evaluable, a modified intent-to-treat (MITT) population, and an intent-to-treat (ITT) population.

Clinically Evaluable Population

Patients in the clinically evaluable population had the correct indication as documented by sinus imaging results and the minimum required clinical signs and symptoms at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy for other concurrent infections; did not take a prior systemic antibacterial within 48 hours prior to the first dose of study medication; had their clinical assessments of signs and symptoms performed within the TOC window; and did not have a randomization violation, resistant baseline pathogen, or a condition preventing clinical evaluation. Patients were not excluded from this data set due to having no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the TOC window specified in the protocol.

Microbiologically-Clinically Evaluable Population

The microbiologically-clinically evaluable patients had no known protocol violations that might have affected the efficacy assessments. Any of the protocol violations that resulted in exclusion from the clinically evaluable analyses plus missing microbiologic data at baseline, no proven baseline pathogen, or off-schedule cultures resulted in exclusion of patient data from the microbiologically-clinically evaluable patient analyses.

MITT Population

Patients in the MITT population had the correct indication as documented by sinus imaging results, received study medication, had at least 1 baseline pathogen, and had a follow-up culture or clinical assessment of signs and symptoms.

The ITT population

The ITT population were those patients randomized to treatment. Patients who had no baseline pathogen or no follow-up culture plus no follow-up clinical assessment were considered to have microbiologic persistence in the ITT analyses. Patients who had no follow-up clinical assessment were categorized as clinical failures in the ITT analyses.

Clinically qualified patients were clinically evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits, had a clinical assessment performed within the LTFU window, and did not develop any confounding infection between the TOC and LTFU visits. Microbiologically-clinically qualified patients also had to meet these criteria but

could be disqualified if they had the LTFU culture outside of the LTFU window.

Sample Size

An estimated sample size of 190 clinically evaluable patients per randomized group was required to provide at least 80% probability (power) of demonstrating the equivalence of clinical cure rates of cefdinir and amox/clav. An overall response rate of 90% and an equivalence threshold of $\pm 10\%$ were assumed to assess the equivalence of the cefdinir and amox/clav clinical cure rates at the TOC visit, using the two-tailed, 95% confidence interval method.

The efficacy objectives of this study were to estimate the clinical and microbiologic response rates of cefdinir QD, cefdinir BID, and amox/clav; and to evaluate the equivalence of the clinical response rates of cefdinir QD versus amox/clav, cefdinir BID versus amox/clav, and cefdinir QD versus cefdinir BID at the TOC visit, based on predefined fixed criteria.

The primary outcome measure was the clinical cure rate in the clinically evaluable patients at the TOC visit. Secondary outcome measures were the microbiologic eradication rate by pathogen and the microbiologic eradication rate by patient. No inferential analyses were performed on microbiologic eradication data. The primary analysis time point was the TOC visit; the LTFU visit was a secondary analysis time point. ~~Data from the LTFU visit were summarized and presented as supporting information.~~ No inferential analyses were performed on LTFU data.

Descriptive statistics used in this study consisted primarily of frequency counts and response rates. Means, standard errors, minima, maxima, and medians were used where appropriate.

At baseline, the demographic data, microbiologic results, clinical signs and symptoms, and some history data were summarized to facilitate baseline treatment group comparisons.

At TOC, the clinical cure rates and mean patient and sinus clinical signs/symptoms scores were calculated for each treatment group in the clinically evaluable, microbiologically-clinically evaluable, and ITT patient populations. The microbiologic eradication rates by pathogen and by patient were calculated for each treatment group in the microbiologically-clinically evaluable, MITT, and ITT patient populations.

At LTFU, the clinical cure rates (i.e., the "no recurrence" rates) and mean patient and sinus clinical signs/symptoms scores were calculated for each treatment group in the clinically qualified, microbiologically-clinically qualified, and ITT patient populations. The microbiologic eradication rates by pathogen and by patient (i.e., the "no relapse" rates) were calculated for each treatment group in the microbiologically-clinically qualified patient population.

Statistical Methods

Two methods of investigating treatment equivalence at TOC were used. One method was based

on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient in the analysis, and were calculated as the total number of cures in the study population, divided by the total number of cases.

The second method used a categorical modeling procedure to obtain center-adjusted estimates of the response rates and their standard errors. The model contained terms for study center, treatment group, and treatment-by-center interaction. The resulting parameter estimates were used to construct estimates of the treatment group response rates and standard errors in which each center was given equal weight.

Pairwise treatment differences were defined as cefdinir QD or BID minus amox/clav, and cefdinir QD minus cefdinir BID. The estimated response rate differences and their standard errors were used to construct a two-tailed, 95% confidence interval for each treatment difference, using a standard normal approximation⁽¹⁸⁾. Each 95% confidence interval was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the 2 rates (pooled or center-adjusted) under comparison (Table 7). To demonstrate equivalence, each 95% confidence interval must contain zero and its limits must fall within the indicated bounds.

TABLE 6. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate of the 2 Treatment Groups	Treatments Are Equivalent If 95% Confidence Interval for Treatment Difference Is Within Bounds
90% or greater	-10%, +10%
80% - 89%	-15%, +15%
- 70% - 79%	-20%, +20%

Results of the 2 methods were compared for consistency. When the 2 methods agreed, the pooled analysis was presented as the final analysis. If results from the 2 methods disagreed, the differences were addressed and results from both methods were presented. A side-by-side comparison of all results from the 2 analysis methods is shown in Appendix D.1.

An exploratory Cochran-Mantel-Haenzel (CMH) analysis adjusting for center was performed to look for possible treatment group differences in the clinical cure rates. Results of the Breslow-Day test were reviewed in evaluating the consistency of the relationship between treatment and response among centers.

For each statistical procedure adjusting for center, study centers contributing 12 or fewer patients, or 2 or fewer patients in any treatment group were pooled prior to analysis. Pooling was performed independently for each analysis population after any required data exclusions were made.

TABLE 7. Patient Characteristics - ITT Patients
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav		Total	
	QD N = 403	BID N = 412	N = 414		N = 1229	
Sex						
Male	150 (37.2)	148 (35.9)	155 (37.4)	453 (36.9)		
Female	253 (62.8)	264 (64.1)	259 (62.6)	776 (63.1)		
Race						
White	358 (88.8)	366 (88.8)	356 (86.0)	1080 (87.9)		
Hispanic	23 (5.7)	21 (5.1)	23 (5.6)	67 (5.5)		
Black	19 (4.7)	18 (4.4)	32 (7.7)	69 (5.6)		
Other ^a	3 (0.7)	6 (1.5)	3 (0.7)	12 (1.0)		
Age, yr						
Median	36	36	36	36		
Range	12-83	13-88	13-79	12-88		
Distribution						
6 to <13 ^b	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)		
13 to <18	32 (7.9)	31 (7.5)	33 (8.0)	96 (7.8)		
18 to <65	351 (87.1)	354 (85.9)	363 (87.7)	1068 (86.9)		
≥65	19 (4.7)	27 (6.6)	18 (4.3)	64 (5.2)		

^a Black/White mix, Caucasian/Tongan, Filipino, Hispanic, Jordanian, Native American, Oriental, Pakistan, Romanian, Spanish, Tongan

^b One patient was 12 years old at the start of the study.

**TABLE 8. Patient Exposure to Study Medication - All Patients
[Number of Patients]**

Days of Study Medication	Cefdinir		Amox/Clav N = 414
	QD N = 403	BID N = 412	
1	2	1	5
2	3	4	3
3	4	4	5
4	4	5	8
5	3	6	5
6	1	1	3
7	2	5	3
8	3	4	4
9	2	3	0
10	339	242	122
11	27	128	234
12	3	2	8
13	0	1	2
14	1	0	1
15	0	0	1
16	0	0	1
Median	10	10	11
Unknown*	8	6	8

* Includes 4 patients who received no study medication

Table 9. Selected Demographics, All Enrolled Patients (Intent-to-Treat Population)

Baseline Parameters	Cefdinir 600mg QD	Cefdinir 300 mg BID	Augmentin 500 mg TID
Age (years) med.	36.0	36.0	36.0
min.	12.0	13.0	13.0
max.	83.0	88.0	79.0
Weight (kg) med.	73.2	71.2	73.6
min.	40.0	43.2	36.4
max.	151.8	140.9	141.8
Height (cm) med.	167.6	167.6	167.6
min.	146.8	134.6	133.4
max.	203.2	198.1	198.1

Table 10. Selected Demographics, Clinically Evaluable Patients

Baseline Parameters	Cefdinir 600mg QD	Cefdinir 300 mg BID	Augmentin 500 mg TID
Age (years) med.	36.0	35.0	36.0
min.	12.0	13.0	13.0
max.	83.0	88.0	79.0
Weight (kg) med.	72.7	72.7	72.7
min.	40.0	43.2	36.4
max.	151.8	140.9	141.8
Height (cm) med.	167.6	167.6	167.6
min.	148.1	134.6	133.4
max.	203.2	198.1	198.1

Table 11. Selected Demographics, Microbiologically-Clinically Evaluable Patients

Baseline Parameters	Cefdinir 600mg QD	Cefdinir 300 mg BID	Amox./clav. 500 mg TID
Age (years) med.	36.0	36.0	36.0
min.	13.0	13.0	14.0
max.	83.0	88.0	72.0
Weight (kg) med.	76.6	72.3	76.4
min.	40.5	43.2	51.4
max.	143.2	113.6	141.8
Height (cm) med.	170.2	170.2	168.9
min.	152.4	146.3	152.4
max.	203.2	193.0	188.0

Medical Officer's Comment

The comparison of demographic characteristics between ITT patients, clinically-evaluable patients, and microbiologically-clinically evaluable patients show no significant differences in the median age, weight, or stature between treatment groups or between populations for analysis. The median stature of the patients in the Cefdinir treatment groups of the microbiologically-clinically evaluable population was about 2.4 cm taller than the median stature of those treatment groups in the ITT and the clinically evaluable population. The median stature of the patients in the Augmentin treatment group of the microbiologically-clinically evaluable population was about 1.3 cm taller than the median stature of that treatment groups in the ITT and the clinically evaluable population.

Clinical Signs and Symptoms

Sixteen patients (1%) had no baseline nasal discharge and 33 patients (3%) had no baseline facial pain. Only 2 patients (Patient 13, Center 21 and Patient 264, Center 36) were missing both of these signs/symptoms at baseline. Most patients entered the study with facial tenderness and nasal obstruction on at least one side, and also had headache and alteration of smell. Only 2% of patients had a fever at baseline. There were no apparent differences in baseline signs and symptoms between treatment groups, or between the ITT, clinically evaluable, and microbiologically-clinically evaluable patient populations (Table 13).

**TABLE 12. Signs and Symptoms at Baseline
(Percent of Patients)**

	ITT Patients N = 1229	Clinically Evaluable Patients N = 977	Microbiologically-Clinically Evaluable Patients N = 242
Patient Signs and Symptoms			
Headache	87	87	82
Alteration of Smell	60	61	60
Fever	2	2	3
Sinus Signs and Symptoms			
Left Purulent Nasal Discharge	90	90	89
Right Purulent Nasal Discharge	88	89	86
Left Facial Pain	86	86	82
Right Facial Pain	85	86	81
Left Facial Tenderness	76	76	73
Right Facial Tenderness	75	75	71
Left Nasal Obstruction	85	85	85
Right Nasal Obstruction	83	84	82

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TABLE 13. Distribution of Patients by Baseline Pathogen - All
Patients With Baseline Pathogens
(Number of Patients)

Baseline Pathogen	Cefdinir		Amox/Clav N = 414 ^a
	QD	BID	
	N = 403 ^a	N = 412 ^a	
Gram-Positive			
<i>Staphylococcus aureus</i>	12	19	8
<i>Staphylococcus epidermidis</i>	0	0	1
<i>Staphylococcus salivarius</i>	0	1	0
<i>Streptococcus agalactiae</i>	1	0	2
<i>Streptococcus anginosus</i>	2	2	0
<i>Streptococcus equi</i>	1	0	0
<i>Streptococcus equisimilis</i>	0	2	1
<i>Streptococcus pneumoniae</i>	19	21	17
<i>Streptococcus pyogenes</i>	4	1	5
<i>Streptococcus</i> Group G	0	1	0
Gram-Negative			
<i>Citrobacter diversus</i>	0	0	1
<i>Enterobacter aerogenes</i>	1	1	1
<i>Escherichia coli</i>	1	1	2
<i>Eikenella corrodens</i>	1	0	0
<i>Haemophilus influenzae</i>	16	15	21
<i>Haemophilus parahaemolyticus</i>	0	1	1
<i>Haemophilus parainfluenzae</i>	2	5	6
<i>Klebsiella pneumoniae</i>	1	0	2
<i>Moraxella catarrhalis</i>	10	9	9
<i>Morganella morganii</i>	1	0	0
<i>Neisseria meningitidis</i>	1	0	0
<i>Proteus mirabilis</i>	0	0	1
Multiple^b	25	22	33
Total^c	98	101	111

^a Number of patients randomized to treatment.

^b See Appendix C.4, Vol. 198, NDA 50-739, for a complete summary.

^c Patients with baseline pathogens.

Clinical Outcome Evaluation by Medical Officer

A random sampling of ten percent of the patients from each treatment arm of the study was made. Among the random sample of forty (40) patients of the treatment group receiving Cefdinir 600 mg q.d., there were two patients whose sponsor-designated outcome the medical officer disputed. One was deemed a failure by sponsor, but a cure by medical officer (site 13, patient 11). The other was deemed a cure by the sponsor and a failure by the medical officer (site 18, patient 223). The medical officer questioned but did not absolutely disagree with the outcomes for five of the patients deemed cures by the sponsor. Among the random sample of forty-one (41) patients of the treatment group receiving Cefdinir 300 mg b.i.d., there were five patients whose sponsor-designated outcome the medical officer questioned. Three of these were deemed failures by the sponsor. The medical officer deemed site 10, patient 211 and site 21, patient 8 each to have a good clinical response. The medical officer would have excluded site 30, patient 6 at the outset for lack of findings on sinus radiographs. The sponsor deemed site 43, patient 225 a cure, and although this patient was not deemed "cured" by the investigator, the combined investigator/sponsor clinical assessment of "cured" was within the protocol's rules for clinical assessment.

Among the random sample of forty-one (41) patients of the treatment group receiving Amoxicillin/clavulanate 500 mg t.i.d., there were twelve patients whose sponsor-designated outcome the medical officer questioned. Six of the twelve were deemed failures and six were deemed cures by the sponsor. Any effect of disputed interpretation should have been canceled by the equal numbers of questioned outcomes.

Assuming that the random ten percent samplings accurately reflect the validity of the sponsor's assessments overall, the sponsor's evaluation of clinical efficacy can be reviewed.

Table 14. Patients by Treatment Arm and by Analysis Population.

	Cefdinir QD	Cefdinir BID	Amox/Clav	Total (%)
Enrolled (ITT)	403	412	414	1229 (100%)
Clinically Evaluable	323	326	333	982 (79.9%)
Micro-Clinically Evaluable	74	79	89	242 (19.7%)

Table 15. Clinical and Microbiologic/Clinical Outcomes.

Clinically Cured: at TOC at LTFU	233/323 (72%) 182/209 (87%)	240/326 (74%) 184/212 (87%)	248/333 (74%) 189/216 (88%)	721/982 (73%) 555/637 (87%)
Micro/Clin Cured at LTFU	43/49 (88%)	48/56 (86%)	57/66 (86%)	148/171 (87%)

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TABLE 16. Patient Characteristics - Clinically Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir				Amox/Clav N = 333		Total N = 982	
	QD N = 323		BID N = 326					
Sex								
Male	124	(38.6)	119	(36.5)	127	(38.4)	370	(38.1)
Female	199	(61.6)	207	(63.5)	206	(61.9)	612	(62.3)
Race								
White	292	(90.4)	291	(89.3)	285	(85.6)	868	(88.4)
Hispanic	18	(5.6)	18	(5.5)	20	(6.0)	56	(5.7)
Black	13	(4.0)	10	(3.1)	26	(7.9)	49	(5.0)
Other ^a	0	(0.0)	6	(1.8)	2	(0.6)	8	(0.8)
Age, yr								
Median	36		35		36		36	
Range	12-83		13-88		13-79		12-88	
Distribution								
6 to <13 ^b	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
13 to <18	28	(8.7)	26	(8.0)	26	(7.8)	80	(8.1)
18 to <65	278	(86.1)	278	(85.3)	292	(87.7)	848	(86.4)
≥65	16	(5.0)	22	(6.7)	15	(4.5)	53	(5.4)

^a Caucasian/Tongan, Hispanic, Jordanian, Native American, Oriental, Pakistan, Romanian, Spanish

^b One patient was 12 years old at the start of the study.

Medical Officer's Comments

Clinical cure rates were similar between both Cefdinir treatment arms, and both were comparable to the Augmentin treatment arm. Clinical cure rates were comparable both with and without the patients from site 38 included in the analysis. There was a slightly higher rate of clinical cure with the regimen of Cefdinir 600 mg qd versus Cefdinir 300 mg bid in the analysis excluding site 38 (67.5% versus 63.7%), but the difference was not statistically significant.

Table 17. Statistical Comparisons of Clinically Evaluable Patients by Treatment Arms.

	Cefdinir QD	Cefdinir BID	Amox/Clav
Clinical Response Rates			
All Sites	72.1% (233/323)	73.6% (240/326)	74.5% (248/333)
Excluding Site 38	72.0% (216/300)	70.8% (209/295)	72.5% (222/306)

	Cefdinir QD vs. Amox/Clav		Cefdinir BID vs. Amox/Clav	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
All Sites	(-9.1%, 4.4%)	0.677	(-7.6%, 5.8%)	0.817
Excluding Site 38	(-7.7%, 6.7%)	0.925	(-8.9%, 5.5%)	0.739

	Cefdinir QD vs. Cefdinir BID	
	Unadjusted 95% CI	CMH p-value
All Sites	(-8.3%, 5.4%)	0.792
Excluding Site 38	(-6.1%, 8.4%)	0.706

Table 18. Statistical Comparisons of ITT Patients by Treatment Arms.

	Cefdinir QD	Cefdinir BID	Amox/Clav
Clinical Response Rates			
All Sites	67.0% (270/403)	66.0% (272/412)	68.8% (285/414)
Excluding Site 38	67.5% (247/366)	63.7% (237/372)	68.5% (257/375)

	Cefdinir QD vs. Amox/Clav		Cefdinir BID vs. Amox/Clav	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
All Sites	(-8.2%, 4.6%)	0.597	(-9.2%, 3.6%)	0.375
Excluding Site 38	(-7.8%, 5.7%)	0.793	(-11.6%, 2.0%)	0.156

	Cefdinir QD vs. Cefdinir BID	
	Unadjusted 95% CI	CMH p-value
All Sites	(-5.5%, 7.5%)	0.737
Excluding Site 38	(-3.1%, 10.6%)	0.261

Confirmed Microbiologic Diagnosis and Baseline Susceptibility

At the baseline visit, 45% (547/1229) of patients randomized to treatment underwent a sinus aspiration. Of these, 57% (310/547) had a confirmed baseline pathogen(s). The most common single pathogens were *Streptococcus pneumoniae* (57 patients), *Haemophilus influenzae* (52 patients), *Staphylococcus aureus* (39 patients), and *Moraxella catarrhalis* (28 patients). Multiple pathogens were cultured from 80 patients (Table 11).

A total of 405 pathogens were isolated at baseline (Table 12). Of these, 16 isolates were resistant to cefdinir and 17 were resistant to amox/clav. Of *H. influenzae* isolates with documented β -lactamase results 34/80 (43%) were β -lactamase positive; none were resistant to cefdinir and 1 was resistant to amox/clav. Except for 1 isolate that had intermediate susceptibility to cefdinir, all β -lactamase-negative *H. influenzae* isolates were susceptible to both study drugs (1 isolate had unknown susceptibility to both drugs). A total of 40/44 (91%) of *M. catarrhalis* isolates with β -lactamase results were β -lactamase positive; none were resistant to either cefdinir or amox/clav. All β -lactamase-negative *M. catarrhalis* isolates were also sensitive to both study drugs.

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TABLE 19. Distribution of Patients by Baseline Pathogen - All
Patients With Baseline Pathogens
(Number of Patients)

Baseline Pathogen	Cefdinir		Amox/Clav N = 414 ^a
	QD N = 403 ^a	BID N = 412 ^a	
Gram-Positive			
<i>Staphylococcus aureus</i>	12	19	8
<i>Staphylococcus epidermidis</i>	0	0	1
<i>Staphylococcus salivarius</i>	0	1	0
<i>Streptococcus agalactiae</i>	1	0	2
<i>Streptococcus anginosus</i>	2	2	0
<i>Streptococcus equi</i>	1	0	0
<i>Streptococcus equisimilis</i>	0	2	1
<i>Streptococcus pneumoniae</i>	19	21	17
<i>Streptococcus pyogenes</i>	4	1	5
<i>Streptococcus</i> Group G	0	1	0
Gram-Negative			
<i>Citrobacter diversus</i>	0	0	1
<i>Enterobacter aerogenes</i>	1	1	1
<i>Escherichia coli</i>	1	1	2
<i>Eikenella corrodens</i>	1	0	0
<i>Haemophilus influenzae</i>	16	15	21
<i>Haemophilus parahaemolyticus</i>	0	1	1
<i>Haemophilus parainfluenzae</i>	2	5	6
<i>Klebsiella pneumoniae</i>	1	0	2
<i>Moraxella catarrhalis</i>	10	9	9
<i>Morganella morganii</i>	1	0	0
<i>Neisseria meningitidis</i>	1	0	0
<i>Proteus mirabilis</i>	0	0	1
Multiple^b	25	22	33
Total^c	98	101	111

^a Number of patients randomized to treatment.

^b See Appendix C.4 for a complete summary.

^c Patients with baseline pathogens.

**TABLE 20. Patient Characteristics - Microbiologically-Clinically
Evaluable Patients**
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav N = 89	Total N = 242
	QD N = 74	BID N = 79		
Sex				
Male	33 (44.6)	37 (46.8)	35 (39.3)	105 (43.4)
Female	41 (55.4)	42 (53.2)	54 (60.7)	137 (56.6)
Race				
White	68 (91.9)	71 (89.9)	71 (79.8)	210 (86.8)
Hispanic	4 (5.4)	4 (5.1)	11 (12.4)	19 (7.9)
Black	2 (2.7)	2 (2.5)	7 (7.9)	11 (4.5)
Other ^a	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.4)
Age, yr				
Median	36	36	36	36
Range	13-83	13-88	14-72	13-88
Distribution				
13 to <18	4 (5.4)	5 (6.3)	3 (3.4)	12 (5.0)
18 to <65	66 (89.2)	69 (87.3)	79 (88.8)	214 (88.4)
≥65	4 (5.4)	5 (6.3)	7 (7.9)	16 (6.6)

^a Hispanic, Jordanian

Clinical Cure

For microbiologically-clinically evaluable patients, the clinical cure rate was 55/74 (74%) for the cefdinir QD group, 63/79 (80%) for the cefdinir BID group, and 76/89 (85%) for the amox/clav group. These rates were similar to those of clinically evaluable patients with a baseline sinus aspiration (see Section 6.2.1.1, Table 20).

Microbiologic Eradication by Pathogen

The microbiologic eradication rate by pathogen was 69/92 (75%) for the cefdinir QD group, 76/94 (81%) for the cefdinir BID group, and 100/118 (85%) for the amox/clav group. Because of the small number of microbiologically-clinically evaluable patients, no pairwise analyses are presented for the microbiologic eradication rates. These eradication rates were based primarily

on presumed eradication (i.e., if no follow-up sinus puncture was performed, microbiologic eradication was presumed based on clearing of clinical signs and symptoms). Of the pathogens considered eradicated, 58/69 (84%) in the cefdinir QD group, 70/76 (92%) in the cefdinir BID group, and 90/100 (90%) in the amox/clav group were presumed eradicated. There were no major differences between treatment groups in eradication rates according to pathogen (Table 21). Cefdinir QD treatment showed the highest eradication rate for *H. influenzae* (84% versus 71% to 73%), whereas cefdinir BID showed the highest eradication rate for *S. aureus* (85% versus 71% to 76%), and amox/clav showed the highest eradication rate for *S. pneumoniae* (96% versus 82% to 88%). Cefdinir BID had a lower eradication rate for *M. catarrhalis* (69%) than either cefdinir QD (92%) or amox/clav (91%).

The microbiologic eradication rates were 56/74 (76%) for the cefdinir QD group, 64/79 (81%) for the cefdinir BID group, and 74/89 (83%) for the amox/clav group. There were no apparent differences in microbiologic eradication rate by patient according to baseline pathogen(s) for the different treatment groups (Table 23). Of the patients who were assessed as having their pathogen(s) eradicated, 48/56 (86%) in the cefdinir QD group, 59/64 (92%) in the cefdinir BID group, and 69/74 (93%) in the amox/clav group had presumed eradication.

Clinical Cure

The microbiologically-clinically evaluable patients who achieved a cure at TOC and continued to satisfy protocol requirements until the LTFU visit were assessed for continued response. The clinical cure rate at LTFU was 43/49 (88%) for the cefdinir QD group, 48/56 (86%) for the cefdinir BID group, and 57/66 (86%) for the amox/clav group. Therefore, for microbiologically-clinically evaluable patients, the percentage of patients who were cured at TOC and remained cured at LTFU was high and similar for all 3 treatment groups.

Microbiologic Eradication by Pathogen

Microbiologically-clinically evaluable patients who had persistence at TOC were automatically considered to have persistence at LTFU. Of the qualified patients who had presumed eradication at the TOC visit, 53/60 (88%) in the cefdinir QD group, 55/64 (86%) in the cefdinir BID group, and 76/87 (87%) in the amox/clav group also had microbiologic eradication at the LTFU visit. Thus, the observed relapse rates were similar for all treatment groups.

Microbiologic Eradication by Patient

In microbiologically-clinically evaluable patients with eradication at TOC, the continued presumed eradication rate by patient was similar for all treatment groups: 42/49 (86%) for the cefdinir QD group, 47/55 (86%) for the cefdinir BID group, and 56/64 (88%) for the amox/clav group.

Modified Intent-to-Treat Analyses

Test-of-Cure Visit (6-15 Days Post-therapy)

In the MITT population, the amox/clav treatment group achieved a higher eradication rate by pathogen and by patient than either cefdinir group (Table 24).

TABLE 21. Microbiologic Efficacy Results at TOC - MITT Patients

Treatment Group	Eradication Rate by Pathogen		Eradication Rate by Patient	
	n/N ^a	%	n/N ^b	%
Cefdinir QD	93/124	75.0	68/93	73.1
Cefdinir BID	91/120	75.8	74/97	76.3
Amox/Clav	118/143	82.5	85/104	81.7

^a Number of pathogens eradicated or presumed eradicated/total number of pathogens

^b Number of patients with eradication or presumed eradication/total number of patients

Intent-to-Treat Analyses

Test-of-Cure Visit (6-15 Days Post-therapy)

The clinical cure rates for the ITT population at TOC were 270/403 (67%) for the cefdinir QD group, 272/412 (66%) for the cefdinir BID group, and 285/414 (69%) for the amox/clav group. The 95% CIs about each pairwise comparison showed that the ITT cure rates for the cefdinir treatment groups were statistically equivalent to amox/clav and to each other based on predefined criteria for equivalence. The 95% CIs were (-8.25%, 4.56%) about the difference between the cefdinir QD group and the amox/clav group, (-9.21%, 3.57%) about the difference between the cefdinir BID group and the amox/clav group, and (-5.50%, 7.46%) about the difference between the 2 cefdinir groups. The exploratory CMH test showed no significant difference between cefdinir QD and amox/clav treatment ($p = 0.597$) or between cefdinir BID and amox/clav treatment ($p = 0.375$).

Long-Term Follow-Up Visit (21-35 Days Post-therapy)

The clinical cure rates for all patients at the LTFU visit were 206/403 (51%) for the cefdinir QD group, 206/412 (50%) for the cefdinir BID group, and 218/414 (53%) for the amox/clav group. These rates were calculated from all patients randomized to treatment regardless of clinical assessment at TOC.

Table 22. Microbiological Eradication, by Pathogen

	Cefdinir QD	Cefdinir BID	Amox/Clav
Eradiation	69/92 (75%)	76/94 (81%)	100/118(85%)
Proportion presumed eradicated	58/69 (84%)	70/76 (92%)	90/100 (100%)
Eradiation proved by repeat culture (clinical failure)	11/69 (16%)	6/76 (8%)	- 0 -

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TABLE 23. Microbiologic Eradication Rate by Pathogen at TOC - Pathogens From Microbiologically-Clinically Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID		n/N	%
	n/N	%	n/N	%		
Gram-Positive						
<i>Staphylococcus aureus</i>	10/14	71.4	23/27	85.2	16/21	76.2
<i>Staphylococcus salivarius</i>	0/0	—	1/1	100.0	0/0	—
<i>Streptococcus agalactiae</i>	2/2	100.0	0/0	—	3/3	100.0
<i>Streptococcus anginosus</i>	2/2	100.0	1/1	100.0	0/0	—
<i>Streptococcus equi</i>	1/1	100.0	0/0	—	0/0	—
<i>Streptococcus equisimilis</i>	1/1	100.0	2/2	100.0	1/1	100.0
<i>Streptococcus pneumoniae</i>	14/17	82.4	14/16	87.5	21/22	95.5
<i>Streptococcus pyogenes</i>	2/5	40.0	1/1	100.0	7/7	100.0
<i>Streptococcus simulans</i>	0/0	—	1/1	100.0	0/0	—
<i>Streptococcus</i> Group G	0/0	—	0/1	0.0	0/0	—
Gram-Negative						
<i>Acinetobacter calcoaceticus</i> var <i>anitratus</i>	0/0	—	0/1	0.0	0/0	—
<i>Acinetobacter calcoaceticus</i> var <i>lwoffi</i>	0/1	0.0	0/0	—	3/3	100.0
<i>Citrobacter diversus</i>	0/0	—	1/1	100.0	2/2	100.0
<i>Enterobacter aerogenes</i>	0/0	—	0/0	—	1/1	100.0
<i>Enterobacter cloacae</i>	0/0	—	0/0	—	1/1	100.0
<i>Escherichia coli</i>	3/5	60.0	0/1	0.0	4/5	80.0
<i>Eikenella corrodens</i>	0/1	0.0	0/0	—	0/0	—
<i>Haemophilus influenzae</i>	16/19	84.2	12/17	70.6	19/26	73.1
<i>Haemophilus parahaemolyticus</i>	0/0	—	1/1	100.0	0/1	0.0
<i>Haemophilus parainfluenzae</i>	3/5	60.0	5/5	100.0	9/10	90.0
<i>Klebsiella oxytoca</i>	1/1	100.0	0/0	—	0/0	—
<i>Klebsiella pneumoniae</i>	2/4	50.0	3/3	100.0	½	50.0
<i>Moraxella catarrhalis</i>	11/12	91.7	9/13	69.2	10/11	90.9
<i>Neisseria meningitidis</i>	0/1	0.0	0/0	—	0/0	—
<i>Proteus mirabilis</i>	1/1	100.0	2/2	100.0	2/2	100.0
Total	69/92	75.0	76/94	80.9	100/118	84.7

n/N = Number of pathogens eradicated/total number of pathogens

Among the microbiologically-clinically evaluable patients there were 24/62 β -lactamase-positive *H. influenzae* isolates and 33/36 β -lactamase-positive *M. catarrhalis* isolates. It did not appear that the presence of β -lactamase decreased the microbiologic eradication rates for either cefdinir or amox/clav (Table 24).

TABLE 24. Microbiologic Eradication Rate by β -Lactamase Status of *Haemophilus influenzae* and *Moraxella catarrhalis* at TOC - Pathogens From Microbiologically-Clinically Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
<i>Haemophilus influenzae</i>						
β L+	6/6	100.0	5/6	83.3	8/12	66.7
β L-	10/13	76.9	7/11	63.6	11/14	78.6
<i>Moraxella catarrhalis</i>						
β L+	11/12	91.7	7/11	63.6	9/10	90.0
β L-	0/0	—	2/2	100.0	1/1	100.0

β L = β -Lactamase

n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens

Microbiologic Eradication by Patient

The microbiologic eradication rates were 56/74 (76%) for the cefdinir QD group, 64/79 (81%) for the cefdinir BID group, and 74/89 (83%) for the amox/clav group. There were no apparent differences in microbiologic eradication rate by patient according to baseline pathogen(s) for the different treatment groups (Table 23). Of the patients who were assessed as having their pathogen(s) eradicated, 48/56 (86%) in the cefdinir QD group, 59/64 (92%) in the cefdinir BID group, and 69/74 (93%) in the amox/clav group had presumed eradication.

Table 25. Microbiological Eradication by Patient.

	Cefdinir QD	Cefdinir BID	Amox/Clav
Eradiation	56/74 (76%)	64/79 (81%)	74/89 (83%)
Proportion presumed eradicated	48/56 (86%)	59/64 (92%)	69/74 (93%)
Eradiation proved by repeat culture (clinical failure)	8/56 (14%)	5/64 (8%)	5/74 (7%)

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TABLE 26. Microbiologic Eradication Rate by Patient at TOC -
Microbiologically-Clinically Evaluable Patients

	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
<i>Staphylococcus aureus</i>	6/10	60.0	15/19	78.9	7/8	87.5
<i>Staphylococcus salivarius</i>	0/0	--	1/1	100.0	0/0	--
<i>Streptococcus agalactiae</i>	1/1	100.0	0/0	--	2/2	100.0
<i>Streptococcus anginosus</i>	2/2	100.0	1/2	50.0	0/0	--
<i>Streptococcus equi</i>	1/1	100.0	0/0	--	0/0	--
<i>Streptococcus equisimilis</i>	0/0	--	2/2	100.0	1/1	100.0
<i>Streptococcus pneumoniae</i>	11/14	78.6	17/21	81.0	16/17	94.1
<i>Streptococcus pyogenes</i>	1/2	50.0	0/0	--	4/4	100.0
<i>Streptococcus salivarius</i>	0/0	--	1/1	100.0	0/0	--
<i>Streptococcus Group G</i>	0/0	--	0/1	0.0	0/0	--
Gram-Negative						
<i>Citrobacter diversus</i>	0/0	--	0/0	--	1/1	100.0
<i>Escherichia coli</i>	1/1	100.0	0/1	0.0	1/2	50.0
<i>Eikenella corrodens</i>	0/1	0.0	0/0	--	0/0	--
<i>Haemophilus influenzae</i>	10/13	76.9	9/12	75.0	11/17	64.7
<i>Haemophilus parahaemolyticus</i>	0/0	--	1/1	100.0	0/1	0.0
<i>Haemophilus parainfluenzae</i>	2/2	100.0	5/5	100.0	6/6	100.0
<i>Klebsiella pneumoniae</i>	1/1	100.0	0/0	--	1/21	100.0
<i>Moraxella catarrhalis</i>	8/9	88.9	7/9	77.8	7/8	87.5
<i>Neisseria meningitidis</i>	0/1	0.0	0/0	--	0/0	--
<i>Proteus mirabilis</i>	0/0	--	0/0	--	1/1	100.0
Multiple	12/16	75.0	10/14	71.4	19/23	82.6
Total Patients	56/74	75.7	64/79	81.0	74/89	83.1

n/N = Microbiologically-clinically evaluable patients with all baseline pathogens eradicated/all
microbiologically-clinically evaluable patients

Medical Officer's Comment

For the pathogens generally agreed upon as the leading causes of acute maxillary sinusitis in adults and children, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, microbiologic eradication rates at the TOC visit were as follows:

Table 27. Microbiologic Eradication Rate, by Pathogen, at TOC, from All Sites.

	Cefdinir QD	Cefdinir BID	Cefdinir (combined)	Amox/Clav
<i>S. pneumoniae</i>	14/17 (82.4%)	14/16 (87.5%)	28/33 (84.8%)	21/22 (95.5%)
<i>H. influenzae</i>	16/19 (84.2%)	12/17 (70.6%)	28/36 (77.8%)	19/26 (73.1%)
<i>M. catarrhalis</i>	11/12 (91.7%)	9/13 (69.2%)	20/25 (80.0%)	10/11 (90.9%)

Table 28. Microbiologic Eradication Rate, by Patient, at TOC, from All Sites.

	Cefdinir QD	Cefdinir BID	Cefdinir (combined)	Amox/Clav
<i>S. pneumoniae</i>	11/14 (78.6%)	17/21 (81.0%)	28/35 (80.0%)	16/17 (94.1%)
<i>H. influenzae</i>	10/13 (76.9%)	9/12 (75.0%)	19/25 (76.0%)	11/17 (64.7%)
<i>M. catarrhalis</i>	8/9 (88.9%)	7/9 (77.8%)	15/18 (83.3%)	7/8 (87.5%)

Table 29. Microbiologic Eradication Rate, by Pathogen, at TOC, from All Sites Except Site 38.

	Cefdinir QD	Cefdinir BID	Cefdinir (combined)	Amox/Clav
<i>S. pneumoniae</i>	14/17 (82.3%)	14/16 (87.5%)	28/33 (84.8%)	20/21 (95.2%)
<i>H. influenzae</i>	16/19 (84.2%)	11/16 (68.7%)	27/35 (77.8%)	18/25 (72.0%)
<i>M. catarrhalis</i>	10/11 (90.9%)	8/12 (66.7%)	18/23 (80.0%)	7/8 (87.5%)

Medical Officer's Comment

The comparison of the microbiologic eradication rates, by pathogen, with and without the data from site 38 included demonstrate the same rates of eradication of the most important three pathogens in acute maxillary sinusitis. The efficacy of cefdinir was similar to that of amoxicillin/clavulanate overall in the microbiologic eradication of these major pathogens, with acceptable levels of eradication in all three. Amoxicillin/ clavulanate was superior in the eradication of *S. pneumoniae*, both in the comparison against each cefdinir arm and in the aggregate. Cefdinir QD was superior to Amoxicillin/clavulanate in the eradication of both *H. influenzae* and *M. catarrhalis*, but Amoxicillin/clavulanate was superior to cefdinir BID in the eradication of both of these pathogens.

When the patients from site 38 were excluded, the aggregate numbers of isolates of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* treated with cefdinir were still more than sufficient to meet the recommended number of clinical isolates in trials of therapy for acute maxillary sinusitis, per the *Points to Consider* document. (That document recommends successful outcome [clinical, microbiological, and radiographic] in at least 100 patients, with at least 25 isolates of *S. pneumoniae*, 25 isolates of *H. influenzae*, and at least 15 isolates of *M. catarrhalis*.) There were consistently higher rates of microbiological eradication of *H. influenzae* and *M. catarrhalis* with cefdinir administered QD than with cefdinir BID. In the treatment of *S. pneumoniae*, the pathogen of highest incidence in culture-positive acute maxillary sinusitis, however, cefdinir BID consistently had higher eradication rates, by pathogen and by patient, than did cefdinir QD. The differences in eradication rates between cefdinir regimens was highest in the case of *M. catarrhalis*, in the evaluation of eradication rate by pathogen. The rate of eradication of *H. influenzae*, by patient, was nearly identical for the QD and BID cefdinir regimens.

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Safety

Of the patients randomized to treatment, 2 in the cefdinir QD group and 2 in the cefdinir BID group did not receive drug and were not included in the safety summary.

Adverse Events

Overview

A total of 552 patients (45%) experienced at least 1 adverse event during the study (Table 26). The incidence was highest in patients treated with amox/clav, 50% of whom experienced an adverse event. In the cefdinir QD group, 42% of patients experienced an adverse event, and in the cefdinir BID group, 43% of patients experienced an adverse event. During the 10-day treatment period, the incidence of adverse events was 33%, 35%, and 38% for the cefdinir QD, cefdinir BID, and amox/clav treatment groups, respectively. There was no significant difference in the incidence of adverse events between the cefdinir treatment groups, but the incidence of adverse events in the cefdinir QD group was significantly lower than the amox/clav group ($p = 0.016$).

The incidence of associated adverse events showed a similar trend: 26%, 27%, and 31% of patients in the cefdinir QD, cefdinir BID, and amox/clav groups, respectively. These differences were not statistically significant.

No deaths occurred during this study. One cefdinir QD-treated patient died of lung cancer 108 days after being withdrawn from the study. His disease and death were not considered associated with cefdinir (see Patient Narratives, Appendix B.2). Only 5 patients experienced a serious adverse event. Thirty-five patients discontinued treatment as a result of an adverse event: 6 (2%) in the cefdinir QD group, 10 (2%) in the cefdinir BID group, and 19 (5%) in the amox/clav group. The rate of discontinuation was highest in the amox/clav group and lowest in the cefdinir QD group ($p = 0.011$). Twenty-nine of the discontinuations were due to an associated adverse event. Seventeen additional patients withdrew from the study because of an adverse event that occurred after completing treatment but before the LTFU visit (5 in the cefdinir QD group, 6 in the cefdinir BID group, and 6 in the amox/clav group). Seven of these withdrawals events were due to drug-associated adverse events.

TABLE 30. Summary of Adverse Events - All Patients [Number (%) of Patients]
(Page 1 of 2)

	Cefdinir		Amox/Clav N = 414
	QD N = 401	BID N = 410	
Adverse Events During Study			
All Adverse Events	168 (41.9)	178 (43.4)	206 (49.8)
Associated ^a Adverse Events	104 (25.9)	109 (26.6)	129 (31.2)
Adverse Events During Treatment			
All Adverse Events	131 (32.7)	144 (35.1)	159 (38.4)
Adverse Events by Sex^b			
All Adverse Events			
Male	53 (35.6)	61 (41.5)	76 (49.0)
Female	115 (45.6)	117 (44.5)	130 (50.2)
Associated Adverse Events			
Male	29 (19.5)	31 (21.1)	45 (29.0)
Female	75 (29.8)	78 (29.7)	84 (32.4)
Adverse Events by Race^c			
All Adverse Events			
White	152 (42.7)	162 (44.5)	177 (49.7)
Hispanic	8 (34.8)	6 (27.3)	12 (52.2)
Black	6 (31.6)	7 (38.9)	15 (46.9)
Asian	0 (0.0)	1 (100.0)	0 (0.0)
Other	2 (66.7)	2 (40.0)	2 (66.7)
Associated Adverse Events			
White	96 (27.0)	102 (28.0)	113 (31.7)
Hispanic	4 (17.4)	3 (13.6)	6 (26.1)
Black	2 (10.5)	3 (16.7)	8 (25.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (66.7)	1 (20.0)	2 (66.7)
Adverse Events by Age^d			
All Adverse Events			
6 to <13 years	0 (0.0)	0 (0.0)	0 (0.0)
13 to <18 years	15 (46.9)	16 (51.6)	15 (45.5)
18 to <65 years	146 (41.8)	153 (43.5)	182 (50.1)
≥65 years	7 (36.8)	9 (33.3)	9 (50.0)
Associated Adverse Events			
6 to <13 years	0 (0.0)	0 (0.0)	0 (0.0)
13 to <18 years	7 (21.9)	4 (12.9)	9 (27.3)
18 to <65 years	93 (26.6)	102 (29.0)	114 (31.4)
≥65 years	4 (21.1)	3 (11.1)	6 (33.3)

^a Considered by the investigator to be possibly, probably, or definitely related to study medication.

^b Percentages based on total numbers of males or females in a treatment group

^c Percentages based on total numbers of patients of each race in a treatment group

^d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age group.

TABLE 30. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 2 of 2)

	Cefdinir				Amox/Clav N = 414	
	QD N = 401		BID N = 410			
Adverse Events by Maximum Intensity*						
All Adverse Events						
Mild	117	(29.2)	127	(31.0)	148	(35.7)
Moderate	61	(15.2)	64	(15.6)	79	(19.1)
Severe	12	(3.0)	14	(3.4)	20	(4.8)
Associated Adverse Events						
Mild	75	(18.7)	77	(18.8)	92	(22.2)
Moderate	30	(7.5)	31	(7.6)	43	(10.4)
Severe	6	(1.5)	6	(1.5)	11	(2.7)
Serious Adverse Events						
	1	(0.2)	3	(0.7)	1	(0.2)
Deaths						
	0	(0.0)	0	(0.0)	0	(0.0)
Discontinuation of Treatment Due to Adverse Events						
All Adverse Events	6	(1.5)	10	(2.4)	19	(4.6)
Associated Adverse Events	6	(1.5)	6	(1.5)	17	(4.1)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	5	(1.2)	6	(1.5)	6	(1.4)
Associated Adverse Events	1	(0.2)	3	(0.7)	3	(0.7)

* Patients with multiple adverse events were counted once in each applicable category.

Adverse Events by Age

Among patients treated with cefdinir, the overall incidence of adverse events was slightly higher in the youngest age group (13 to <18 years of age). However, the incidence of associated adverse events was higher in the intermediate age group (18 to <65 years of age). The incidence of adverse events among cefdinir-treated patients, both all and associated, was similar for patients 18 to <65 and ≥65 years old. However, there were too few patients in the ≥65 age group to make any definitive comparison.

Whereas 20% of patients 18 to <65 years old who were treated with cefdinir QD experienced diarrhea, only 3% of patients 13 to <18 years old experienced this adverse event. Similarly, 21% of patients 18 to <65 years old who were treated with cefdinir BID experienced diarrhea versus 7% of patients 13 to <18 years old. All of the cases of vaginal moniliasis experienced by cefdinir-treated patients were also in the 18 to <65 age group. Two adverse events that occurred more frequently in younger patients treated with cefdinir QD were abdominal pain and

pharyngitis. In the cefdinir QD treatment group, 13% of patients 13 to <18 years old experienced abdominal pain, versus 2% of patients 18 to <65 years old; and 9% of patients 13 to <18 experienced pharyngitis, versus 2% of patients 18 to <65. Patients ≥65 years of age had a similar toxicity profile to patients in the 18 to <65 age group. The only notable difference was that elderly patients treated with cefdinir BID had a lower rate of diarrhea (7%) than patients in the intermediate age group (21%). The rates of diarrhea were similar between these 2 age groups for cefdinir QD- and amox/clav-treated patients.

For patients treated with amox/clav, the overall incidence of adverse events and associated adverse events was somewhat greater in the 18 to <65 age group than in younger patients. The incidence of diarrhea was also greater in the 18 to <65 age group (21%) than in the 13 to <18 age group (12%). There were no other noteworthy differences in incidence of specific adverse events among age groups, including elderly patients.

Adverse Events by Sex

Overall, females had a slightly higher incidence of adverse events than males in all treatment groups. This was largely because females had a higher incidence of adverse events related to the urogenital system, such as vaginal moniliasis, vaginitis, and dysmenorrhea. There were no clinically relevant differences in adverse event profiles between the sexes.

Adverse Events by Race

Over 88% of patients in the study were white. No clinically important differences in adverse event profiles were apparent based on race.

Adverse Events by Intensity

Most patients experienced only mild or moderate adverse events. Twelve patients (3%) in the cefdinir QD group, 14 patients (3%) in the cefdinir BID group, and 20 patients (5%) in the amox/clav group experienced at least 1 severe adverse event. Diarrhea was the most common severe adverse event (18 patients), followed by headache (8 patients), and nausea (5 patients). Six patients in the cefdinir QD group, 6 patients in the cefdinir BID group, and 11 patients in the amox/clav group experienced a treatment-associated severe adverse event. These included abdominal pain, headache, diarrhea, nausea, dyspepsia, rectal disorder, vomiting, and bilirubinemia. With the exception of a patient in the cefdinir QD group who died of lung cancer unrelated to treatment after the study ended (Patient 204, Center 38) (see Appendix B.2, Patient Narratives), all severe adverse events were completely reversible.

Adverse Events by Day of Onset

Most adverse events began during the first 5 days of treatment, regardless of treatment regimen.

Medical Officer's Comment

The most common adverse events in this study were diarrhea, nausea, vomiting, headache, abdominal pain, and vaginal moniliasis. A summary of these AEs, condensed from Table 27 of the sponsor's report, shows the incidences of these and the comparable frequencies of occurrence between treatment groups. There was no trend of greater frequency or severity of adverse events in patients receiving therapy with cefdinir when compared with those receiving amoxicillin/clavulanate.

Table 31. Summary of Most Frequent Adverse Events, All Patients [Number (%) of Patients].

Adverse Event	<u>Cefdinir</u>				<u>Amox/ Clav</u>	
	600 mg	QD, N=401	300 mg	BID, N=410	N=	414
	All	Assoc	All	Assoc	All	Assoc
Diarrhea	75 (18.7)	62 (15.5)	77 (18.8)	73 (17.8)	84 (20.3)	78 (18.8)
Nausea	17 (4.2)	12 (3.0)	13 (3.2)	8 (2.0)	26 (6.3)	23 (5.6)
Headache	12 (3.0)	5 (1.2)	15 (3.7)	5 (1.2)	19 (4.6)	1 (0.2)
Abdominal Pain	10 (2.5)	4 (1.0)	11 (2.7)	7 (1.7)	14 (3.4)	12 (2.9)
Vaginal Moniliasis	13 (5.1)	13 (5.1)	11 (4.2)	10 (3.8)	15 (5.8)	15 (5.8)
Rash	4 (1.0)	2 (0.5)	6 (1.5)	3 (0.7)	9 (2.2)	6 (1.4)

Medical Officer's Comments

The most frequently seen adverse events with cefdinir therapy occurred no more often than with the use of amoxicillin/clavulanate in comparable use on a comparable patient population. These treatment-emergent signs and symptoms were no more often associated with cefdinir therapy than with amoxicillin/clavulanate therapy. Overall incidences of adverse events were slightly lower in the cefdinir arms than in the amoxicillin/clavulanate therapy arm. The incidence of withdrawal from therapy due to adverse events, both overall and with likely association of the adverse events with study therapy, was slightly lower in the cefdinir arms of the study than in the amoxicillin/clavulanate arm. None of these differences was statistically significant.

Medical Officer's Conclusions From Trial #983-6

Trial #983-6
Acute Maxillary Sinusitis

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TRIAL #983-37**OBJECTIVE/RATIONALE**

The objective of this study was to evaluate the efficacy and safety of cefdinir treatment (600 mg QD or 300 mg BID) for 10 days versus amox/clav (500 mg TID, expressed as the amoxicillin component) for 10 days in the treatment of adult patients with acute maxillary sinusitis.

Cefdinir is active in vitro against organisms commonly associated with sinus infections, including *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, *Streptococcus pyogenes*, anaerobic gram-positive cocci, and many other gram-negative bacteria.⁽¹⁰⁾ This study was designed to compare the efficacy and safety of cefdinir with amoxicillin/clavulanate (amox/clav, Augmentin®) in patients with acute maxillary sinusitis. Amox/clav contains both amoxicillin, an ampicillin analog, and clavulanic acid, a β -lactam that protects amoxicillin from degradation by β -lactamases.

STUDY DESIGN

This was an investigator-blinded, randomized, comparative, multi center study with 3 parallel-treatment groups.

The protocol and CRFs specified the test-of-cure (TOC) visit occur 7 to 14 days post-therapy (i.e, Days 17 through 24 for patients completing treatment on Day 10). For many patients, the TOC visit beginning on Day 17 was actually 6 days post-therapy since patients who started BID or TID treatment late on Day 1 ended treatment on Day 11. For analysis purposes, the TOC window was widened to 6 to 15 days post-therapy to include these patient data. The long-term follow-up (LTFU) window (21 to 35 days post-therapy) was not changed.

Medical Officer's Comment

This study was identical to trial #983-6 in rationale, objective, and design, with one, important difference: this study was intended to enroll only patients who were eligible for both clinical and microbiological examination and outcome evaluation. All enrolled patients were to undergo diagnostic sinus aspiration.

STUDY MANAGEMENT

Sixteen centers throughout Europe participated in this study, which was monitored by the sponsor, Parke-Davis Pharmaceutical Research (Table 1). Investigators met to review the protocol on September 25, 1992. Identical protocols and case report forms (CRFs) were used by all centers. The study was conducted in compliance with the United States Food and Drug Administration's (FDA) good clinical practice guidelines and according to the Declaration of

Helsinki. Individual ethics committee (EC) approvals were obtained before the study began at each center and written informed patient consents were obtained from each center prior to patient enrollment.

The first patient began treatment on December 10, 1992, and the last patient visit occurred on August 25, 1994. A central laboratory was used by Centers 1, 2, 3, and 21, and local laboratories were used by the rest of the centers to analyze the microbiological and clinical laboratory specimens collected during the study. Randomization codes for all patients were released to the study manager on March 23, 1995.

Cefdinir capsules and amox/clav tablets were packaged and provided by Parke-Davis Pharmaceutical Research (Table 2).

TABLE 32. Study Medication

	Lot	Formulation
Cefdinir 300-mg Capsules	CM 0660492 9	134393-25
	CM 0700492 9	134393-25
	CM 106061 9	134393-25
	CM 1781292 9	134393-25
Amox/Clav 500-mg Tablets ^a	TM2947 9	Marketed
	TS0111 9	Marketed
	WT0924	Marketed

^a Each tablet contains 500 mg amoxicillin and 125 mg clavulanate.

Methods of Assigning Patients to Treatment

An independent randomization schedule was prepared for each study center. A block size of 6 patients was used with 2 treatment replicates per block, consistent with the planned treatment group ratio of 1:1:1 for cefdinir 600 mg QD, cefdinir 300 mg BID, and amox/clav 500 mg TID, respectively.

POPULATION

The inclusion and exclusion criteria employed in this trial were identical to those used in Trial #983-6, described above.

Evaluability criteria were identical to those used in protocol #983-6.

The scheme of medical history, physical examinations, clinical assessments, sinus aspiration(s), laboratory testing, radiography, adverse events monitoring, and dosing assessments was identical to that in protocol #983-6. The scheme is displayed in Table 5 of Parke-Davis Research Report (RR) 720-03416.

Medical Officer's Comment

The reviewer agrees with the design of the clinical study as presented by the applicant.

Statistical Methodology

Sample Size

This investigator-blind, randomized, comparative multi center study of cefdinir versus amox/clav was designed with a sample size of 112 evaluable patients per randomized group (336 total evaluable patients).

A microbiologic eradication rate of 90% across all randomized groups was assumed in the sample size calculations. Equivalence was to be assessed by comparing a 95% lower confidence limit for the difference (cefdinir minus amox/clav) in microbiologic eradication rates to a set of predetermined, fixed criteria (defined below). The sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and amox/clav microbiologic eradication rates at the TOC visit, using this confidence limit method.

Analyses

Efficacy and safety data summaries were generated and statistical analyses were performed for the cefdinir QD, cefdinir BID, and amox/clav treatment groups. These investigative statistical methods are described below. All summaries and analyses were carried out using SAS (Version 6).

Efficacy

The efficacy objectives of this study were to estimate the microbiologic and clinical response rates of cefdinir QD, cefdinir BID, and amox/clav in the treatment of acute maxillary sinusitis, and to evaluate the equivalence of the response rates of cefdinir QD and cefdinir BID each versus amox/clav at the TOC visit, based on predefined fixed criteria.

The primary outcome measures were the microbiologic eradication rate by pathogen, the microbiologic eradication rate by patient, and the clinical cure rate by patient in the evaluable

population at TOC. Data from the LTFU visit were summarized and presented as supporting information, but no inferential analyses were performed on LTFU data.

Descriptive statistics used in this study consisted primarily of frequency counts and response rates. Means, standard errors, minima, maxima, and medians were used where appropriate.

At baseline, the demographic data, microbiologic results, clinical signs and symptoms, and some history data were summarized to facilitate baseline treatment group comparisons.

At TOC, the primary end point, the microbiologic eradication rates by pathogen and by patient were calculated for each treatment group in the evaluable, MITT, and ITT patient populations. Clinical cure rates and mean clinical signs/symptoms scores were calculated for each treatment group in the evaluable, clinically evaluable, and ITT patient populations.

At LTFU, the secondary end point, the microbiologic eradication rates by pathogen and by patient (i.e., the "no relapse" rates) were calculated for each treatment group in the qualified and ITT patient populations. The clinical cure rates (i.e., the "no recurrence" rates) and mean clinical signs/symptoms scores were calculated for each treatment group in the qualified and ITT patient populations.

Two methods of investigating treatment equivalence at TOC were used. One method was based on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient (or each pathogen, for the by-pathogen case) in the analysis, and were calculated as the total number of cures or eradications in the study population, divided by the total number of cases.

The second method used a categorical modeling procedure to obtain center-adjusted estimates of the response rates and their standard errors. The model contained terms for study center, treatment group, and center-by-treatment interaction. The resulting parameter estimates were used to construct estimates of the treatment group response rates and standard errors in which each center was given equal weight.

Pairwise treatment differences were defined as cefdinir QD or BID minus amox/clav. The estimated response rate differences and their standard errors were used to construct a 95% lower confidence limit (i.e., a one-tailed test) for each treatment difference, using a standard normal approximation.⁽¹⁹⁾ Each 95% lower confidence limit was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the 2 rates (pooled or center-adjusted) under comparison (Table 7). To demonstrate equivalence, each 95% lower confidence limit must be below 0 and above the indicated bounds. Two-tailed 95% confidence intervals were also calculated for the evaluable population.

TABLE 33. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Cefdinir is Equivalent to or Better Than Amox/Clav if 95% Lower Confidence Limit for Treatment Difference Is Greater Than
90% or greater	-10%
80%-89%	-15%
70%-79%	-20%

Results of the 2 methods were compared for consistency. When the 2 methods agreed, the pooled analysis was presented as the final analysis. If results from the 2 methods disagreed, the differences were addressed and a conclusion was drawn based on the overall weight of the evidence across both methods. A comparison of the 2 analyses can be found in Appendix D.1.

An exploratory Cochran-Mantel-Haenszel (CMH) analysis adjusting for center was also performed to test treatment group differences in the microbiologic eradication and clinical cure rates. Pairwise comparisons among the treatment groups were made. Results of the Breslow-Day tests were reviewed in evaluating the consistency of the relationship between treatment and response among centers.

Study centers contributing 12 or fewer patients, or 2 or fewer patients in any treatment group, were pooled for center-adjusted analyses (except that for the ITT analysis by pathogen, the same pooling rule applied to the number of available pathogens). Pooling was performed independently for each analysis population after any required data exclusions were made.

Patient Population

The participating investigators, and their enrollment numbers, are listed in Table 34.

TABLE 34. List of Investigators

Center	Investigator	Country	Number of Patients		
			Randomized to Treatment	Completed Treatment	Evaluable ^a
1	M. Sorri	Finland	106	95	59
2	S. Savolainen	Finland	56	56	39
3	M. Pietola	Finland	57	52	23
5	H. Meyer-Bothling	Germany	33	28	13
6	M. Fischer	Germany	25	24	19
7	B. Bertrand	Belgium	5	3	0
8	P. Rivas	Spain	69	62	31
9	J. Daele	Belgium	11	11	5
10	C. Benning	Germany	21	20	12
12	P. Comte	Switzerland	11	11	7
13	R. Nyffenegger	Switzerland	49	49	32
14	H. Stierlen	Germany	15	13	9
15	M. Penttillä	Finland	55	53	24
17	P. Schenk	Austria	43	38	19
20	V. Kuhlicke	Germany	3	3	1
21	J. Väyrynen	Finland	10	9	2
Total			569	527	295

^a Microbiologically and clinically evaluable

The demographic characteristics of the enrolled patients are listed in Table 35.

TABLE 35. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav N = 189	Total N = 569
	QD N = 182	BID N = 198		
Sex				
Male	107 (58.8)	115 (58.1)	114 (60.3)	336 (59.1)
Female	75 (41.2)	83 (41.9)	75 (39.7)	233 (40.9)
Race				
White	182 (100.0)	198 (100.0)	186 (98.4)	566 (99.5)
Asian	0 (0.0)	0 (0.0)	3 (1.6)	3 (0.5)
Age, yr				
Median	30.0	32.0	29.0	31.0
Range	14-74	13-73	13-73	13-74
Distribution				
13 to <18	4 (2.2)	4 (2.0)	6 (3.2)	14 (2.5)
18 to <65	169 (92.9)	184 (92.9)	175 (92.6)	528 (92.8)
≥65	9 (4.9)	10 (5.1)	8 (4.2)	27 (4.7)

The demographic characteristics of the clinically evaluable patients are listed in Table 36.

TABLE 36. Patient Characteristics - Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir		Amox/Clav N = 106	Total N = 295
	QD N = 93	BID N = 96		
Sex				
Male	63 (67.7)	58 (60.4)	63 (59.4)	184 (62.4)
Female	30 (32.3)	38 (39.6)	43 (40.6)	111 (37.6)
Race				
White	93 (100.0)	96 (100.0)	105 (99.1)	294 (99.7)
Asian	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
Age, yr				
Median	30.0	29.0	25.5	27.0
Range	17-72	13-72	13-69	13-72
Distribution				
13 to <18	1 (1.1)	2 (2.1)	5 (4.7)	8 (2.7)
18 to <65	87 (93.5)	90 (93.8)	96 (90.6)	273 (92.5)
≥65	5 (5.4)	4 (4.2)	5 (4.7)	14 (4.7)

Medical Officer's Comment

The population studied in this trial differed significantly from the population in trial #983-6 in gender predominance, racial proportion, and median age. In both the entire enrolled population and in the clinically evaluable group, men predominated, in about the same proportion between treatment groups; the study population was almost entirely white; and the median ages in the treatment groups were 25.5 to 32.0 years.

Confirmed Microbiologic Diagnosis and Baseline Susceptibility¹

The sponsor reviewed the list of pathogens from the central and local laboratories and identified some as organisms not to be considered pathogenic in acute maxillary sinusitis. These organisms are listed in Appendix C.6.

During the study, one or more baseline pathogens were isolated from the maxillary sinus aspirates of 375 (66%) patients (Table 37). Forty-eight percent (274/569) of patients had 1 pathogen and 18% (101/569) had multiple pathogens isolated at baseline. These isolates

⁽¹⁾ Appendix C.6, Organisms Not Considered Pathogenic; C.7, Distribution of Patients by Baseline Pathogen

included 21 anaerobic species.

H. influenzae was the most common baseline pathogen isolated (148 isolates); it occurred as a single pathogen in 14% (77/569) of patients. *S. pneumoniae* (110 isolates), *M. catarrhalis* (49), and *S. aureus* (45) were the next most common pathogens isolated at baseline.

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TABLE 37. Distribution of Patients by Baseline Pathogen— All Patients
With Baseline Pathogens
(Number of Patients)

Baseline Pathogen	Cefdinir		Amox/Clav N = 189
	QD N = 182	BID N = 198	
Gram-Positive			
<i>Corynebacterium pyogenes</i>	0	0	1
<i>Gemella morbillorum</i>	1	0	3
<i>Staphylococcus aureus</i>	11	14	7
<i>Staphylococcus epidermidis</i>	3	3	2
<i>Streptococcus mitis</i>	0	1	0
<i>Streptococcus pneumoniae</i>	22	25	19
<i>Streptococcus pyogenes</i>	2	2	3
<i>Streptococcus</i> Group C	1	0	1
<i>Streptococcus</i> Group F	1	0	0
<i>Streptococcus</i> , β -hemolytic ^a	2	1	0
Gram-Negative			
<i>Acinetobacter junii</i>	1	0	0
<i>Citrobacter diversus</i>	0	0	1
<i>Comamonas acidovorans</i>	0	0	1
<i>Enterobacter amnigenus</i> ^b	0	0	1
<i>Enterobacter cloacae</i>	1	0	0
<i>Escherichia coli</i>	2	1	2
<i>Haemophilus aphrophilus</i>	0	1	0
<i>Haemophilus ducreyi</i>	1	0	0
<i>Haemophilus influenzae</i>	20	28	29
<i>Haemophilus parainfluenzae</i>	1	1	8
<i>Haemophilus</i> sp	0	1	0
<i>Klebsiella pneumoniae</i>	1	0	0
<i>Moraxella catarrhalis</i>	10	9	10
<i>Moraxella lacunata</i>	1	0	0
<i>Proteus mirabilis</i>	3	5	4
<i>Serratia marcescens</i>	0	0	1
<i>Serratia proteamaculans</i>	0	1	0
Anaerobic			
<i>Actinomyces israelii</i>	0	1	0
<i>Bacteroides eggerthii</i>	1	0	0
<i>Prevotella loescheii</i>	1	0	0

<i>Prevotella oralis</i>	0	0	1
Multiple ^c	31	33	37
Total	117 (64.3)	127 (64.1)	131 (69.3)

^a Not otherwise speciated

^b Biotype 1

^c Appendix C.7 has a complete summary.

Medical Officer's Comment

The frequency of isolation of various pathogens in this trial reflected the predominant roles of *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis*, in that order of decreasing frequency, as the responsible pathogens in acute maxillary sinusitis.

At baseline, 5% (23/499) of pathogens were resistant to cefdinir and 3% (15/495) were resistant to amox/clav (Table 11). No statistically significant differences were observed in the numbers of cefdinir- and amox/clav-resistant isolates for all pathogens ($p = 0.117$), *H. influenzae* ($p = 0.317$), *S. pneumoniae* ($p = 0.157$), or *M. catarrhalis* ($p = 0.317$).

The majority of *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis* isolates were susceptible to study medication at baseline regardless of their β -lactamase status. Three β -lactamase-negative *H. influenzae* isolates were cefdinir-resistant and 1 was amoxicillin-resistant. One β -lactamase-positive *M. catarrhalis* isolate was also cefdinir-resistant.

TABLE 38. Distribution of Baseline Pathogens by Susceptibility to Study Medication - Pathogens From All Patients With Baseline Pathogens
(Number of Pathogens)
(Page 1 of 3)

Baseline Pathogen	N	Cefdinir				Amox/Clav			
		S	I	R	U	S	I	R	U
Gram-Positive									
<i>Corynebacterium pyogenes</i>	2	2	0	0	0	2	0	0	0
<i>Corynebacterium spp</i>	2	1	0	0	1	1	0	0	1
<i>Enterococcus faecalis</i>	1	0	0	1	0	1	0	0	0
<i>Gemella morbillorum</i>	4	3	0	1	0	4	0	0	0
<i>Staphylococcus aureus</i>	45	45	0	0	0	42	0	3	0
<i>Staphylococcus epidermidis</i>	15	12	1	2	0	14	0	1	0
<i>Staphylococcus hominis</i>	1	1	0	0	0	1	0	0	0
<i>Staphylococcus lugdunensis</i>	1	1	0	0	0	1	0	0	0
<i>Staphylococcus</i> , Coagulase-Negative	1	1	0	0	0	1	0	0	0
<i>Streptococcus agalactiae</i>	1	1	0	0	0	1	0	0	0
<i>Streptococcus anginosus</i>	5	4	0	1	0	5	0	0	0
<i>Streptococcus mitis</i>	3	3	0	0	0	3	0	0	0
<i>Streptococcus pneumoniae</i>	110	106	2	2	0	107	0	0	3
<i>Streptococcus pyogenes</i>	8	8	0	0	0	8	0	0	0
<i>Streptococcus</i> Group C	3	3	0	0	0	3	0	0	0

<i>Streptococcus</i> Group F	2	2	0	0	0	2	0	0	0
<i>Streptococcus</i> , α -hemolytic ^a	2	1	0	0	1	1	0	0	1
<i>Streptococcus</i> , β -hemolytic ^a	3	3	0	0	0	3	0	0	0
Total	209	197	3	7	2	200	0	4	5

N = Number of Pathogens; S = Susceptible; I = Moderate or intermediate susceptibility; R = Resistant; U = Unknown susceptibility.

^a Not otherwise speciated

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TABLE 38. Distribution of Baseline Pathogens by Susceptibility to Study
Medication - Pathogens From All Patients With Baseline Pathogens
(Number of Pathogens)

(Page 2 of 3)

Baseline Pathogen	N	Cefdinir				Amox/Clav			
		S	I	R	U	S	I	R	U
Gram-Negative									
<i>Acinetobacter calcoaceticus</i> var <i>anitratus</i>	2	1	0	1	0	2	0	0	0
<i>Acinetobacter junii</i>	1	0	1	0	0	0	1	0	0
<i>Citrobacter diversus</i>	2	2	0	0	0	1	0	1	0
<i>Citrobacter freundii</i>	1	1	0	0	0	0	0	1	0
<i>Comamonas acidovorans</i>	1	0	1	0	0	1	0	0	0
<i>Eikenella corrodens</i>	3	3	0	0	0	3	0	0	0
<i>Enterobacter amnigenus</i>	1	0	0	1	0	0	0	1	0
<i>Enterobacter cloacae</i>	1	0	1	0	0	0	0	1	0
<i>Escherichia coli</i>	7	7	0	0	0	7	0	0	0
<i>Escherichia vulneris</i>	1	1	0	0	0	0	0	1	0
<i>Haemophilus aphrophilus</i>	1	1	0	0	0	1	0	0	0
<i>Haemophilus ducreyi</i>	1	1	0	0	0	0	0	1	0
<i>Haemophilus influenzae</i> , β -lactamase +	16	16	0	0	0	16	0	0	0
<i>Haemophilus influenzae</i> , β -lactamase -	132 ^b	126 ^b	3	3	0	131 ^b	0	1	0
<i>Haemophilus parainfluenzae</i> , β -lactamase -	17	16	1	0	0	16	0	0	1
<i>Haemophilus</i> spp	2	1	0	1	0	2	0	0	0
<i>Klebsiella oxytoca</i>	1	1	0	0	0	1	0	0	0
<i>Klebsiella pneumoniae</i>	3	3	0	0	0	3	0	0	0
<i>Moraxella catarrhalis</i> , β -lactamase +	31	29	1	1	0	31	0	0	0
<i>Moraxella catarrhalis</i> , β -lactamase -	18	18	0	0	0	17	1	0	0
<i>Moraxella lacunata</i>	1	0	0	1	0	1	0	0	0
<i>Proteus mirabilis</i>	16	15	1	0	0	16	0	0	0
<i>Proteus vulgaris</i>	1	1	0	0	0	1	0	0	0
<i>Serratia marcescens</i>	2	0	0	2	0	0	0	2	0
<i>Serratia proteamaculans</i>	2	0	0	2	0	0	0	2	0
Total	264	243	9	12	0	250	2	11	1
Anaerobic									
<i>Actinomyces israelii</i>	1	1	0	0	0	1	0	0	0
<i>Actinomyces odontolyticus</i>	1	1	0	0	0	1	0	0	0
<i>Bacteroides eggerthii</i>	1	0	0	1	0	1	0	0	0
<i>Bacteroides fragilis</i>	1	1	0	0	0	0	1	0	0
<i>Bacteroides</i> sp	1	0	0	0	1	0	0	0	1
<i>Eubacterium</i> sp	1	1	0	0	0	1	0	0	0
<i>Fusobacterium nucleatum</i>	5	4	0	0	1	4	0	0	1
<i>Fusobacterium</i> sp	1	0	0	0	1	0	0	0	1
<i>Lactobacillus</i> sp	1	1	0	0	0	1	0	0	0
<i>Peptostreptococcus anaerobius</i>	2	2	0	0	0	2	0	0	0
<i>Peptostreptococcus micros</i>	5	5	0	0	0	5	0	0	0
<i>Prevotella buccae</i>	1	1	0	0	0	1	0	0	0

N = Number of Pathogens; S = Susceptible; I = Moderate or intermediate susceptibility; R = Resistant; U = Unknown susceptibility.

• Two isolates included in these totals were not tested for β -lactamase activity.

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TABLE 38. Distribution of Baseline Pathogens by Susceptibility to Study Medication - Pathogens From All Patients With Baseline Pathogens (Number of Pathogens)
(Page 3 of 3)

Baseline Pathogen	N	Cefdinir				Amox/Clav			
		S	I	R	U	S	I	R	U
Anaerobic (continued)									
<i>Prevotella intermedia</i>	1	1	0	0	0	1	0	0	0
<i>Prevotella loescheii</i>	2	1	0	1	0	2	0	0	0
<i>Prevotella melaninogenica</i>	2	1	0	0	1	1	0	0	1
<i>Prevotella oralis</i>	2	1	0	1	0	2	0	0	0
<i>Prevotella oris</i>	2	1	0	1	0	2	0	0	0
<i>Prevotella ruminicola</i>	1	1	0	0	0	1	0	0	0
<i>Prevotella</i> sp	1	1	0	0	0	1	0	0	0
Anaerobic Streptococcus ^a	2	0	0	0	2	0	0	0	2
Anaerobic Gram-Positive Bacillus ^a	1	0	0	0	1	0	0	0	1
Total	35	24	0	4	7	27	1	0	7
Total	508	464	12	23	9	477	3	15	13

N = Number of Pathogens; S = Susceptible; I = Moderate or intermediate susceptibility; R = Resistant; U = Unknown susceptibility.

^a Not otherwise speciated

5.1.3. Clinical Signs and Symptoms²

Patient signs and symptoms were similar for each of the patient populations and treatment groups at baseline (Table 12). At baseline, patient clinical scores could range from 0 through 5, and the score in at least 1 sinus had to range from 2 through 21. Actual patient, left sinus, and right sinus clinical scores at baseline ranged from 2.2 to 2.5 across patient populations and treatment groups.

⁽²⁾ Appendices C.8 through C.13, Patient and Sinus Clinical Signs and Symptoms

TABLE 39. Signs and Symptoms at Baseline
(Percentage of Patients)

Signs and Symptoms	All Patients			Evaluable Patients		
	Cefdinir		Amox/Clav N = 189	Cefdinir		Amox/Clav N = 106
	QD N = 182	BID N = 198		QD N = 93	BID N = 96	
Patient						
Headache	83.0	88.9	84.1	80.6	88.5	84.0
Alteration of Smell	59.9	61.1	59.3	61.3	65.6	66.0
Fever	17.0	14.1	11.6	21.5	18.8	14.2
Sinus						
Left Purulent Nasal Discharge	86.3	83.8	88.9	87.1	86.5	91.5
Right Purulent Nasal Discharge	83.5	85.9	85.2	84.9	82.3	85.8
Left Facial Pain	67.0	66.7	64.0	60.2	68.8	67.9
Right Facial Pain	60.4	65.7	63.0	57.0	60.4	66.0
Left Facial Tenderness	57.1	63.1	55.6	52.7	68.8	58.5
Right Facial Tenderness	57.7	61.1	61.9	58.1	56.3	63.2
Left Nasal Obstruction	87.9	88.4	93.1	86.0	89.6	93.4
Right Nasal Obstruction	87.9	88.9	83.6	90.3	83.3	85.8

Medical History and Secondary Diagnoses

One hundred patients (34 cefdinir QD-treated patients, 39 cefdinir BID-treated patients, and 27 amox/clav-treated patients) had a history of sinusitis. Nine (5%) cefdinir QD-treated patients, 14 (7%) cefdinir BID-treated patients, and 15 (8%) amox/clav-treated patients reported medical history items considered by the medical monitor to predispose them to acute maxillary sinusitis. Common predisposing conditions included medical histories of allergic rhinitis, nasal surgical procedures (eg, ethmoid surgery), fractured nasal bones, and nasal polyps.

Almost half of the patients in each of the treatment groups reported a significant medical history item (cefdinir QD, 46%; cefdinir BID, 49%; and amox/clav, 46%). Measles and mumps were the most common history items reported. Tonsillectomy and appendectomy were the most common procedures reported.

Prior Medications for Sinusitis

Doxycycline (3% of patients), amox/clav and amoxicillin (both 2%), and penicillin and cefaclor (both 1%) were the most frequently used antibacterial agents for sinusitis within 30 days of study

start.

Concurrent Medications

Xylometazoline (42% of patients), xylometazoline hydrochloride (13%), and oxymetazoline (10%) were reported as the most common concurrent medications. They were nasal decongestants that could be used up to 4 days after the sinus puncture procedure. Acetylcysteine (10% of patients) was also a common concurrent medication.

Disulfiram (Antabuse®) was not used by patients during the study.

Patient Treatment

The median patient exposure was 10 days for cefdinir QD- and BID-treated patients and 11 days for amox/clav-treated patients for each patient population (Table 13). Patients starting cefdinir BID or amox/clav late on Day 1 finished medication on Day 11, thereby contributing to the large number of patients with 11 days exposure. In all treatment groups, patients who missed doses during treatment and took them at the end of therapy also contributed to the number of patients who took study medication longer than the prescribed 10-day treatment period.

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**TABLE 40. Patient Exposure to Study Medication - All Patients
(Number of Patients)**

Days of Study Medication	Cefdinir		Amox/Clav N = 189
	QD N = 182	BID N = 198	
1	0	1	1
2	1	2	1
3	1	0	0
4	0	3	1
5	2	4	0
6	0	0	2
7	0	3	1
8	0	0	2
9	0	0	6
10	174	126	78
11	0	52	94
Median	10	10	11
Unknown ^a	4	7	3

^a Includes 1 cefdinir QD- and 1 cefdinir BID-treated patient who received no study medication

Medical Officer's Comment

The population enrolled was appropriate by history. The occurrence of predisposing medical history, such as prior sinus surgery, was expected and did not compromise evaluability of the patients. The coincident use of nasal decongestants was allowed by protocol. The use of antibiotics within 30 days of entrance into the study was also not frequent enough to pose a problem.

Patient Disposition

Of the 569 patients who entered the study, 527 (93%) completed treatment (according to the investigator), 549 (97%) completed the TOC visit, and 500 (88%) completed the LTFU visit (Table 14). Two centers (Centers 1 and 2) that were military installations probably contributed to the high completion rates observed in this study.

TABLE 41. Patient Disposition - All Patients
[Number (%) of Patients]

Disposition	Cefdinir		Amox/Clav	Total
	QD	BID		
Randomized to Treatment	182	198	189	569
Withdrawn Prior to End of Treatment				
Adverse Event	2 (1.1)	12 (6.1)	12 (6.3)	26 (4.6)
Lack of Compliance	1 (0.5)	4 ^a (2.0)	3 (1.6)	8 (1.4)
No Baseline Pathogen	2 ^a (1.1)	0 (0.0)	0 (0.0)	2 (0.4)
Resistant Baseline Pathogen	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.4)
Lack of Efficacy	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Other ^b	0 (0.0)	1 (0.5)	2 (1.1)	3 (0.5)
Completed Treatment ^c	176 (96.7)	181 (91.4)	170 (89.9)	527 (92.6)
Completed Follow-Up Visits^c				
TOC	175 (96.2)	193 (97.5)	181 (95.8)	549 (96.5)
LTFU	166 (91.2)	170 (85.9)	164 (86.8)	500 (87.9)

^a Two patients (1 cefdinir QD- and 1 cefdinir BID-treated) were randomized but did not receive study medication.

^b Patients in this category either lost their study medication, had it stolen, or the patient was lost to follow-up.

^c Based on the investigator assessment of patient status at the end of treatment.

Medical Officer's Comment

The population of patients randomized to treatment was more than sufficient by the statistical goals of the protocol design. The proportions of patients completing treatment and completing TOC and LTFU visits, in all arms, were high.

Protocol variations that did not exclude patients from the evaluable analyses included patients who had no ongoing purulent nasal discharge at baseline (6 patients); had endoscopy also performed at baseline (69 patients); had a history of sensitivity to β -lactams (3); had abnormal hepatic enzyme levels at baseline (7); had patient numbers mistakenly assigned out of order (6); had an investigator assessment done on a different day than the assessment of clinical signs and symptoms (5); and were less than the center-specified (but not protocol-specified) age limit (1). Appendix A.8 contains a complete list of these patients.

Efficacy Evaluations

Patients were most frequently excluded from the evaluable efficacy (TOC) analyses because no pathogen was proven at baseline, medication was not taken as prescribed (i.e., insufficient duration of treatment, significant number (>30%) of missed doses, or an overdose), a follow-up sinus x-ray was missed, or baseline pathogens were resistant to either study medication (Table 15).

Patients were most frequently disqualified from the qualified efficacy (LTFU) analyses because of concurrent use of antibacterial agents and clinical assessment performed outside the specified range of study days. A complete list of reasons for excluding patients from the clinically evaluable and MITT analyses appear in the appendices.

Table 16 provides a comparison of the numbers of patients in each of the patient populations for analysis.

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**TABLE 42. Reasons Patients Were Not Evaluable at TOC or Disqualified at LTFU^a
(Number of Patients)**

	Cefdinir		Amox/Clav
	QD	BID	
Reasons Patients Were Not Clinically Evaluable for TOC Analyses			
Medication Not Taken as Prescribed ^b	8	20	9
Follow-Up X-ray Missed	8	14	13
Baseline Pathogen Resistant to Either Study Drug	9	11	10
Clinical Assessment Out of Range ^b	7	11	8
Clinical Assessment Missed	4	7	4
Concurrent Antibacterial Agent	5	2	3
Disallowed Prior Antibacterial	1	1	2
Baseline X-ray Missed	1	0	2
No Baseline Signs or Symptoms	0	1	0
Total Patients Not Clinically Evaluable	31	43	31
Additional Reasons Patients Were Not Evaluable for TOC Analyses			
No Proven Baseline Pathogen	66	71	58
Culture Out of Range ^b	4	6	3
No Baseline Susceptibility Tests	4	3	2
Total Patients Not Evaluable	89	102	83
Patients Who Were Evaluable at TOC	93	96	106
Reasons Clinically Evaluable Patients Were Disqualified From LTFU Analyses			
Concurrent Antibacterial Agent ^b	9	12	7
Clinical Assessment Out of Range ^b	6	8	13
Clinical Assessment Missed	6	7	8
Total Patients Clinically Disqualified	20	27	26
Reasons Evaluable Patients Were Disqualified from LTFU Analyses			
Concurrent Antibacterial Agent ^b	5	9	5
Clinical Assessment Out of Range ^b	3	4	8
Culture Out of Range ^b	1	3	1
Clinical Assessment Missed	0	0	1
Total Patients Disqualified	8	14	14

Patients Who Were Qualified at LTFU

85

82

92

- ^a Patients who had multiple reasons for being nonevaluable or disqualified were counted for each reason that applied.
- ^b Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early recurrences were not removed from the analyses for these reasons. Patients who had a culture done early because they were early recurrences were not removed from the microbiologically-clinically evaluable analyses for this reason.

TABLE 43. Patients Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir		Amox/Clav
	QD	BID	
Intent-to-Treat (ITT)	182 (100.0)	198 (100.0)	189 (100.0)
Modified Intent-to-Treat (MITT)	116 (63.7)	124 (62.6)	127 (67.2)
Clinically Evaluable	151 (83.0)	155 (78.3)	158 (83.6)
Evaluable	93 (51.1)	96 (48.5)	106 (56.1)
Qualified ^a	85 (91.4)	82 (85.4)	92 (86.8)

^a As a percentage of Evaluable patients.

6.2.2.1.1. Microbiologic Eradication by Pathogen³

For evaluable patients, the microbiologic eradication rates by pathogen were 98% (121/123) for the cefdinir QD treatment group, 90% (118/131) for cefdinir BID, and 93% (128/138) for amox/clav (Table 17).

The 95% lower confidence limit for the difference between cefdinir QD versus amox/clav was +1.5% under the pooled analysis and -0.3% under the center-adjusted analysis (fixed criteria, -10%). These lower confidence limits showed that cefdinir QD is superior to amox/clav under the pooled analysis because the limit lies above 0, and equivalent to or better than amox/clav under the center-adjusted analysis. The 95% lower confidence limit for the difference between cefdinir BID versus amox/clav was -8.3%, showing that cefdinir BID was equivalent to or better than amox/clav (fixed criteria, -10%). The exploratory CMH tests showed a significant difference

⁽³⁾ Appendices C.29 and C.30, Microbiologic Response Rates at TOC

between cefdinir QD versus amox/clav ($p = 0.039$) in favor of cefdinir QD and no significant difference between cefdinir BID versus amox/clav ($p = 0.496$).

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TABLE 44. Microbiologic Eradication Rate by Pathogen at TOC - Pathogens From Evaluable Patients

(Page 1 of 2)

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
<i>Corynebacterium pyogenes</i>	0/0	-	0/0	-	1/1	100.0
<i>Corynebacterium</i> sp	0/0	-	1/1	100.0	0/0	-
<i>Gemella morbillorum</i>	1/1	100.0	0/0	-	2/2	100.0
<i>Staphylococcus aureus</i>	15/15	100.0	13/15	86.7	7/10	70.0
<i>Staphylococcus epidermidis</i>	3/3	100.0	5/5	100.0	3/3	100.0
<i>Staphylococcus hominis</i>	1/1	100.0	0/0	-	0/0	-
<i>Streptococcus agalactiae</i>	0/0	-	0/1	0.0	0/0	-
<i>Streptococcus anginosus</i>	2/2	100.0	0/0	-	1/1	100.0
<i>Streptococcus mitis</i>	0/0	-	2/2	100.0	0/0	-
<i>Streptococcus pneumoniae</i>	35/35	100.0	30/31	96.9	25/26	96.1
<i>Streptococcus pyogenes</i>	3/3	100.0	1/1	100.0	2/2	100.0
<i>Streptococcus</i> Group C	2/2	100.0	0/0	-	1/1	100.0
<i>Streptococcus</i> Group F	1/1	100.0	0/0	-	1/1	100.0
<i>Streptococcus</i> , α -hemolytic ^a	1/1	100.0	0/0	-	0/0	-
<i>Streptococcus</i> , β -hemolytic ^a	2/2	100.0	1/1	100.0	0/0	-
Gram-Negative						
<i>Acinetobacter calcoaceticus</i> var <i>anitratus</i>	0/0	-	0/0	-	1/1	100.0
<i>Citrobacter diversus</i>	1/1	100.0	0/0	-	0/0	-
<i>Eikenella corrodens</i>	0/0	-	0/1	0.0	0/0	-
<i>Escherichia coli</i>	3/3	100.0	1/1	100.0	2/2	100.0
<i>Haemophilus aphrophilus</i>	0/0	-	1/1	100.0	0/0	-
<i>Haemophilus influenzae</i> , β -lactamase +	3/4	75.0	2/2	100.0	6/6	100.0
<i>Haemophilus influenzae</i> , β -lactamase -	19/19	100.0	34/39 ^b	87.2	46/50 ^b	92.0
<i>Haemophilus parainfluenzae</i> , β -lactamase -	7/7	100.0	1/1	100.0	5/6	83.3
<i>Haemophilus</i> sp	1/1	100.0	0/0	-	0/0	-
<i>Klebsiella oxytoca</i>	0/0	-	0/0	-	1/1	100.0
<i>Klebsiella pneumoniae</i>	3/3	100.0	0/0	-	0/0	-
<i>Moraxella catarrhalis</i> , β -lactamase +	7/8	87.5	8/8	100.0	9/9	100.0
<i>Moraxella catarrhalis</i> , β -lactamase -	3/3	100.0	8/8	100.0	4/4	100.0
<i>Proteus mirabilis</i>	2/2	100.0	2/3	66.7	6/7	85.7
<i>Proteus vulgaris</i>	0/0	-	0/0	-	1/1	100.0

n/N = Number of pathogens eradicated/total number of pathogens.

^a Not otherwise speciated^b Two pathogens, 1 from a cefdinir BID-treated patient and 1 from an amox/clav-treated patient, were not tested for β -lactamase production but are included in these totals.

TABLE 44. Microbiologic Eradication Rate by Pathogen at TOC - Pathogens From Evaluable Patients

(Page 2 of 2)

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID		n/N	%
	n/N	%	n/N	%		
Anaerobic						
<i>Actinomyces israelii</i>	0/0	—	1/1	100.0	0/0	—
<i>Actinomyces odontata</i>	0/0	—	1/1	100.0	0/0	—
<i>Bacteroides fragilis</i>	1/1	100.0	0/0	—	0/0	—
<i>Eubacterium</i> sp	0/0	—	1/1	100.0	0/0	—
<i>Fusobacterium nucleatum</i>	0/0	—	2/2	100.0	0/0	—
<i>Lactobacillus</i> sp	0/0	—	1/1	100.0	0/0	—
<i>Peptostreptococcus anaerobius</i>	1/1	100.0	0/0	—	0/0	—
<i>Peptostreptococcus micros</i>	1/1	100.0	½	50.0	1/1	100.0
<i>Prevotella buccae</i>	0/0	—	0/0	—	1/1	100.0
<i>Prevotella intermedia</i>	1/1	100.0	0/0	—	0/0	—
<i>Prevotella loescheii</i>	1/1	100.0	0/0	—	0/0	—
<i>Prevotella melaninogenica</i>	1/1	100.0	0/0	—	0/0	—
<i>Prevotella oralis</i>	0/0	—	0/0	—	1/1	100.0
<i>Prevotella oris</i>	0/0	—	0/0	—	1/1	100.0
<i>Prevotella ruminicola</i>	0/0	—	0/1	0.0	0/0	—
<i>Prevotella</i> sp	0/0	—	1/1	100.0	0/0	—
Total	121/123	98.4	118/131	90.1	128/138	92.8

n/N = Number of pathogens eradicated/total number of pathogens.

Microbiologic Eradication by Patient

For evaluable patients, the microbiologic eradication rates by patient were 98% (91/93) for the cefdinir QD treatment group, 89% (85/96) for cefdinir BID, and 93% (99/106) for amox/clav (Table 18).

The 95% lower confidence limit for the difference between cefdinir QD versus amox/clav was -0.2%. This result shows that cefdinir QD was equivalent to or better than amox/clav (fixed criteria, -10%). For cefdinir BID, analysis by the 2 different methods resulted in differing conclusions. In the pooled analysis, the lower confidence limit for the difference between cefdinir BID and amox/clav was -11.5 showing amox/clav is better than cefdinir BID (fixed criteria, -10%). In the center-adjusted analysis, the lower confidence limit was -9.1 showing that cefdinir BID is equivalent to or better than amox/clav (fixed criteria, -10%). The fact that the

lower confidence limit in the pooled analysis was very close to the -10% cutoff and the center-adjusted lower confidence limit was within the -10% cutoff indicates that cefdinir BID and amox/clav are marginally equivalent. The CMH tests showed no significant differences between cefdinir QD versus amox/clav ($p = 0.169$) or between cefdinir BID versus amox/clav ($p = 0.243$).

TABLE 45. Microbiologic Eradication Rate by Patient (According to Baseline Pathogen) at TOC - Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
<i>Gemella morbillorum</i>	1/1	100.0	0/0	—	2/2	100.0
<i>Staphylococcus aureus</i>	10/10	100.0	10/12	83.3	4/7	57.1
<i>Staphylococcus epidermidis</i>	2/2	100.0	3/3	100.0	2/2	100.0
<i>Streptococcus mitis</i>	0/0	—	1/1	100.0	0/0	—
<i>Streptococcus pneumoniae</i>	18/18	100.0	19/20	95.0	18/18	100.0
<i>Streptococcus pyogenes</i>	2/2	100.0	1/1	100.0	2/2	100.0
<i>Streptococcus</i> Group C	1/1	100.0	0/0	—	1/1	100.0
<i>Streptococcus</i> Group F	1/1	100.0	0/0	—	0/0	—
<i>Streptococcus</i> , β -hemolytic ^a	2/2	100.0	1/1	100.0	0/0	—
Gram-Negative						
<i>Escherichia coli</i>	2/2	100.0	1/1	100.0	2/2	100.0
<i>Haemophilus aphrophilus</i>	0/0	—	1/1	100.0	0/0	—
<i>Haemophilus influenzae</i>	16/17	94.1	14/19	73.7	25/25	100.0
<i>Haemophilus parainfluenzae</i>	1/1	100.0	1/1	100.0	4/5	80.0
<i>Klebsiella pneumoniae</i>	1/1	100.0	0/0	—	0/0	—
<i>Moraxella catarrhalis</i>	8/9	88.9	8/8	100.0	9/9	100.0
<i>Proteus mirabilis</i>	2/2	100.0	2/3	66.7	3/4	75.0
Anaerobic						
<i>Actinomyces israelii</i>	0/0	—	1/1	100.0	0/0	—
<i>Prevotella loescheii</i>	1/1	100.0	0/0	—	0/0	—
<i>Prevotella oralis</i>	0/0	—	0/0	—	1/1	100.0
Multiple^b	23/23	100.0	22/24	91.7	26/28	92.9
Total	91/93	97.8	85/96	88.5	99/106	93.4

n/N = Number of patients with eradication/total number of patients.

^a Not otherwise specified

^b Appendix C.31 has a complete summary of patients with multiple pathogens.

Four patients each had a *S. pneumoniae* isolate that was either intermediately susceptible or resistant to cefdinir in in vitro assays. Two of the patients were treated with cefdinir QD, 1 with cefdinir BID, and 1 with amox/clav. All 4 of these patients were classified as clinical cures and all 4 *S. pneumoniae* isolates were eradicated.

At TOC, 2 evaluable cefdinir QD-treated patients, 11 cefdinir BID-treated patients, and 7 amox/clav-treated patients had 2, 13, and 10 persistent pathogens, respectively (Appendix E.2). For cefdinir QD-treated patients with persistent pathogens, 1 *H. influenzae* isolate remained susceptible to study medication at TOC and 1 *M. catarrhalis* was not tested. For cefdinir BID-treated patients, 8 persistent pathogens remained susceptible, and 5 were not tested; for amox/clav-treated patients, 4 remained susceptible and 6 were not tested. *H. influenzae* and *S. aureus* were the most common persistent pathogens at TOC for the cefdinir BID (5 and 2 isolates, respectively) and amox/clav (4 and 3 isolates, respectively) treatment groups.

Clinical Cure

The clinical cure rates presented below are based on combined investigator/sponsor assessments. At the TOC visit, all evaluable patients in each of the 3 treatment groups had the same clinical assessment on both the investigator and combined assessment scales of clinical response (Table 46).

TABLE 46. Investigator vs Combined Investigator/Sponsor Clinical Response Determination at the TOC Visit - Evaluable Patients

Investigator Determination	Combined Investigator/Sponsor Determination					
	Cefdinir QD N = 93		Cefdinir BID N = 96		Amox/Clav N = 106	
	Cure	Failure	Cure	Failure	Cure	Failure
Cure	88	0	86	0	102	0
Failure	0	5	0	10	0	4
Not Assessable	0	0	0	0	0	0

For evaluable patients, the clinical cure rates by patient were 95% (88/93) for the cefdinir QD treatment group, 90% (86/96) for cefdinir BID, and 96% (102/106) for amox/clav (Table 20).

The 95% lower confidence limit for the difference between cefdinir QD versus amox/clav was

-6.5% and between cefdinir BID versus amox/clav was -12.6% showing that cefdinir QD was equivalent to or better than amox/clav while amox/clav was better than cefdinir BID (fixed criteria, -10%). The CMH tests showed no significant differences between cefdinir QD versus amox/clav ($p = 0.594$) or between cefdinir BID versus amox/clav ($p = 0.074$).

TABLE 47. Clinical Cure Rate by Patient (According to Their Baseline Pathogens) at TOC - Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
<i>Gemella morbillorum</i>	1/1	100.0	0/0	—	2/2	100.0
<i>Staphylococcus aureus</i>	10/10	100.0	11/12	91.7	7/7	100.0
<i>Staphylococcus epidermidis</i>	2/2	100.0	3/3	100.0	2/2	100.0
<i>Streptococcus mitis</i>	0/0	—	1/1	100.0	0/0	—
<i>Streptococcus pneumoniae</i>	18/18	100.0	18/20	90.0	18/18	100.0
<i>Streptococcus pyogenes</i>	2/2	100.0	1/1	100.0	2/2	100.0
<i>Streptococcus</i> Group C	1/1	100.0	0/0	—	1/1	100.0
<i>Streptococcus</i> Group F	1/1	100.0	0/0	—	0/0	—
<i>Streptococcus</i> , β -hemolytic ^a	2/2	100.0	1/1	100.0	0/0	—
Gram-Negative						
<i>Escherichia coli</i>	2/2	100.0	1/1	100.0	2/2	100.0
<i>Haemophilus aphrophilus</i>	0/0	—	1/1	100.0	0/0	—
<i>Haemophilus influenzae</i>	15/17	88.2	14/19	73.7	24/25	96.0
<i>Haemophilus parainfluenzae</i>	1/1	100.0	1/1	100.0	4/5	80.0
<i>Klebsiella pneumoniae</i>	0/1	0.0	0/0	—	0/0	—
<i>Moraxella catarrhalis</i>	7/9	77.8	8/8	100.0	9/9	100.0
<i>Proteus mirabilis</i>	2/2	100.0	3/3	100.0	4/4	100.0
Anaerobic						
<i>Actinomyces israelii</i>	0/0	—	1/1	100.0	0/0	—
<i>Prevotella loescheii</i>	1/1	100.0	0/0	—	0/0	—
<i>Prevotella oralis</i>	0/0	—	0/0	—	1/1	100.0
Multiple^b	23/23	100.0	22/24	91.7	26/28	92.9
Total	88/93	94.6	86/96	89.6	102/106	96.2

n/N = Number of patients who were cured (according to the combined investigator/sponsor clinical assessment)/total number of patients.

^a Not otherwise speciated

^b Appendix C.33 has a complete summary of patients with multiple pathogens.

Microbiologic Versus Clinical Response Rates

Most (91%, 268/295) evaluable patients had successful microbiologic and clinical outcomes (i.e., microbiologic eradication plus clinically cured); another 12 had failing responses (i.e., persistent pathogens plus clinical failure) (Table 21). For those patients who had inconsistent microbiologic and clinical outcomes (i.e., eradication plus failure or persistence plus cure), McNemar's test did not detect a significant pattern to the discordant assessments for any treatment group (cefdinir QD, $p = 0.083$; cefdinir BID, $p = 0.705$; amox/clav, $p = 0.180$).

TABLE 48. Microbiologic Versus Clinical Response at the
Test-of-Cure Visit - Evaluable Patients
[Number (%) of Patients]

Microbiologic Response	Clinical Response	
	Cure ^a	Failure
Cefdinir QD, N = 93		
Patients With Eradication	88	3
Patients With Persistence	0	2
Cefdinir BID, N = 96		
Patients With Eradication	82	3
Patients With Persistence	4	7
Amox/Clav, N = 106		
Patients With Eradication	98	1
Patients With Persistence	4	3

^a Combined investigator/sponsor clinical determination

Medical Officer's Comment

The clinical and microbiological outcomes demonstrated comparable efficacy between cefdinir and amoxicillin/clavulanate. Eradication of the three main pathogens (*Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis*) appeared to be greater with cefdinir qd than with cefdinir bid

Safety

Adverse Events

Overview

Safety was evaluated using data from the 567 patients who received study medication. Forty-one percent (75/181) of these patients in the cefdinir QD treatment group, 45% (88/197) in the cefdinir BID group, and 50% (94/189) in the amox/clav group experienced at least 1 adverse event (Table 30). Thirty-three percent (60/181) of the patients in the cefdinir QD group, 36% (70/197) in the cefdinir BID group, and 39% (74/189) in the amox/clav group had adverse events considered by the investigator to be drug-associated.

Two percent (3 patients) of the cefdinir QD group and 6% each (12 patients) of the cefdinir BID and amox/clav groups discontinued treatment due to an adverse event. One additional cefdinir BID-treated patient withdrew from the study due to an adverse event after completing treatment. Nine patients (1 in the cefdinir QD group, 3 in the cefdinir BID group, and 5 in the amox/clav group) experienced a serious adverse event. No deaths occurred during the study.

All and Drug-Associated Adverse Events

Most adverse events that occurred were related to the digestive system and body as a whole for each of the 3 treatment groups (Table 31). Most of the adverse events that related to the digestive and urogenital systems, skin and appendages, and to the metabolic and nutritional area were considered drug-associated by investigators.

Although most adverse events occurred in the amox/clav treatment group, there were no significant differences between the numbers of patients experiencing adverse events when the cefdinir QD and amox/clav groups ($p = 0.074$) or the cefdinir BID and amox/clav groups ($p = 0.473$) were compared. In addition, there were no significant difference between the cefdinir QD and amox/clav groups ($p = 0.140$) or the cefdinir BID and amox/clav groups ($p = 0.550$) when the numbers of patients experiencing drug-associated adverse events were compared.

The most frequent adverse events experienced were diarrhea (29%), vaginal moniliasis/vaginitis (based on total number of females only, 4%), and headache (3%) in the cefdinir QD group; diarrhea (33%), vaginal moniliasis/vaginitis (females only, 6%), and headache (3%) in the cefdinir BID group; and diarrhea (30%), vaginal moniliasis/vaginitis (females only, 9%), abdominal pain (4%), urticaria (3%), headache (2%), and pain (2%) in the amox/clav group. All

other adverse events occurred in <2% of patients. There were no significant differences in the incidence of diarrhea when the cefdinir QD and amox/clav groups ($p = 0.603$) or the cefdinir BID and amox/clav groups ($p = 0.364$) were compared.

Diarrhea rates varied by country. In particular, high rates were seen in Finland (approximately 40%), where many of the patients were military conscripts. It is postulated that the increased reporting of diarrhea in this patient population was due to the fact that a report of diarrhea would excuse a soldier from the strenuous physical activities involved in military duty.

During treatment, the most frequent adverse events were diarrhea (27%) and headache (2%) in the cefdinir QD group; diarrhea (29%) in the cefdinir BID group; and diarrhea (29%), abdominal pain (3%), vaginal moniliasis (3%), headache (2%), and urticaria (2%) in the amox/clav group. All other adverse events during treatment occurred in <2% of patients.

Medical Officer's Comment

The adverse effects profile of cefdinir in this trial was comparable to its profile in trial #983-6.

Medical Officer's Conclusions

1. Cefdinir is effective and safe in both the 300 mg bid and 600 mg qd regimens for the treatment of acute maxillary sinusitis.
2. The pathogens for which approval is recommended are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
3. The once-daily regimen appears to have a slightly lower incidence of adverse events, and with the exception of *Streptococcus pneumoniae*, a higher rate of microbiologic eradication. The clinical pharmacokinetic profile of the drug, however, suggest that twice-daily use should be a useful alternative regimen.

/S/

Andrew M. Bonwit, M.D.
Medical Officer

30 June 1999

cc:

Original NDA 50-739
Original NDA 50-749
HFD-520/Division Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/SMO/J. Soreth
HFD-340
HFD-40/DDMAC

Concurrence:

HFD-520/DivDir/G. Chikami

Gary K. Cal
7/1/99

Trial #983-37
Acute Maxillary Sinusitis

Joint Medical & Statistical Review of NDA 50-739, 50-749

General Information

Applicant:

Parke-Davis Pharmaceutical Research
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047
(313)996-7000

Contact Person:

Drusilla Scott, Ph.D.

Submission/review dates

Date of Submission:

September 3, 1996 (NDA 50-739)
December 30, 1996 (NDA 50-749)
Date of major amendment, June 23, 1997

CDER Stamp Dates:

September 4, 1996 (NDA 50-739)
December 31, 1996 (NDA 50-749)
Date of major amendment, June 24, 1997

Date Received by Reviewer:

October, 1996

Date Review Begun:

November, 1996

Drug Identification

Generic Name:

Cefdinir 300 mg Capsules (NDA 50-739)
Cefdinir Oral Suspension 125 mg/5ml (NDA 50-749)

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

Proposed Trade Name:

OMNICEF™ Capsules and Oral Suspension

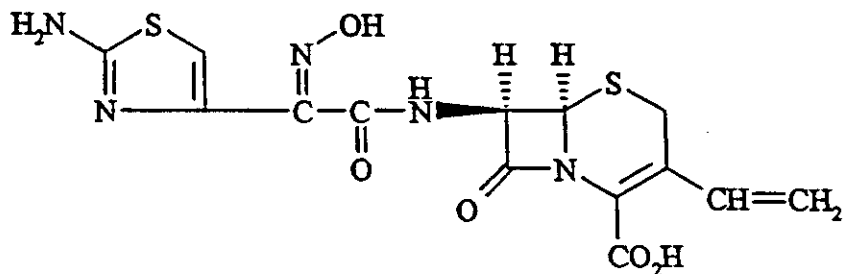
Chemical Name:

[6R-[6 α ,7 β (Z)]]-7[[[(2-amino-4-thiazolyl)(hydroxyimin)acetyl]
a,omp-3-ethynyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-
carboxylic acid

Chemical Structure:

C₁₄H₁₃N₅O₅S₂

Molecular Formula:



Cefdinir

Molecular Weight:

395.42

Pharmacologic Category:

Semisynthetic cephalosporin

Route of Administration:

Oral

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

Related Drugs:

NA

Material Reviewed

NDA Volumes Reviewed:

Volume 1 through 427

Regulatory Background:

The following is the regulatory background as provided by Mr. Carmen DeBellas (DAIDP project manager) :

- ▶ May 2, 1990 -- IND submitted.
- ▶ May 31, 1990 to June 5, 1990 -- Three teleconference discussions of minor deficiencies between FDA and Applicant. DAIDP recommended that study be allowed to begin.
- ▶ June 26, 1990 -- Teleconference discussion concerning dose escalation in studies.
- ▶ August 3, 1990 -- Teleconference regarding comments on preliminary review for Phase I pharmacokinetic study.
- ▶ August 20, 1990 -- Teleconference initiated by Applicant regrading Phase I pharmacokinetic trial in healthy volunteers.
- ▶ August 31, 1990 -- Teleconference providing comments on review of preliminary laboratory data.
- ▶ September 26, 1990 -- Request for information on two drug interactions from studies.
- ▶ October 12, 1990 -- Discussion of dosing schedule for pharmacokinetic studies.
- ▶ October 19, 1990 -- Teleconference regarding initiation of the urinary tract infection study before comment on the protocol is made.
- ▶ November 27, 1990 -- Meeting with Applicant to discuss Phase II/III protocols.
- ▶ January 23, 1991 -- Teleconference clarifying Applicant's meeting minutes.
- ▶ January 23, 1991 -- Teleconference providing comments on multiple recent submissions.
- ▶ January 28, 1991 -- Applicant initiated teleconference for clarification of lower respiratory tract infection protocols.
- ▶ February 8, 1991 -- Teleconference for further discussion of deficiencies in lower respiratory tract infection protocols.
- ▶ February 20, 1991 -- Teleconference providing comments on Phase II/III protocols with emphasis on lower respiratory tract infection.
- ▶ March 23, 1991 -- Teleconference discussing otitis media protocol
- ▶ April 10, 1991 -- Teleconference providing comments on protocol dealing with effect of iron on CI-983.
- ▶ May 28, 1991 -- Letter to sponsor reiterating some comments not addressed since the meeting on November 27, 1990.
- ▶ July 8, 1991 -- Teleconference providing comments on pediatric studies.

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

- ▶ **July 30, 1991** -- Teleconference providing comments on lower respiratory tract infection protocol and pharmacokinetic study.
- ▶ **August 8, 1991** -- Two teleconferences to discuss comments on pharmacokinetic studies in pediatric patients.
- ▶ **November 6 and 8, 1991** -- Teleconferences providing comments on protocols for the community acquired pneumonia and skin and skin structure protocols.
- ▶ **December 16, 1991** -- Teleconference providing comments on otitis media and skin and skin structure protocols.
- ▶ **January 13, 1992** -- Phase II meeting occurred.
- ▶ **October 2, 1992** -- Teleconference providing comments on the pharmacokinetic study evaluating subjects with different degrees of renal function.
- ▶ **February 17, 1993** -- Teleconference discussing sinusitis protocol.
- ▶ **November 24, 1993** -- Meeting regarding discussion of CANDA.
- ▶ **September 22, 1994** -- Meeting presenting clinical development plan for cefdinir.
- ▶ **January 24, 1995** -- Meeting presenting CANDA demonstration.
- ▶ **February 23, 1995** -- Meeting for discussion of criteria used to define adverse event laboratory values.
- ▶ **August 10, 1995** -- Pre-NDA meeting occurred.
- ▶ **September 3, 1996** -- NDA 50,739 submitted for capsule formulation.
- ▶ **December 30, 1996** -- NDA 50,749 submitted for suspension formulation.

Chemistry/Manufacturing Controls

Dr. Shrikant Pagay of DAIDP's Chemistry team reviewed the Applicant's chemistry submission for NDA 50-739. See this document for a complete chemistry review.

Cefdinir is a semisynthetic cephalosporin containing aminothiazole and oxime moieties (see diagram of chemical structure above). There are 2 chiral centers (C-6 and C-7) and cefdinir is prepared and marketed as the 6R-[6 α ,7 β (Z)]isomer. The absolute configuration of cefdinir and the Z-configuration of the oxime moiety have been established through NMR studies. The molecule has three ionizable groups (-COOH, -NH₂ and =N-OH).

The solubility of cefdinir is pH dependent, and it is insoluble in water and other common organic solvents. It is slightly soluble in an acid solution with a pH 4.0 and sparingly soluble in a buffered solution with a pH of 7.4, but insoluble in a buffered solution with a pH 4.0 to 7.4. It is freely soluble in sodium bicarbonate. These findings support a J-shaped pH solubility curve with minimum solubility at pH ~3-4 and maximum solubility at pH ~6-7. Maximum pH stability was observed in aqueous buffered solution to be from pH 3 to 7. This is supported by animal studies which demonstrate the greatest drug stability in the stomach and small intestine.

The capsule formulation is a 300 mg hard gelatin capsule manufactured, tested, and packaged under contract by Eli Lilly Industries in Puerto Rico, with bulk drug substance supplied from

This formulation is identical to

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

300 mg capsules used in the clinical pivotal trials. The *in vitro* dissolution method and specification for capsules conforms to USP requirements.

The suspension formulation is a strawberry-creme flavored powder for oral suspension containing 125 mg/5ml upon constitution with water. The suspension product will be manufactured, tested and packaged under contract by Eli Lilly Industries in Puerto Rico. This formulation differs from the drug used in the clinical trials in that the latter drug has raspberry flavoring and less sucrose (2.9 gm vs 1.5 gm per 5 ml). The Applicant will include the quantity of sucrose in the label so that diabetic patients and those treating diabetic patients will be aware. *In vivo* bioequivalence was established between the proposed formulation and the formulation used in the clinical trials.

DAIDP's chemistry review is not approvable for manufacturing and controls under section 507 of the Act. Deficiencies were found by DAIDP's chemistry reviewer under the following headings: Drug Substance [Description and Characteristics, Specifications and Analytical Methods, Stability]; Drug Product [Components/Composition, Specifications and Methods for Drug Product components, Manufacturer, Specifications and Methods for Drug Product, Container/Closure System, Stability]; Investigational Formulations and Labeling. See Chemistry Review completed by reviewer on April 24, 1997.

Animal Pharmacology/Toxicology:

Dr. Oluwadare Adeyemo of DAIDP's Pharmacotoxicology team reviewed the Applicant's pharmacotoxicology submission and concluded that there are no outstanding issues with respect to this part of the application. The following reflects the summary of Dr. Adeyemo's review. Doses as high as 1000 mg/kg were tested as follows with no observable effects:

Central Nervous System

- ▶ general behavior in rats
- ▶ locomotor activities in the tract test in mice
- ▶ sleeping time induced by hexobarbital in mice
- ▶ the analgesic test in mice
- ▶ the conditioned avoidance response in rates
- ▶ the spinal reflex in rabbits

Autonomic Nervous System

- ▶ epinephrine-induced hypertensive response in rats
- ▶ the contractile response of isolated guinea pig ileum to acetylcholine or histamine
- ▶ the contractile response of isolated rat vas deferens to norepinephrine
- ▶ sympathetic transmission in dogs
- ▶ salivary secretion in dogs

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

Respiratory and Cardiovascular System

- ▶ blood pressure in conscious or anesthetized dogs or conscious rats
- ▶ heart rate in conscious or anesthetized dogs
- ▶ ECG in conscious dogs
- ▶ blood flow in the common carotid artery and femoral artery in dogs

Gastrointestinal Tract

- ▶ gastric secretion in rats
- ▶ restraint stress ulcer in rats
- ▶ intestinal charcoal meal transit in rats

Hematological system

- ▶ bleeding time in mice
- ▶ coagulation time in rats
- ▶ no hemolysis in rabbit blood at 20% concentration

Urinary System and Others

- ▶ the spontaneous contraction of isolated nonpregnant and pregnant rat uterus.

The above items summarize those evaluations performed for assessment of safety pharmacology which found no effect at the dose of 1000 mg/kg. Findings that did emerge are as follows: (1) cefdinir did produce a dose-dependent inhibition of ADP- and collagen-induced aggregation of human platelets, with IC_{50} s of 3.9×10^{-3} g/ml and 4.3×10^{-3} g/ml, respectively; and (2) it also increased urine volume and excretion of Na^+ and K^+ in rats at 1000 mg/kg, po.

Pharmacokinetic and ADME studies on Cefdinir

- ▶ cefdinir distribution is rapid following iv administration
- ▶ V_d approximates extracellular fluid volume
- ▶ $T_{1/2}$ is longer following po than iv administration suggesting absorption rate is slower than elimination rate
- ▶ 76.1% of the iv dose is eliminated unchanged in the urine (renal excretion)
- ▶ plasma cefdinir concentrations in juvenile rats were higher and in juvenile dogs were lower than adult rats and adult dogs, respectively, probably due to effects of age on tubular secretion and volume of distribution, respectively

Toxicokinetic studies on Cefdinir

- ▶ cefdinir distributed rapidly and widely throughout body with V_d equal to the extracellular fluid volume
- ▶ after po dosing in rats, [^{14}C]cefdinir distributed to most tissues in the body, excluding brain, bone marrow, and thyroid

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

- ▶ [¹⁴C]cefdinir reached highest radioequivalents in the gastrointestinal tract, urinary bladder and kidney, with higher and more persistent levels in the bladder and kidney consistent with renal excretion as the primary route of elimination
- ▶ after iv dosing, radioactivity distribution and elimination were similar to that observed following an oral dose

Toxicology studies on Cefdinir

- ▶ 26 week oral toxicity study of cefdinir in rats treated at 5 doses up to 1000 mg/kg demonstrated a NOEL level 100 mg/kg po and resulted in no deaths and no ophthalmic findings, but higher doses showed persistent dark red feces and cecal involvement at autopsy with absolute and relative kidney weights increased 12 and 18% in male rats
- ▶ 26 week oral toxicity study of cefdinir in dogs treated at 4 doses up to 800 mg/kg demonstrated no histopathologic changes on autopsy, dark red stools were observed and attributed to the presence of iron complexed with cefdinir in the gastrointestinal tract
- ▶ nephrotoxicity study of cefdinir in rats treated orally at 4 doses up to 560 mg/kg for 14 days with or without furosemide did not demonstrate nephrotoxicity or exacerbate the effects of furosemide
- ▶ eye mucosa and primary skin irritation studies in rabbits demonstrated that cefdinir is an ocular nonirritant and has low dermal irritation potential
- ▶ cefdinir was not teratogenic in rats or rabbits and it exhibited no adverse effects on fertility, general reproduction and did not affect offspring survival, development, behavior or reproduction

The divisional pharmacology review found cefdinir to be relatively non-toxic and tolerated at high doses *in vivo* animal studies. The only labeling suggestion was that the relevant animal studies be expressed in terms of total body surface area in mg/m² unless AUC ratios can be calculated from animal and human values.

Microbiology

The information in this section was synopsised from Applicant's submission. When relevant, the recommendations and findings of Dr. Sousan Altaie's review (DAIDP's microbiology review team) are incorporated in the Medical officer's notes. Like other cephalosporins, cefdinir exerts its antibacterial activity by inhibiting bacterial cell wall synthesis by inhibiting the transpeptidase enzyme responsible for cross-linking nascent peptidoglycan.

The Applicant reports mean peak plasma concentration (C_{max}) of 2.87 µg/mL was obtained from subjects given a single 600-mg oral dose of cefdinir; a 300-mg dose resulted in a mean C_{max} of 1.6 µg/mL and suggests that these achievable plasma concentrations support the following MIC interpretive breakpoints: Susceptible, MIC ≤ 1 µg/mL; Intermediate, MIC = 2 µg/mL; and Resistant, MIC ≥ 4 µg/mL.

Cefdinir is active *in vitro* against a wide range of gram-positive and gram-negative

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

bacteria. Since cefdinir is highly stable in the presence of many common β -lactamase enzymes, it is active *in vitro* against some β -lactamase producing organisms. A summary of cefdinir for MICs for target organisms as determined in preclinical studies and clinical trials is shown in Table 1 which has been reproduced from the Applicant's submission. The Applicant states that cefdinir is active against most strains of the following microorganisms at concentrations of 1 μ g/mL or less *in vitro*, and in clinical infections:

Gram-Positive Aerobes: *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus pyogenes* (Group A, β -hemolytic streptococci), *Streptococcus agalactiae* (Group B), and *Streptococcus pneumoniae* (penicillin-susceptible strains).

Gram-Negative Aerobes: *Haemophilus influenzae* (including β -lactamase producing strains), *Haemophilus parainfluenzae* (including β -lactamase producing strains), *Moraxella catarrhalis* (including β -lactamase producing strains), *Escherichia coli*, and *Klebsiella pneumoniae*.

The applicant also claims that cefdinir exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μ g/mL or less against ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of cefdinir in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes: *Gemella morbillorum*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Streptococcus* Group C, *Streptococcus* Group G, *Streptococcus intermedius*, *Streptococcus mitis*, and *Streptococcus sanguis*.

Gram-Negative Aerobes: *Aeromonas hydrophila*, *Citrobacter diversus*, *Enterobacter sakazakii*, *Escherichia hermanii*, *Klebsiella oxytoca*, *Pantoea (Enterobacter) agglomerans*, *Pasteurella multocida*, and *Proteus mirabilis*.

Anaerobes: *Peptostreptococcus anaerobius*, *Peptostreptococcus asaccharolyticus*, *Peptostreptococcus magnus*, and *Peptostreptococcus micros*.

Cefdinir is inactive against most strains of *Enterococcus*, methicillin-resistant *Staphylococcus*, *Pseudomonas*, and *Enterobacter* spp.

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

TABLE 1. Summary of Cefdinir MICs for Target Organisms

Pathogen	Preclinical Studies			Clinical Trial Results			
	N	Range	MIC ₉₀	N	Range	MIC ₉₀	MIC ₉₀
Pathogens in Indications & Usage Labeling							
<i>Staphylococcus aureus</i>							
Methicillin/oxacillin unspecified	1865	≤0.002->128	0.8	1108	0.016-0.5	0.016	0.5
Methicillin/oxacillin-resistant	925	0.2->128	>64				
Methicillin/oxacillin-susceptible	1609	0.008-25	0.5				
<i>Streptococcus agalactiae</i>	402	≤0.008-0.5	≤0.03	109	0.16-2.0	0.06	0.12
<i>Streptococcus pneumoniae</i>							
Penicillin susceptibility unspecified	744	≤0.002-8.0	0.1	701	0.008-16.0	0.06	0.5
Penicillin-susceptible	858	0.008-1	0.12				
Penicillin-intermediate	319	0.015-16	4.0				
Penicillin-resistant	404	≤0.03->16	8.0				
<i>Escherichia coli</i>	3248	0.008-128	0.5	169	0.03-16.0	0.25	0.5
<i>Haemophilus influenzae</i>	2035	≤0.015-25	0.5	1139	0.008-16.0	0.5	1.0
<i>Haemophilus parainfluenzae</i>	62	0.03-1	0.05	661	0.008-8.0	0.25	0.5
<i>Klebsiella pneumoniae</i>	1591	≤0.01->128	0.40	173	0.016-16.0	0.12	0.25
<i>Moraxella catarrhalis</i>	1088	≤0.01-32	0.25	375	0.008-16.0	0.25	0.5
Pathogens on In Vitro List in Labeling							
<i>Gemella morbillorum</i>	10	0.05-0.4	0.4	4	0.06-4.0	ND	
<i>Staphylococcus epidermidis</i>							
<i>Staphylococcus haemolyticus</i>							
Methicillin/oxacillin unspecified	208	≤0.025->128	>64	0			
Methicillin/oxacillin-resistant	7	16->128	ND ^a	0			
Methicillin/oxacillin-susceptible	33	0.03->64	0.5	0			
<i>Staphylococcus hominis</i>							
Methicillin/oxacillin unspecified	17	0.03-0.4	0.1	1	0.25	ND	ND
Methicillin/oxacillin-susceptible	12	0.03-0.12	0.12	0			
<i>Streptococcus anginosus</i>	52	0.016-0.25	0.1	6	0.16-16.0	ND	ND
<i>Streptococcus constellatus</i>	25	≤0.025-0.1	0.1	0			
<i>Streptococcus</i> Group C	10	≤0.016-0.03	ND	3	0.016-0.25	ND	ND
<i>Streptococcus</i> Group G	32	0.008-0.03	0.016	14	0.016-1.0	0.03	0.03
<i>Streptococcus intermedius</i>	25	≤0.025-0.2	0.05	0			
<i>Streptococcus mitis</i>	27	0.016-6.25	0.4	3	0.016-1.0	ND	ND
<i>Streptococcus sanguis</i>	31	≤0.025-0.2	0.05	0			
<i>Aeromonas hydrophila</i>	72	≤0.03->16.0	0.5	2	0.25-0.5	ND	ND
<i>Citrobacter diversus</i>	141	≤0.015-64	0.25	21	0.12-0.5	0.12	0.25
<i>Enterobacter sakazakii</i>	13	0.06-2.0	0.25	2	0.5-0.5	ND	ND
<i>Escherichia hermannii</i>	0			9	0.06-1.0	ND	ND
<i>Klebsiella oxytoca</i>	559	≤0.008-128	0.25	54	0.03-0.25	0.125	0.25
<i>Pantoea (Enterobacter) agglomerans</i>	31	≤0.03->4.0	0.5	43	0.008-16.0	0.25	2.0
<i>Pasteurella multocida</i>	9	0.008-0.12	ND	5	0.016-1.0	ND	ND
<i>Proteus mirabilis</i>	1224	≤0.01-100	0.13	68	0.03-16.0	0.125	0.5
<i>Peptostreptococcus anaerobius</i>	28	≤0.025-12.5	0.8	1	0.06	ND	ND
<i>Peptostreptococcus asaccharolyticus</i>	39	≤0.025-0.4	0.2	0			
<i>Peptostreptococcus magnus</i>	51	≤0.025-16.0	0.4	0			
<i>Peptostreptococcus micros</i>	16	≤0.025-0.1	≤0.025	1	0.06	ND	ND

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

Resistance to β -lactam antibiotics such as cefdinir is primarily due to the production of inactivating enzymes (β -lactamases) by both gram-positive and gram-negative bacteria. The Applicant states that cefdinir is able to resist enzymatic hydrolysis by commonly found β -lactamases and functions as an inhibitor of these enzymes.

Medical officer's note: *Dr. Altaie's review mentions that cefdinir is able to resist enzymatic hydrolysis to the most commonly found β -lactamases, but the activity of cefdinir and other cephalosporins can be decreased by coupling diminished uptake in specifically constructed porin-deficient mutants with an enhanced expression of β -lactamase production.*

The Applicant claims that such a profile allows for broad spectrum of activity against certain β -lactamase producing bacterial species such as *Staphylococcus aureus*, *S. epidermidis*, and many commonly encountered gram-negative species. The Applicant also claims that like other oral cephalosporins, susceptibility to other β -lactamases renders cefdinir ineffective against some gram-negative species and anaerobes, such as *Pseudomonas aeruginosa* and other *Pseudomonas* species, *Citrobacter freundii*, *Enterobacter aerogenes*, *E. cloacae*, *Morganella morganii*, *Proteus vulgaris*, *Serratia marcescens*, *Bacteroides* species and *Clostridium difficile*. In addition, alteration of PBS by mutation renders penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus* species resistant to cefdinir.

The applicant tested the development of spontaneous resistance to cefdinir by studying multiple concentrations of cefdinir and very high bacterial inocula. The development of resistance was rare at all concentrations used, and when bacteria were passed through multiple transfers using increasing concentrations of drug, resistance developed in a slow and stepwise fashion.

In the clinical trials, the Applicant found seven of 3,309 (0.02%) pathogens isolated from adult patients developed resistance following treatment with cefdinir. Four of 600 isolates of *Haemophilus influenzae* developed resistance. Other organisms that developed resistance to cefdinir included *Staphylococcus aureus*, *Serratia proteamaculans*, *Klebsiella oxytoca*, and *K. pneumoniae*. No resistance development was seen in isolates from pediatric patients.

Medical officer's note: *Dr. Altaie's review agreed with the Applicant's assessment of cefdinir resistance.*

The Applicant proposes the following breakpoints for interpreting results in clinical microbiology laboratories:

“ **Diffusion Techniques:** Reports from the laboratory providing results of the standardized single disk susceptibility test using a 5- μ g cefdinir disk should be interpreted according to the following criteria when testing organisms other than *Streptococcus pneumoniae*:

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

Susceptible: ≥ 20 mm (MIC equivalent ≤ 1 $\mu\text{g/mL}$)
Intermediate: 17 to 19 mm (MIC equivalent = 2 $\mu\text{g/mL}$)
Resistant: ≤ 16 mm (MIC equivalent ≥ 4 $\mu\text{g/mL}$)

Isolates of *S. pneumoniae* should be tested against a 1- μg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to penicillin and can be considered susceptible to cefdinir.

Cephalosporin "class" disks should not be used to test susceptibility to cefdinir.

The 5- μg cefdinir disk should give the following zone diameters in laboratory test quality control strains:

TABLE3. Quality Control Guidelines for Disk Diffusion Susceptibility Tests	
Organism	Quality Control Ranges (Zone Diameter in mm)
<i>Staphylococcus aureus</i> ATCC 25923	28 to 37
<i>Escherichia coli</i> ATCC 25922	24 to 28
<i>Haemophilus influenzae</i> ATCC 49766	24 to 31
<i>Neisseria gonorrhoeae</i> ATCC 49226	40 to 49
<i>Streptococcus pneumoniae</i> ATCC 49619	26 to 31

Dilution Technique: The MIC values obtained by broth, microbroth or agar dilution should be interpreted according to the following criteria when testing organisms other than *Streptococcus pneumoniae*:

Susceptible: MIC ≤ 1 $\mu\text{g/mL}$
Intermediate: MIC = 2 $\mu\text{g/mL}$
Resistant: MIC ≥ 4 $\mu\text{g/mL}$

A pneumococcal isolate that is susceptible to penicillin (MIC ≤ 0.06 $\mu\text{g/mL}$) can be considered susceptible to cefdinir. Testing of cefdinir against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for cefdinir against *S. pneumoniae* are not available.

Cefdinir susceptibility powder should give the following MIC values against laboratory test control organisms:

TABLE 4. Quality Control Ranges for Dilution Tests

Organism	Quality Control Ranges ($\mu\text{g/mL}$)
<i>Staphylococcus aureus</i> ATCC 29213	0.12 to 0.5
<i>Escherichia coli</i> ATCC 25922	0.12 to 0.5
<i>Haemophilus influenzae</i> ATCC 49766	0.12 to 0.5
<i>Neisseria gonorrhoeae</i> ATCC 49226	0.008 to 0.03
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03 to 0.25

Medical Officer's Note: Dr. Altaie's review found these breakpoints -- for diffusion and dilution techniques -- acceptable and did not recommend any changes. In addition, the recommendation of cefdinir susceptibility for *S. pneumoniae* when the isolate is susceptible to penicillin at MIC $\leq 0.06 \mu\text{g/mL}$ is also acceptable.

Human Pharmacokinetics/Pharmacodynamics

DAIDP's Clinical Pharmacology/Biopharmaceutics Review was written by Dr. Philip M. Colangelo and this summary reflects that review. There are no unresolved deficiencies found in the human pharmacokinetics or pharmacodynamics submission.

Bioequivalence between clinical trials capsule and suspension formulations and between market image capsules and Phase III clinical trials capsules was established. The effect of eating a high fat meal and timing of such a meal on the bioavailability of the capsules was determined to be minimal.

Medical Officer's Note: Both the bioequivalence between capsule and suspension and the effect of eating a high fat being minimal are included in the Applicant's proposed label.

The *in vitro* plasma protein binding of cefdinir was determined to be moderate (60 to 70%) and linear over clinically relevant plasma concentrations in both adult and pediatric subjects. The methods and specifications for *in vitro* dissolution testing of capsules were adequate. Currently, the proposed methods and specifications for the *in vitro* dissolution testing of the suspension's market image formulation were not provided, but the Applicant has agreed to provide the proposed dissolution methods, specifications, and data from the pilot scale batches of the market image suspension as interim data. The Applicant has also agreed to provide dissolution results for the full scale production batches of the suspension manufactured at the contract facility in Phase IV commitment.

Drug interactions that were significant with a 300 milligram dose of cefdinir include the following:

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

- ▶ 1000 mg probenecid coadministration — Mean cefdinir C_{max} and AUC were increased by ~1.5 and ~2.0-fold, respectively. Mean renal clearance was reduced ~65% from 192 to 67.6 ml/min, and mean cefdinir T_{1/2} was increased 1.5 fold from 1.4 hours to 2.1 hours. This suggests that coadministration of probenecid with cefdinir approximately doubled systemic exposure to cefdinir, reduced creatinine clearance, and substantially increased cefdinir T_{1/2}. The mechanism of action appears to be due to inhibition of active renal tubular secretion of cefdinir by probenecid.
- ▶ 30 ml Maalox® TC coadministration and administration 2 hours prior to and after taking cefdinir — Coadministration resulted in substantial reductions in C_{max}, T_{max}, AUC and Ae% (the % of cefdinir excreted in the urine as unchanged drug). There were no observed changes in cefdinir renal clearance or T_{1/2}. This decrease appears to be due to a reduction in systemic availability (i.e., AUC). The Applicant recommends that, if an aluminum or magnesium containing antacid is to be taken with cefdinir therapy, cefdinir should be given at least 2 hours before or after the antacid.
- ▶ oral iron supplements (both ferrous sulphate with 60 mg elemental iron and multivitamins with 10 mg of elemental iron were evaluated), coadministration and administration 2 hours prior to and after taking cefdinir — Coadministration of either ferrous sulphate or a multivitamin containing 10 mg of elemental iron reduced systemic exposure (mean C_{max}, AUC, and Ae%) to cefdinir in a fashion dose-related to the amount of elemental iron ingested. Changes in renal clearance and T_{1/2} were not significantly changed suggesting no effect on elimination. If the iron was taken 2 hours before or after cefdinir, the reduction in systemic exposure was no different than if the cefdinir were taken alone. The Applicant believes that iron reduces the absorption of cefdinir from the gastrointestinal tract by formation of nonabsorbable iron-cefdinir complexes in the gut. The Applicant recommends that if iron supplements are necessary during cefdinir therapy, cefdinir should be taken either 2 hours before or after the iron supplement.
- ▶ the effect of iron-fortified infant formula (~2.7 mg elemental iron) on cefdinir pharmacokinetics in healthy infants was also evaluated (15 subjects aged 6-12 mos, 2-way crossover design) — Coadministration of a single 7 mg/kg dose of cefdinir suspension with an iron fortified infant formula to healthy infants significantly reduced mean C_{max} by ~20%, but did not significantly alter T_{max}, AUC, or the apparent elimination T_{1/2}. The Applicant concluded that iron supplementation in infant formula has little effect on the rate and extent of cefdinir absorption.

Medical officer's note: Dr. Colangelo found the Applicant's conclusion with respect to the coadministration of cefdinir with iron-fortified infant formula acceptable.

Meta-analyses were performed using data from pooled pharmacokinetic studies to evaluate predictive influence of several adults and pediatric subject/patient covariates on cefdinir

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

pharmacokinetics. Furthermore, a population pharmacokinetic (PPK) analysis was performed from the pharmacokinetic database that was created to determine the mean PPK parameter values for adults and children. From this, the population bioavailability estimates for the capsule and suspension were calculated to be 16 to 21 % and 25 %, respectively.

The following two Tables duplicated from the Applicant's submission reflect the conclusions of the PPK analysis:

Table 5 Population Mean Cefdinir Pharmacokinetic Parameter Values in Healthy Subjects Following Administration of 300- and 600-mg Oral Cefdinir Capsules

Parameter	Mean	SD	%RSD	N
Dose = 300 mg				
C _{max} , µg/mL	1.84	0.756	41.1	115
AUC(0-∞), µg·hr/mL	8.49	3.84	45.3	115
V _{d_{area}} /F, L	123	83.7	68.2	181 ^a
V _{d_{area}} /F, L/kg	1.68	1.21	72.2	181 ^a
CL/F, mL/min	849	454	53.5	181 ^a
CL/F, mL/min/kg	11.6	5.96	51.6	181 ^a
Ae%	18.4	6.36	34.6	158 ^a
Dose = 600 mg				
C _{max} , µg/mL	2.63	0.904	34.3	39
AUC(0-∞), µg·hr/mL	10.7	3.86	36.2	39
V _{d_{area}} /F, L	147	55.3	37.6	39
V _{d_{area}} /F, L/kg	2.12	0.683	32.1	39
CL/F, mL/min	1059	372	35.1	39
CL/F, mL/min/kg	15.5	5.41	34.8	39
Ae%	11.6	4.62	40.0	39

^a Parameter calculated using data following doses of 200 to 400 mg.

Table 6 Population Mean Cefdinir Pharmacokinetic Parameter Values in Healthy Pediatric Subjects Following Administration of 7- and 14-mg/kg Oral Doses of Cefdinir Suspension

Parameter	Mean	SD	%RSD	N
Dose = 7 mg/kg				
C _{max} , µg/mL	1.70	0.753	44.3	27
AUC(0-∞), µg·hr/mL	6.77	2.54	37.5	27
Dose = 14 mg/kg				
C _{max} , µg/mL	3.86	0.652	16.9	12
AUC(0-∞), µg·hr/mL	13.4	2.75	20.6	12

In addition, the following two conclusions were drawn by the Applicant:

- (1) In adults, CrCl is the most relevant covariate to predict cefdinir pharmacokinetics and dosage adjustments required in patients with renal impairment; and
- (2) In children, BSA was the best predictor of pharmacokinetics.

The Applicant's evaluation of pharmacokinetics in special populations consisted of the following:

- Systemic exposure to cefdinir was significantly decreased in an elderly population when compared to a young population (16 patients aged 20-27 years versus 16 patients aged 65-91 years). Significant reductions were observed in the C_{max}, AUC, renal clearance, apparent oral clearance and volume of distribution. Because the A_e% remained unchanged in the two populations, the finding is believed due to reduced cefdinir elimination resulting from age related decline in renal function. The Applicant has proposed that the labeling state that elderly patients do not require dosage adjustment unless they have intrinsic renal dysfunction (< 30 mg/ml CrCl).

Medical officer's note: Dr. Colangelo found this labeling appropriate because the relatively modest increases in the short T_{1/2} resulted in minimal drug accumulation in elderly patients with repeated bid or qd dosing.

- Plasma concentrations of cefdinir following a single 300 mg dose in subjects with moderate or severe renal impairment were higher and persisted long when compared to subjects with normal renal function [8 subjects with normal renal function (CrCl > 60 ml/min, mean 99 ml/min) versus 4 subjects with moderate renal impairment (CrCl > 30-60 ml/min, mean 44 ml/min) versus 9 subjects with severe renal impairment (CrCl < 30 ml/min, mean 20 ml/min)]. In subjects with renal impairment, significant increases were observed in the AUC and mean cefdinir C_{max}. Among the subjects with severe renal impairment, a prolonged higher C_{max} occurred. The findings were due to significant reduction in cefdinir elimination with decreases in both renal and apparent oral clearances of ~70-80% in the moderately impaired group and ~85-90% in the severely impaired group. These reductions in clearance resulted in a T_{1/2} increase to 11.4 hours in the severely impaired group and 3.9 hours in the moderately impaired group (normal 1.6 hours). The Applicant proposes that the label recommend that the dose of cefdinir be reduced to 300 mg once daily in patients with severe renal impairment (CrCl < 30 ml/min).

Medical officer's note: Dr. Colangelo found this labeling appropriate because although clearance was moderately reduced in subjects with moderate and severe renal impairment, T_{1/2} was not significantly increased in the moderately impaired group and predicted drug

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

accumulation would be minimal (<10%) for these subjects at a dosing of either 12 or 24 hours. The only caveat with respect to this recommendation is that it is based on evaluating only four subjects with moderate renal impairment.

- ▶ Following administration of a single 300 mg dose of cefdinir to 8 patients on hemodialysis, systemic drug exposure while not on dialysis was substantially increased, demonstrated by increases in C_{max} and AUC. Apparent elimination increased substantially, with T_{1/2} estimates ranging from 13 to 24 hours (mean 15.9 hours). Hemodialysis cleared cefdinir, and the Applicant estimates that a 4 hour dialysis treatment would remove ~63% of the drug from the systemic circulation. The Applicant proposes labeling stating the the initial dosage regimen of cefdinir in hemodialysis patients be adjusted to 300 mg given every other day, with 300 mg administered at the end of each dialysis session.

Medical officer's note: Dr. Colangelo was in agreement with the Applicant's proposal dosing cefdinir in patients undergoing hemodialysis.

- ▶ With respect to the suspension for pediatric use, a dose of 7 mg/kg was demonstrated to be equivalent to an adult capsule dose of 300 mg, and a dose of 14 mg/kg was demonstrated to be equivalent to an adult capsule dose of 600 mg. See Tables 19 and 21 reproduced from Applicant's submission above.
- ▶ Penetration into multiple tissue and fluid sites of interest were evaluated by the Applicant, see Table on the following page duplicated from the Applicant's submission.

TABLE 7. Mean (Range) Plasma and Fluid/Tissue Cefdinir Concentrations and Fluid/Tissue to Plasma Ratios Following Administration of Single Cefdinir Doses

Fluid/Tissue	Dose (mg)	N	Time of Sample Collection (hr postdose)	Plasma Concentration (µg/mL)	Fluid/Tissue Concentration (µg/mL)	Fluid/Tissue-to-Plasma Ratio
Tonsil	300	6	4	1.13 (0.6-2.0)	0.28 (0.22-0.46)	0.27 (0.16-0.43)
	600	6	4	2.17 (1.1-3.4)	0.44 (0.22-0.80)	0.21 (0.14-0.29)
Sinus	300	6	4	0.97 (0.7-1.4)	0.12 (0.0-0.46) ^a	0.12 (0.0-0.42) ^a
	600	6	4	2.27 (0.8-3.5)	0.46 (0.0-2.0) ^b	0.20 (0.0-0.57) ^b
Bronchial Mucosa	300	8	4	2.79 (1.40-8.00)	0.77 (0-1.33)	0.37 (0 - 0.67)
	600	8	4	4.46 (3.05-6.40)	1.08 (0-1.92)	0.25 (0-0.35)
Epithelial Lining Fluid	300	8	4	2.79 (1.40-8.00)	0.97 (0-4.73)	0.65 (0 - 3.26)
	600	8	4	4.46 (3.05-6.40)	0.38 (0-0.59)	0.09 (0-0.14)
Middle Ear Effusion	7 mg/kg	6	3	1.96 (0.80-3.22)	0.23 (0.0-0.94)	0.10 (0.0-0.40)
	14 mg/kg	8	3	3.37 (0.89-5.54)	0.63 (0.0-1.42)	0.20 (0.0-0.35)

^a 11 samples from 6 subjects

^b 10 samples from 6 subjects

Cefdinir tissue penetration was evaluated by relating drug concentrations measured in blister, tonsil, lung, sinus and middle ear fluids/tissues of infection following clinical doses of either 300 or 600 mg of the capsules or 7 and 14 mg/kg of the suspension with the MIC₉₀ values for the causative organisms. The following chart which submitted by the Applicant summarizes the findings of these studies:

TABLE 8. Tissue/Fluid Cefdinir Concentrations Following Administration of Single 300-mg (7 mg/kg) and 600-mg (14 mg/kg) Doses Compared with MIC₉₀ Values for Causative Pathogens

Tissue/Fluid	Blister Fluid		Tonsil Tissue		Sinus Tissue		Bronchial Mucosa		Epithelial Lining Fluid		Middle Ear Effusion Fluid		
Dose	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	7 mg/kg	14 mg/kg	
Concentration, µg/mL	0.674	1.091	0.28	0.44	0.12	0.46	0.77	1.06	0.97	0.38	0.23	0.63	
Pathogen	MIC ₉₀												
Gram Positive													
<i>S. aureus</i> ^a	0.5	A	A	-	-	B	A	A	A	A	B	B	A
<i>S. pneumoniae</i> ^a	0.125	-	-	-	-	A	A	A	A	A	A	A	A
<i>S. pyogenes</i> (Group A)	0.03	A	A	A	A	A	A	A	A	A	A	A	A
<i>S. agalactiae</i> (Group B)	≤0.03	A	A	-	-	-	-	-	-	-	-	-	-
Gram Negative													
<i>H. influenzae</i>	0.5	-	-	-	-	B	A	A	A	A	B	B	A
<i>H. parainfluenzae</i>	0.05	-	-	-	-	A	A	A	A	A	A	-	-
<i>M. catarrhalis</i>	0.25	-	-	-	-	B	A	A	A	A	A	B	A
<i>E. coli</i>	0.5	-	-	-	-	B	A	A	A	A	B	-	-
<i>K. pneumoniae</i>	0.39	A	A	-	-	B	A	A	A	A	A	-	-

A = Adequate tissue/fluid concentrations; B = Inadequate tissue/fluid concentrations; - = Pathogen not associated with infections related to tissue/fluid.

^a Methicillin/oxacillin-susceptible

^b Penicillin-susceptible

- Cefdinir concentrations in middle ear fluid and plasma were measured in pediatric patients with acute otitis media after administration of 7 mg/kg bid or 14 mg/kg qd (8 children receiving 7 mg/kg and 6 children receiving 14 mg/kg). There appeared to be no relationship between concentration of cefdinir in middle ear fluid and in plasma, and the ratios also appeared to be independent of plasma drug concentrations over the range of doses studied. At 14 mg/kg, the mean middle ear fluid concentration of 0.63 mcg/ml was above the MIC₉₀ for the 5 common pathogens associated with acute otitis media. At 7 mg/kg, the mean middle ear fluid concentration of 0.23 mcg/ml was above the MIC₉₀ for the *S. pneumoniae* and *S. pyogenes*, but below those for *S. aureus*, *H. influenzae* and *M. catarrhalis*.

Medical officer's note: These findings are worrisome, and discussion with Dr. Colangelo and reivew of the raw data suggests that the data is scant and inconsistent. See two Tables on the following pages duplicated from the Applicant's submission (Study 983-48, vol 1.33, page1).

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

Table 9 Plasma and Middle Ear Effusion Cefdinir Concentrations (ug/mL)
Approximately 3 Hours After a 7-mg/kg Oral Dose of Cefdinir

Patient	Plasma Cefdinir Concentration	Effusion Sample Weight (mg)	Middle Ear Effusion Fluid Cefdinir Concentration	Cefdinir Effusion Fluid-to-Plasma Ratio
1	1.67	100	0.207	0.124
4	0.802	60.1	0	0
7	1.11	4.9	0	0
8	2.6	27.7	0	0
10	2.34	50.3	0.944	0.402
12	3.22	39.2	0.24	0.075
N	6		6	6
Mean	1.96(0.8-3.2)		0.232(0-0.94)	0.10(0-0.40)
SD	0.93		0.37	0.16
%RSD	47.3		158	156

Limit of Quantitation = 0.016 ug/mL.

a Weight of middle ear effusion fluid sample was estimated due to a possible error in vial weighing during sample processing.

Three patients with levels of "0" at the lower dose may reflect inadequate sample size for assay. Unfortunately, there is no additional supporting data for pharmacokinetics on middle ear fluid levels and the data submitted does not allow extrapolation from fluid levels. A discussion of pharmacokinetics and pharmacodynamics of antibiotics and efficacy in otitis media is attached.¹ This publication proposes that the measurement of middle ear fluid levels is often unreliable, and that the time serum concentrations are above MIC is as useful as middle ear fluid levels in predicting antibiotic efficacy in otitis media.

¹ Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J* 1996;15:255-259.

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

**Table 10. Plasma and Middle Ear Effusion Cefdinir Concentrations (ug/mL)
Approximately 3 Hours After a 14-mg/kg Oral Dose of Cefdinir**

Patient	Plasma Cefdinir Concentration	Effusion Sample Weight (mg)	Middle Ear Effusion Fluid Cefdinir Concentration	Cefdinir Effusion Fluid-to-Plasma Ratio
2	2.98	11.3	0.718	0.241
3	5.54	41.2	0.137	0.025
5	4.52	78.3	0.843	0.187
6	4.02	59.8	1.42	0.353
9	4.14	43.7	1.17	0.283
11	0.894	117.3	0.308	0.345
13	2.48	1.6	0	0
14	2.36	38.8	0.434	0.184
N	8	8	8	8
Mean	3.37(0.9-5.5)	0.629(0-1.4)	0.629(0-1.4)	0.202(0-0.35)
SD	1.5	0.5	0.5	0.13
%RSD	43.7	79.5	79.5	65.8

Limit of Quantitation = 0.016 ug/mL.

See figure 2 on the following page for time curve of serum concentrations of suspension in children.

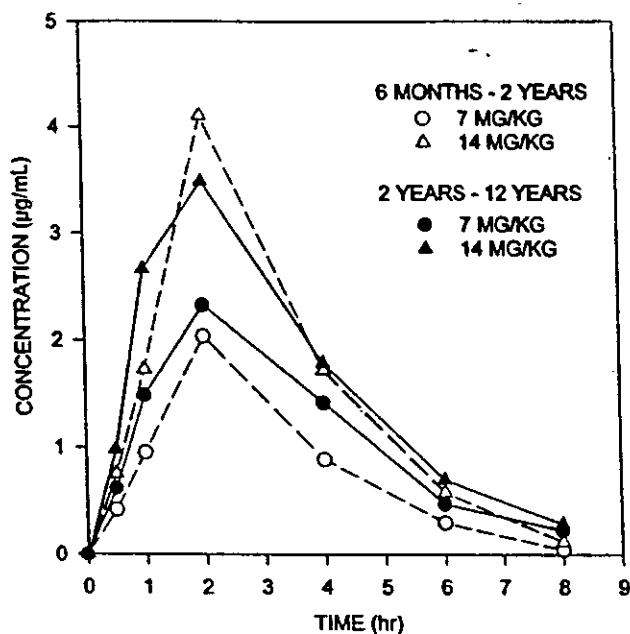


FIGURE 1. Study 983-23: Mean Plasma Cefdinir Concentration-Time Profiles After Administration of Single Suspension Doses of 7 or 14 mg/kg Cefdinir to Subjects Aged 2 to 12 Years and 6 Months to 2 Years

The pharmacokinetic support for the indication of otitis media must be scrutinized carefully if the clinical data submitted is not strongly supportive. The drug's half life is short (1.6 hours) and the time above the MIC for several of the critical pathogens is a small portion of the dosing interval (<30%) when dosed on a 24 hour schedule.

Human Clinical Experience

Foreign Experience:

The drug was originally developed in _____ and is currently being licensed by the _____. A 200 milligram capsule formulation was approved in Japan in 1991 and a pediatric sachet formulation was approved in 1993 and both are currently available in Japan. Recently the drug was approved in the United Kingdom; labeling negotiations are ongoing. The Applicant also plans to submit applications in Canada,

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

Europe, Australia and South Africa. The studies used to support this submission supported the United Kingdom application.

Post-Marketing Experience:

The Applicant reports that extensive post-marketing experience is available from Japan. estimates that as of December 31, 1995, courses of capsules have been dispensed, as well as courses of the pediatric granule formulation for a total of exposures. Surveillance of postmarketing adverse events has been ongoing during this period. Serious adverse events, rarely fatal, have been reported in association with cefdinir use. These events are the same events reported other β -lactam agents and include anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pseudomembranous colitis, hemorrhagic colitis, hepatic dysfunction and failure, interstitial pneumonitis, granulocytopenia, and thrombocytopenia. The Applicant does not anticipate significant future safety information in view of the large numbers of exposures already recorded.

Clinical Studies

Introduction

The clinical effectiveness and safety of cefdinir are described for treating mild to moderate bacterial infections of

- ▶ Community-acquired pneumonia (pneumonia) in adults,
- ▶ Acute exacerbations of chronic bronchitis (AECB) in adults,
- ▶ Secondary bacterial infections of acute bronchitis (acute bronchitis) in adults,
- ▶ Acute suppurative otitis media (otitis media) in children,
- ▶ Acute maxillary sinusitis (sinusitis) in adults,
- ▶ Pharyngitis/tonsillitis (pharyngitis) in adults and children, and
- ▶ Uncomplicated skin and skin structure infections (SSSI or skin infection) in adults and children.

Two cefdinir formulations were evaluated, cefdinir capsules for adults and adolescents aged 13 years and older and cefdinir suspension for children aged 6 months to 12 years. Both

NDA 50-739 (Cefdinir 300 mg capsules) & NDA 50-749 (Cefdinir oral suspension, 125mg/5ml)

formulations were studied under IND Separate capsule and suspension data are presented here from all studies.

Data from 16 Parke-Davis Pharmaceutical Research-sponsored pivotal and supporting clinical studies, 10 in adults and adolescents and 6 in children, demonstrate the efficacy of cefdinir. In these studies, 4622 adults and adolescents were randomized to receive cefdinir 600 mg QD or 300 mg BID, and 2138 children were randomized to receive cefdinir 14 mg/kg QD or 7 mg/kg BID. Efficacy data are presented by indication and study.

Safety data from the 4607 adults and 2133 children who actually received cefdinir in these studies are integrated and discussed. Safety data from 2 small pediatric studies are also included, adding 6 patients from a terminated pharyngitis study and 14 from an otitis media study that measured cefdinir tissue penetration; all received cefdinir 14 mg/kg QD or 7 mg/kg BID. The integrated safety database, then, includes 4607 adults and adolescents and 2153 children. Capsule (adult) and suspension (pediatric) data are presented separately.

Safety data from 3 other clinical studies in adults are described separately. These data are from 2 studies (983-2 and 983-3) in uncomplicated urinary tract infections (UTIs) and one (983-16) in lower respiratory infections (LRTIs). All patients in the UTI studies and some in the LRTI study received cefdinir regimens other than 600 mg/day. Data from patients in Study 983-16, who received cefdinir 600 mg/day and who had pneumonia, AECB, or acute bronchitis, were included in the integrated database described in the previous paragraph.

Safety information from other sources (ie, other than the NDA studies) are also reported. Deaths and adverse event information from ongoing studies reported through June 30, 1996 and from studies conducted for local registration purposes in Italy and France are presented.

Medical officer's note: *The above information was duplicated from the Applicant's submission; the charts beginning on the following page detail the submitted studies.*

Medical officer's note: *Most of the following text has been duplicated from the Applicant's submission as the CANDA allows for copying pieces of the submission. The medical officer's comments appear in the notes.*

Indication: Community Acquired Pneumonia

The portions of the proposed package insert relevant to ^{the} indication of community acquired pneumonia submitted by the Applicant are as follows:

Lower Respiratory Tract Infections

Community-Acquired Pneumonia caused by susceptible strains of *Haemophilus influenzae* (including β -lactamase producing strains), *Haemophilus parainfluenzae* (including β -lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains), *Staphylococcus aureus* (including β -lactamase producing strains), *Moraxella catarrhalis* (including β -lactamase producing strains), *Escherichia coli*, and *Klebsiella pneumoniae*.

Dosage and Administration

Adults and Adolescents (Age 13 years and Older)

Type of Infection	Dosage	Duration
Community-Acquired Pneumonia	300 mg q12h	10 days

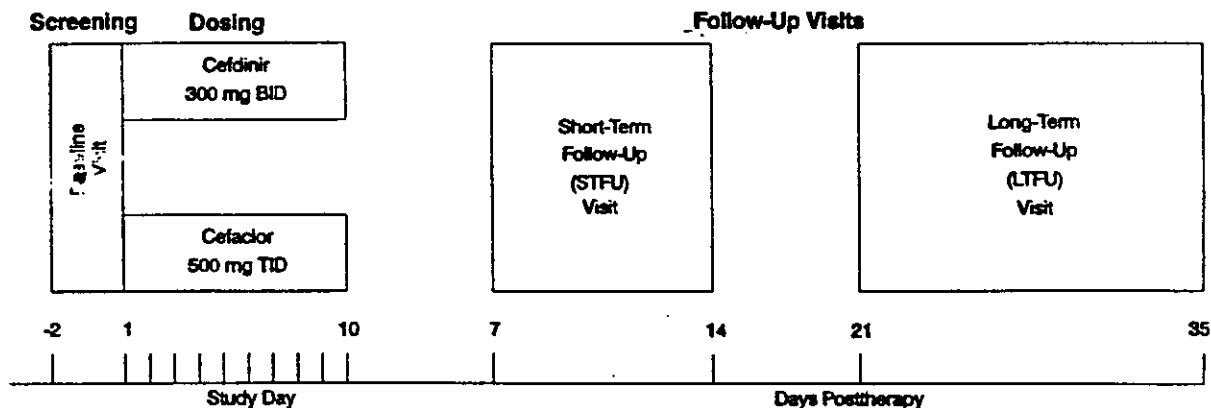
Title and Study Number: A Phase 3, 10-day, double-blind, randomized, comparative, multi center study of cefdinir (CI-983) versus cefaclor in the treatment of adult patients with community-acquired pneumonia (Protocol 983-4)

Objective: The objective of this study was to evaluate the efficacy and safety of cefdinir 300 mg BID and cefaclor 500 mg TID in the treatment of community-acquired pneumonia in adult patients.

Medical officer's note: *A 600 mg qd cefdinir treatment group in the original study was discontinued due to theoretical concerns that qd dosing might not be adequate for treating serious, potentially life-threatening pneumonia (Applicant's Amendment 2). Thus, this was dropped from the original Objective and Study Design.*

Study Design: Protocol 983-4 is a double-blind, randomized, comparative, multi center study with 2 parallel-treatment groups. Duration of therapy was ten days. Forty-eight centers in the

United States enrolled patients. Treatment was followed by short-term (test-of-cure at 6-14 days posttherapy) and long-term (follow up at 21-35 days posttherapy) follow-up visits. A chart detailing study design which was duplicated from the Applicant's submission is presented below.



BEACHJ/CLC/081495/DSGN13
983/13/RR

Figure 2. Protocol 983-4 Study Design

Medical officer's note: Deviations from the Applicant's original protocol are as follows:

- (1) The original randomization schedule involved three treatment arms and was 1:1:1. After the qd dosing arm was dropped, the numbers assigned to that arm were unblinded and not used in the randomization. The randomization schedule assigned to the other two arms (cefdinir BID and cefaclor TID) was adhered to and resulted in a 1:1 randomization.
- (2) Changing the test-of-cure visit from 3 to 7 days posttherapy to 7 to 14 days posttherapy (days 17 through 24 for patients completing treatment on day 10) was another deviation from the original protocol (Applicant's Amendment 2). For many patients, the TOC visit beginning on Day 17 was actually 6 days posttherapy since patients who started BID or TID treatment midday on Day 1 ended treatment on Day 11. For analysis purposes, the TOC window was widened to 6 to 14 days posttherapy to include this patient data.

Protocol Overview

Population and Inclusion/Exclusion Criteria (as duplicated from the Applicant's submission)

Population: Eligible patients were males and nonpregnant, nonlactating females ≥ 13 years of age who had community-acquired pneumonia confirmed by chest x-ray. Females were to be either adolescent and not sexually active, using an effective means of contraception and have a

negative pregnancy test at baseline, postmenopausal, or surgically sterilized.

Inclusion Criteria: Patients were required to have cough and sputum production and could have chest pain, chest sounds (rales, rhonchi), shortness of breath, or fever for study entry. The investigator performed an evaluation of these clinical signs and symptoms and classified all of them (except chest sounds and fever) as absent, mild, moderate, or severe at each visit. Chest sounds were classified as present or absent. Body temperature was recorded by the investigator and fever severity was determined by the sponsor using an objective temperature guideline.

***Medical Officer's Note:** Although this protocol was designed and initiated before the availability of the Guidelines for the Evaluation of Anti-Infective Drug Products¹, because the fact the population was selected based on chest x-ray, and the inclusion criteria required the presence of cough and sputum and possible other findings such as fever, chest pain, chest sounds and shortness of breath, the Guidelines are met and consistent with current DAIDP requirements for study of community acquired pneumonia. No procedures were planned for the Protocol.*

Exclusion Criteria: Patients were excluded from entering the study for any of the following reasons:

- ▶ A disease or condition that would preclude evaluation of the therapeutic response, including cystic fibrosis or significant pulmonary structural defects;
- ▶ Hepatic disease, obstruction of the biliary tract, baseline bilirubin or hepatic enzyme levels (AST, ALT) >2 times the upper limit of normal;
- ▶ Baseline serum creatinine >1.5 times the upper limit of normal or known creatinine clearance <30 mL/min;
- ▶ Use of another systemic antibacterial within 7 days of the start of study medication; or if the interval between the last dose of the prior systemic antibacterial and the first dose of study medication is <5 half-lives of the prior antibacterial;
- ▶ Hypersensitivity to β -lactams;
- ▶ Baseline pathogen(s) known to be resistant to either study medication prior to randomization;

¹ Chow AW, Hall CB, Klein JO, Kammer RB, Meyere RD, Remington JS. Evaluation of New Anti-Infective Drugs for the Treatment of Respiratory Tract Infections CID 1992;15(Suppl 1):S62-S88.

- ▶ Concomitant infection(s) requiring systemic antibacterial therapy;
- ▶ Prior participation in this or any other cefdinir study; or
- ▶ Receipt of any other investigational compound within 4 weeks of study entry.

Medical Officer's Note: *These exclusion criteria are not inconsistent with the Guidelines. They are fair, and the medical officer commends the protocol and study design and is in agreement with inclusion and exclusion criteria.*

Patients requiring concurrent treatment with other systemic antibacterial medications, probenecid, dietary iron containing supplement or multivitamins were to be excluded. Patients requiring aluminum- or magnesium-containing antacids were to withhold antacid therapy for 2 hours before and after study medication dosing.

Medical officer's note: *See Section 6. Human Pharmacokinetics/Pharmacodynamics, page 23, in this review for Applicant's studies which support these prohibitions and limitations. These prohibitions and limitations are also included in the Applicant's label.*

Evaluability Criteria: Patients could be withdrawn from the study because of insufficient efficacy; an adverse event; a clinical laboratory abnormality; lack of patient cooperation; patient or guardian request; failure to isolate a baseline pathogen; or isolation of a baseline pathogen resistant to either cefdinir or cefaclor. Reasons for withdrawal were reported on the appropriate CRF.

Confirmation of bacteriological etiology and *in vitro* susceptibility (or intermediate susceptibility) to both study medications were required for a patient to be evaluable for efficacy analyses. If these conditions were not met, a patient could be discontinued from study medication and given appropriate therapy. The investigator could continue to treat patients who had a baseline pathogen that was resistant to one study medication and susceptible to the other if, in his or her judgement, they were exhibiting satisfactory clinical improvement.

When patients discontinued treatment early, the following were to be completed: sputum culture and susceptibility testing, a clinical assessment (i.e., assessment of signs and symptoms as well as an overall assessment of clinical efficacy), a physical examination, clinical laboratory

tests, as well as records of adverse events and concurrent medications. If additional antibiotics were not required at the time study medication was discontinued and the patient had received at least three days of study medication, both follow-up visits were scheduled to be completed. If additional antibiotics were required or if the patient had no baseline pathogen, follow-up visits were not scheduled.

Assessments of microbiologic and clinical response at the TOC visit, 6 to 14 days posttherapy, were used to evaluate the efficacy of cefdinir. The LTFU visit, 21 to 35 days posttherapy, provided information on recurrence of infection.

Three primary efficacy measures were used in this study: Microbiologic eradication rate by pathogen, microbiologic eradication rate by patient, and clinical cure rate by patient. The appearance of new pathogens was examined as a secondary efficacy parameter.

Medical officer's note: The medical officer agrees with the above evaluability criteria; most patients are carried forward as failures in the intent-to-treat analysis. In addition most patients are carried forward in the modified-intent-to-treat. When assigning outcome, the Applicant consistently selected the outcome least apt to favor therapy in a blinded fashion.

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Endpoints Defined (Clinical and Microbiological)

The following table, duplicated from the Applicant's submission, described what data was collected and at what visits.

Table 11. Schedule of Clinical Observations and Laboratory Measurements

Procedure/Observation	Baseline ^a	Day 1	Days 3-5	Day 10	Posttherapy Visits	
					7 to 14 Days	21 to 35 Days
Medical History	X					
Physical Examination (including x-ray) ^b	X				X	X
Clinical Assessment of Signs and Symptoms ^b	X		X		X	X
Gram Stain, Sputum Culture, and Susceptibility Testing ^b	X		X		X	X
Clinical Laboratory Testing ^b	X				X	X ^c
Assessment of Clinical Efficacy ^b					X	X
Adverse Events		X			X	X
Dosing		X		X		

^a Prior to treatment (within 48 hours)

^b Also performed whenever a patient was withdrawn

^c Performed only if abnormalities were detected at the previous visit

Microbiological endpoints: Specimens were collected for culture at the baseline, TOC, and LTFU visits. At the TOC and LTFU visits, the microbiologic response of each baseline pathogen was classified as:

- ▶ Eradication - Baseline pathogen not present in follow-up culture or no material available to culture at follow-up (presumed eradication);
- ▶ Persistence - Baseline pathogen present in follow-up culture; or
- ▶ Not Assessable - No follow-up data.

Microbiologic eradication rate by pathogen was the percentage of baseline pathogens that were absent from specimens obtained at the TOC or LTFU visits. Patients with multiple baseline pathogens provided multiple observations in the analyses of microbiological efficacy on a per pathogen basis. The eradication rate by pathogen was calculated separately for each of the follow-up visits. Qualified patients who had persistent pathogens at TOC were automatically considered to have persistent pathogens at the LTFU visit. Patients without baseline pathogens could develop a superinfection.

Microbiologic Response by Patient: At the TOC visit, patients were classified by their microbiologic response based on the baseline and 6- to 14-day posttherapy culture results as:

- ▶ **Patients With Eradication** - All baseline pathogens eliminated at TOC or no material available to culture at TOC (i.e., presumed eradication);
- ▶ **Patients With Persistence** - Presence of at least one baseline pathogen in the TOC culture; or
- ▶ **Not Assessable** - No proven baseline pathogen or no follow-up data.

At the LTFU visit, patients were classified by their microbiologic response based on the baseline, 6- to 14-day posttherapy, and 21- to 35-day posttherapy culture results as:

- ▶ **No Relapse** - Patients with eradication at TOC and either continued eradication of all baseline pathogens at LTFU or no material available to culture at LTFU;
- ▶ **Relapse** - Patients with eradication at TOC and reappearance of at least one baseline pathogen at LTFU;
- ▶ **Patients With Persistence** - All patients with persistence at TOC; or
- ▶ **Not Assessable** - No proven baseline pathogen or no follow-up data.

The microbiologic eradication rate by patient was the percentage of patients who had all baseline pathogens eliminated. Each patient provided one observation. The microbiologic eradication rate by patient was calculated separately for each follow-up visit.

The appearance of a new pathogen during or after treatment was classified as:

- ▶ **Superinfection** - The appearance of a nonbaseline pathogen at any time during treatment through the TOC visit and <50% decrease in clinical score at the corresponding clinical evaluation of signs and symptoms relative to baseline;
- ▶ **Reinfection** - The appearance of a new pathogen (i.e., not present at any prior visit) at the LTFU visit, and the clinical assessment of Recurrence at LTFU; or
- ▶ **Not Assessable** - No follow-up data.

The appearance of a new pathogen together with a clinical worsening or failure at the corresponding clinical assessment also constituted a superinfection or a reinfection. If a patient had a new organism(s) isolated in any postbaseline culture, but had no corresponding clinical assessment of signs or symptoms, the determination of pathogenicity was made by the sponsor.

Medical officer's note: The medical officer agrees with these endpoint classifications. The Guidelines were not available at the time the study was designed and initiated. Although these endpoints are not identical to those recommended in the Guidelines, they reflect adequate consideration of the recommended microbiologic endpoints to be valid.

Clinical Response by Patient:

All clinical signs and symptoms were assessed by the investigator at the baseline, TOC, and LTFU visits. The recorded clinical signs and symptoms provided the basis for all assessments of patient clinical response. The investigator's impression of patient clinical response used the following protocol-specified definitions.

Investigator's Assessment of Clinical Response at TOC:

- ▶ Cure - Absence or satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- ▶ Improvement - Satisfactory remission but not complete disappearance of baseline clinical signs and symptoms;
- ▶ Failure - No significant remission of baseline signs and symptoms; further antibacterial therapy required; or
- ▶ Not Assessable - Unable to assess patient; no data.

Investigator's Assessment of Clinical Response at LTFU:

- ▶ Cure - Absence or satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- ▶ Improvement - Satisfactory remission but not complete disappearance of baseline clinical signs and symptoms;
- ▶ Failure/Recurrence - Worsening or no significant remission of baseline signs and symptoms since the previous visit; further antibacterial therapy required; or
- ▶ Not Assessable - Unable to assess patient; no data.

Medical officer's note: The medical officer agrees with these endpoint classifications.

The protocol specified that both investigator and sponsor assessments of patient clinical response would be made. Based on the investigator's follow-up assessments of clinical signs and symptoms (but before unblinding), the sponsor used a scoring algorithm to calculate an assessment of clinical efficacy. This scoring system is described in detail in Applicant's Appendix A.4.

Medical officer's note: Review of Appendix A.4 demonstrates the clinical scoring system developed and used consistently by the Applicant. Clinical signs and symptoms (cough, sputum production, shortness of breath, chest pain, chest sounds and fever) were assigned a score by the investigators based on severity (0, 1, 2, or 3 respectively correlates with absent, mild, moderate or severe). A composite clinical score based on the weighted value was derived. This score could vary from 4 to 28 at baseline and from 0 to 28 at TOC and LTFU.

The Applicant's clinical assessments, based on a quantitative evaluation of the total clinical

score, were defined as follows:

Sponsor's Assessment of Clinical Response at TOC utilizing clinical scoring system:

- ▶ Cure - $\geq 50\%$ decrease in clinical score at TOC relative to baseline;
- ▶ Failure - $< 50\%$ decrease in clinical score at TOC relative to baseline; or
- ▶ Not Assessable - No baseline signs or symptoms or no follow-up data.

Sponsor's Assessment of Clinical Response at LTFU utilizing clinical scoring system:

- ▶ Cure - Cure at TOC and < 2 -point increase in clinical score at LTFU relative to TOC and $\geq 50\%$ decrease in clinical score at LTFU relative to baseline;
- ▶ Recurrence - Cure at TOC and either ≥ 2 -point increase in clinical score at LTFU relative to TOC or $< 50\%$ decrease in clinical score at LTFU relative to baseline;
- ▶ Failure - Failure at TOC; or
- ▶ Not Assessable - No baseline signs or symptoms or no follow-up data.

The sponsor's assessment of clinical response was computerized. Symptoms that were not assessed at baseline or at a follow-up visit were not used in calculating percentage changes from baseline for that visit. If a patient fulfilled the criteria for a particular response, but had important or extenuating circumstances during the study (e.g., very low scores at baseline), the computerized determination of clinical effectiveness could be changed by the sponsor prior to randomization code release.

Medical officer's note: The medical officer believes this to be an unbiased and simple method with which to assign patient endpoints providing that it is consistently adhered to. The medical officer also believes that such clearly defined outcome assignments are more valid than a gestalt assignment after review of the CRF.

A combination of investigator and sponsor assessments, referred to as the combined investigator/sponsor clinical assessment in this report, was used as the primary measure of patient clinical response in the efficacy analyses. If the investigator assessment at TOC was Improvement or Not Assessable and clinical signs and symptoms data had been collected, the patient was reclassified according to the sponsor assessment. Investigator assessments of Cure and Failure were retained regardless of the sponsor assessment.

The combined investigator/sponsor clinical assessment at the LTFU visit depended not only on the investigator assessments at LTFU, but also on the combined investigator/sponsor clinical assessment at TOC. For patients with a combined assessment of Cure at TOC, the rules for the combined assessment at LTFU were analogous to those at TOC: Investigator assessments of Cure and Recurrence took precedence over the sponsor assessment (i.e., were used) while investigator assessments of Improvement and Not Assessable were reclassified according to the sponsor assessment. In contrast, patients with a combined investigator/sponsor assessment of

Failure at TOC were considered failures using the combined investigator/sponsor clinical assessment at LTFU, regardless of investigator determination. (Patients assessed as failures by the sponsor at the TOC visit were automatically considered sponsor failures at LTFU.)

Table 12. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU^{a,b}

Sponsor Assessment at TOC	Investigator Assessment at TOC			
	Cure	Improvement	Failure	Not Assessable
Cure	Cure	Cure	Failure	Cure
Failure	Cure	Failure	Failure	Failure
Not Assessable	Cure	Not Assessable	Failure	Not Assessable
Sponsor Assessment at LTFU	Investigator Assessment at LTFU			
	Cure	Improvement	Recurrence	Not Assessable
Cure	Cure	Cure	Recurrence	Cure
Failure	Cure	Failure	Recurrence	Failure
Recurrence	Cure	Recurrence	Recurrence	Recurrence
Not Assessable	Cure	Not Assessable	Recurrence	Not Assessable

^a The combined assessments are shown in bold typeface.

^b Note: If a patient had a combined clinical assessment of Failure at the TOC visit, the patient was automatically a Failure on the combined assessment scale at LTFU.

The clinical cure rate was the percentage of patients rated as Cure on the combined assessment scale.

***Medical officer's note:** The medical officer believes that as long as this outcome assignment is adhered to consistently, it is acceptable.*

Statistical Considerations

Sample Size: This double-blind, comparative study of cefdinir versus cefaclor was designed with a sample size of 190 evaluable patients per randomized treatment group.

A microbiologic eradication rate of 90% across all randomized groups was assumed in the sample size calculations. Equivalence was to be assessed by comparing a two-tailed 95% confidence interval (CI) for the difference (cefdinir minus cefaclor) in microbiologic eradication rates to a set of predetermined, fixed criteria for equivalence (defined below). Sample size was calculated to provide sufficient power (80%) to assess the equivalence of the cefdinir and cefaclor microbiologic eradication rates at TOC using this CI method.

At TOC, the primary endpoint, the microbiologic eradication rates by pathogen and by patient, were calculated for each treatment group in the evaluable, MITT, and ITT patient populations. Clinical cure rates and mean clinical signs/symptoms scores were calculated for each treatment group in the evaluable, clinically evaluable, and the ITT patient populations.

At LTFU, the secondary endpoint, the microbiologic eradication rates by pathogen and by patient (i.e., the "no relapse" rates) were calculated for each treatment group in the qualified and ITT patient populations. Clinical cure rates (i.e., the "no recurrence" rates) and mean clinical scores were calculated for each treatment group in the qualified and ITT patient populations.

Two methods of investigating treatment equivalence at TOC were used. One method was based on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient (or each pathogen, for the by-pathogen case) in the analysis, and were calculated as the total number of cures or eradications in the study population, divided by the total number of cases.

The second method used a categorical modeling procedure to obtain center-adjusted estimates of the response rates and their standard errors. The model contained terms for study center, treatment group, and treatment-by-center interaction. The resulting parameter estimates were used to construct estimates of the treatment group response rates and standard errors in which each center was given equal weight.

The treatment difference was defined as cefdinir BID minus cefaclor. The estimated response rate differences and their standard errors were used to construct a two-tailed, 95% confidence interval for each treatment difference, using a standard normal approximation. Each 95% confidence interval was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the two rates (pooled or center-adjusted) under comparison. To demonstrate equivalence, each 95% confidence interval must contain zero and its limits must fall within the indicated bounds.

Table 13. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Treatments Are Equivalent If 95% Confidence Interval For Treatment Difference Is Within Bounds
90% or greater	-10%, +10%
80%-89%	-15%, +15%
60%-79%	-20%, +20%

Results under the two methods were compared for consistency. When the two methods agreed, the pooled analysis was presented as the final analysis. If results from the two methods disagreed, the differences were addressed and results from both methods were presented.

Study Results

Investigators and Numbers Enrolled

Table 14. List of Investigators

Center	Investigator	Number of Patients		
		Randomized to Treatment(N)	Completed Treatment(% of N)	Evaluable (% of N)
1	A. Rosenthal	8	4(50)	1(12.5)
2	J. Applegate	16	11(68.8)	10(62.5)
3	R. Chiulli	9	6(66.7)	5(55.6)
4	P. Finch	4	4(100)	3(75)
5	R. Greenberg	47	31(66.0)	19(40.4)
7	K. Guntupalli	16	11(68.8)	11(68.8)
10	M. Kutner	1	1(100)	1(100)
11	A. Puopolo	28	21(75)	16(57.1)
12	J. Scott	11	9(81.8)	10(90.9)
13	A. Robbins	15	11(73.3)	7(46.7)
14	R. Snow	18	12(66.7)	9(50)
15	M. Sperling	17	12(70.6)	9(52.9)

16	T. Littlejohn	28	23(82.1)	20(71.4)
18	H. Collins	5	3(60)	3(60)
20	D. Stryker	9	8(88.9)	6(66.7)
21	A. Sands	1	1(100)	0(0)
25	D. Dark	6	5(83.3)	3(50)
26	J. Salisbury	113	92(81.4)	47(41.6)
27	M. Drehobl	52	33(63.5)	31(59.6)
28	L. Cosmo	1	0(0)	1(100)
29	J. Frey	3	0(0)	2(66.7)
30	G. Mayer	1	1(100)	1(100)
31	R. Kearley	5	2(40)	0(0)
33	S. Pingleton	2	2(100)	2(100)
36	C. Khurana	4	3(75)	2(50)
37	T. Chestnut	2	1(50)	1(50)
38	D. Williams	7	5(71.4)	4(57.1)
40	J. Zaremba	51	35(68.6)	24(47.1)
41	A. Russakoff	5	4(80)	3(60)
50	R. Connor	3	2(66.7)	1(33.3)
53	J. Westerman	4	1(25)	2(50)
56	A. Iravani*	7	4(57.1)	2(28.6)
58	G. Heinz, III	16	16(100)	9(56.2)
59	B. Sherman	4	1(25)	0(0)
61	R. Wainz	1	1(100)	1(100)
62	S. Hirsch	3	3(100)	1(33.3)
63	R. Bianchi	92	64(69.6)	63(98.4)
64	J. Schoenberger	9	7(77.8)	3(33.3)
66	R. Schwartz	1	1(100)	0(0)
69	D. Cernea	10	8(80)	1(10)
70	J. McCarty	3	2(66.7)	1(33.3)
71	B.-Cochran	2	2(100)	2(100)
72	D. Henry	19	17(89.5)	15(78.9)
73	R. Knight	12	7(58.3)	6(50)
74	B. Diener	5	3(60)	2(40)
75	B. Harrison	14	14(50)	7(50)
76	J. Hedrick	7	6(85.7)	6(85.7)
77	W. Ziering	7	7(100)	3(42.9)
	Total	704	517(73.4)	376(53.4)

* Dr. Iravani was eliminated from other studies in this application. See Medical officer's note below for why reanalysis was not performed excluding these two patients.

Medical officer's note: Inspection by DSI personnel raised questions concerning the validity of data obtained by Dr. Iravani at center 56. As the table above demonstrates, he enrolled only seven patients; three to the cefdinir treatment arm and four to the cefaclor treatment arm. Among these seven enrollees, only two were evaluable and both were in the cefaclor treatment arm. The contribution of two evaluable patients to 337 evaluable can have no impact on study results, either with respect to efficacy or safety. Thus, no effort was made to eliminate his data as was done in other indications of this NDA review.

Number of Patients Enrolled per Site, and those Evaluable by Site

See Appendix 1 annexed to the end of this study review for a detailed chart of total number of patients enrolled by each site, and number of patients clinically evaluable and microbiologically/clinically evaluable by site.

Medical officer's note: Review of this Appendix and Table 4 above demonstrates that number of patients enrolled at the 77 centers varied from 0 to 111. Five centers enrolled more than 40 patients (47, 111, 52, 51 and 92). This totals 353 or 50.1% of the 704 patients enrolled. Those evaluable among these sites vary from 19 to 63, with a total of contribution of 184 of 376 evaluables or 48.9%. Another two centers enrolled between 20 and 40 patients (28 patients each) contributing 8.0% of those patients enrolled 36 or 9.6% of those evaluable. The remaining 70 centers enrolled 41.9% of the study population which constitutes 41.5% of those evaluable. Thus, although a few centers enrolled half of all patients, the percent evaluable rate is fairly stable regardless of number enrolled. Randomization appears to have been grossly effective as approximately one-half the patients at each study site are assigned to each treatment arm. No inappropriate biases are suggested by this information.

Demographics, Evaluability

The baseline characteristics of all patients randomized to treatment (N = 704; Table 5) were similar to those of the evaluable patient population (N = 376; Table 16) and the clinically evaluable patient population (N = 453). For all patients randomized to treatment, there were slightly more males (56%) than females (44%); 85% of patients were white; and most patients (75%) were 18 to ≤ 65 years of age.

Patients were similarly distributed by sex, race, and age across the three treatment groups in each patient population.

Table 15. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 14	Cefdinir BID N = 347	Cefaclor N = 343	Total N = 704
Sex				
Male	7 (50.0)	193 (55.6)	192 (56.0)	392 (55.7)
Female	7 (50.0)	154 (44.4)	151 (44.0)	312 (44.3)
Race				
White	12 (85.7)	298 (85.9)	288 (84.0)	598 (84.9)
Black	2 (14.3)	32 (9.2)	44 (12.8)	78 (11.1)
Asian	0 (0.0)	3 (0.9)	1 (0.3)	4 (0.6)
Other ^a	0 (0.0)	14 (4.0)	10 (2.9)	24 (3.4)
Age, year				
Median	46.0	44.0	44.0	44.0
Range	22.0 - 79.0	13.0 - 89.0	13.0 - 93.0	13.0 - 93.0
Distribution				
13 to <18	0 (0.0)	10 (2.9)	8 (2.3)	18 (2.6)
18 to <65	10 (71.4)	255 (73.5)	263 (76.7)	528 (75.0)
≥65	4 (28.6)	82 (23.6)	72 (21.0)	158 (22.4)

^a Other = Hispanic, Filipino, American Indian, and Brazilian.

Table 16. Patient Characteristics - Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 3	Cefdinir BID N = 187	Cefaclor N = 186	Total N = 376
Sex				
Male	1 (33.3)	105 (56.1)	102 (54.8)	208 (55.3)
Female	2 (66.7)	82 (43.9)	84 (45.2)	168 (44.7)
Race				
White	3 (100.0)	161 (86.1)	157 (84.4)	321 (85.4)
Black	0 (0.0)	16 (8.6)	24 (12.9)	40 (10.6)
Asian	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.5)
Other ^a	0 (0.0)	8 (4.3)	5 (2.7)	13 (3.5)
Age, year				
Median	46.0	44.0	45.5	45.0
Range	44.0 - 46.0	13.0 - 87.0	13.0 - 93.0	13.0 - 93.0
Distribution				
13 to <18	0 (0.0)	7 (3.7)	5 (2.7)	12 (3.2)
18 to <65	3 (100.0)	133 (71.1)	140 (75.3)	276 (73.4)
≥65	0 (0.0)	47 (25.1)	41 (22.0)	88 (23.4)

^a Other = Hispanic, American Indian, and Brazilian.

Medical officer's note: There appears to be random and even distribution of sex, age and race by treatment arm among the cefdinir BID and cefaclor arms among those enrolled and those evaluable. Because the cefdinir qd dosing is not submitted for approval, the findings related to

the seven enrolled and the three evaluable patients in this arm are inconsequential with respect to efficacy.

Smoking and Past Medical History: No smoking or tobacco use history was obtained in this study. History of existing or prior pulmonary disease was in an open ended inquiry regarding "Past Medical History" which appeared in the questionnaire. That question provided the follow results for clinically evaluable patients:

Table 17: Prior Pulmonary Diagnoses & Conditions Predisposing to
Community Acquired Pneumonia for All Clinically Evaluable Patients

Pulmonary Diagnosis	cefdinir 300 mg	cefaclor
COPD	56	51
Asthma	30	31
Pneumonia	11	12
Bronchitis	15	15
Lung cancer	2	2
Bronchiectasis	1	1
Pulmonary Fibrosis	0	1
Cor pulmonale	0	1
Pneumonia	0	1
Total	115	115

Medical officer's note: *Although not requested by DAIDP in original review, we have requested the Applicant provide us with any information obtained in study 983-4 with respect to distribution of patients' smoking, tobacco use and past medical history with respect to pulmonary disease to the best of the Applicant's ability. As stated above, no information was obtained with respect to smoking or tobacco use. This remains a potential confounder and the assumption must be made that patient randomization will control for assignment of this variable between the treatment arm. However, it can never be tested or proved because no information is available. Information regarding prior pulmonary diagnoses and conditions predisposing to community acquired pneumonia was obtained via open-ended question. Therefore, the data*

cannot be expected to be complete, and there is no way to determine how thoroughly this patient history was elicited. However, scrutiny of the above table provides the observation that equal numbers of diagnoses such as COPD, asthma, prior pneumonia and bronchitis and lung cancer are evenly distributed by treatment is reassuring that randomization effectively controlled for this potential confounder.

Severity of Illness/Clinical Score upon Enrollment: Among those enrolled, the following rates of signs and symptoms occurred among enrollees: cough, 100%; sputum production; 100%; chest sounds, 95%; shortness of breath, 83%; chest pain, 71%; and fever, 19%. The clinical scoring system allowed for a maximum score of 28. The mean baseline scores at enrollment were 14.2 for the cefdinir, 300 mg bid arm and 14.3 for the cefaclor treatment arm. Among clinically evaluable patients, those receiving cefdinir, 300 mg bid had a mean baseline score of 14.1 and those receiving cefaclor had a mean baseline score of 14.6. Among the evaluable population, those receiving cefdinir bid had a mean baseline score of 14.3 and those receiving cefaclor had a mean baseline score of 14.8.

Medical officer's note: *There does not appear to be differences of note with respect to baseline clinical scores, and clinical scores among evaluable and clinically evaluable patients by treatment arm. Overall, the patients were not severely ill, and fever was fairly uncommon.*

Compliance with study medication**Table 18. Patient Exposure to Study Medication - All Patients**

Days on Study Medication	Cefdinir QD N = 14	Cefdinir BID N = 347	Cefaclor N = 343
1	0	5	2
2	0	2	5
3	0	8	5
4	0	7	16
5	0	11	16
6	0	10	9
7	0	10	13
8	1	13	4
9	0	9	2
10	7	114	112
11	6	146	134
12	0	2	0
13	0	0	2
14	0	1	0
16	0	1	0
21	0	0	1
Median	10.0	10.0	10.0
Unknown*	0	8	22

- * Three cefdinir BID-treated and three cefaclor-treated patients were randomized but received no study medication.

Medical officer's note: The protocol was designed to provide a ten day exposure to either study or comparator drug. The great number of subjects enrolled completed therapy and this validates the equivalence and adequacy of exposure to drug in each study arm.

Efficacy

The numbers of patients randomized to treatment (i.e., the ITT population) are compared to other patient populations in the following table.

Table 19. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	N		Cefdinir QD		Cefdinir BID		Cefaclor	
ITT	704	(100.0)	14	(100.0)	347	(100.0)	343	(100.0)
MITT	509	(72.3)	13	(92.9)	256	(73.8)	240	(70.0)
Clinically Evaluable	453	(89.0)	4	(28.6)	222	(64.0)	227	(66.2)
Evaluable	376	(83.0)	3	(21.4)	187	(53.9)	186	(54.2)
Qualified ^a	278	(73.9)	2	(66.7)	137	(73.3)	139	(74.7)

^a As a percentage of the Evaluable patient population

Medical officer's note: Definitions of these populations appear in footnote below.²

² Analysis populations for efficacy examined in this report include the evaluable, the clinically evaluable, the modified intent-to-treat (MITT), and the intent-to-treat (ITT).

Evaluable patients had no known protocol violations that might have affected efficacy assessments at TOC using the specific, predefined criteria detailed above. Patients who had microbiologic and/or clinical assessments done early (i.e., before the follow-up visit window) or who took a concurrent antibacterial because they were early treatment failures were not removed from the evaluable patient population for these reasons.

A subset of evaluable patients identified as "qualified patients" was examined at LTFU. Qualified patients were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits (e.g., qualified patients did not take concurrent systemic or topical antibacterial agents).

Patients in the clinically evaluable population had the correct indication documented by a baseline chest x-ray; at least one clinical sign and symptom at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy; and had their clinical assessments performed within the range of days specified in the protocol. Patients were not excluded from this data set if they had no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

Patients in the MITT population had the correct indication, had at least one baseline pathogen, and had a follow-up culture. The MITT population was the same at TOC and LTFU.

Patients in the ITT population were those randomized to treatment. Patients who had no baseline pathogen or no follow-up culture were considered to have microbiologic persistence in the ITT analyses. Similarly, patients who had no follow-up clinical assessment were categorized as failures in the ITT analyses. The ITT population was the same at TOC and LTFU.

Table 20. Patient Disposition - All Patients
[Number (%) of Patients]

Patient Disposition	Cefdinir QD		Cefdinir BID		Cefaclor		Total	
Randomized to Treatment	14		347		343		704	
Withdrawn Prior to End of Treatment								
Lack of Compliance ^a	0	(0.0)	14	(4.0)	19	(5.5)	33	(4.7)
No Baseline Pathogen	0	(0.0)	29	(8.4)	34	(9.9)	63	(8.9)
Adverse Event ^b	0	(0.0)	21	(6.1)	16	(4.7)	37	(5.3)
Lack of Efficacy	0	(0.0)	7	(2.0)	6	(1.7)	13	(1.8)
Resistant Baseline Pathogen	1	(1.7)	6	(1.7)	10	(2.9)	17	(2.4)
Other/Administrative ^{c,d}	0	(0.0)	13	(3.7)	11	(3.2)	24	(3.4)
Completed Treatment	13	(92.9)	257	(74.1)	247	(72.0)	517	(73.4)
Completed Follow-Up Visits								
STFU (TOC)	13	(92.9)	266	(76.7)	243	(70.8)	522	(74.1)
LTFU	11	(78.6)	216	(62.2)	197	(57.4)	424	(60.2)

^a Patient 8, Center 31 (cefdinir BID) and Patient 8, Center 1 (cefaclor) were randomized but received no study medication.

^b Patient 4, Center 59 (cefdinir BID) and Patient 7, Center 13 (cefaclor) were randomized but received no study medication.

^c Patient 3, Center 59 (cefdinir BID) and Patient 124, Center 26 (cefaclor) were randomized but received no study medication.

^d Reason includes lost to follow-up.

Medical officer's note: The reasons for disqualification or dropout are justifiable and distributed evenly across the two evaluated treatment arms.

Medical officer's note: The medical officer reviewed case report forms for all patients considered to be nonevaluable or failures and 15% of patients considered to be cures. All data reviewed was consistent with data presented in summary in CANDAs. The medical officer also found the patients to be fairly assigned outcomes as per protocol. Reassignment of outcome would have occurred in <5% of cases and presented no bias with respect to treatment arm (blind was maintained). To check that such random sampling was adequate to confirm the Applicant's findings, finite population bootstrapping to estimate the variance of the predicted lower bound of the confidence interval for the difference in response rates was employed. This technique supported that such a small discrepancy, with nondifferential reassignment, would not significantly effect either the confidence intervals or the corresponding conclusions about equivalence. Thus, the medical reviewer has accepted the Applicant's numbers, outcome assignments and cure rates.

Clinical Efficacy**Test of Cure. Clinical Cure****Table 21. Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the Test-of-Cure Visit – Evaluable Patients**

Investigator Determination	Combined Investigator/Sponsor Determination			
	Cefdinir BID N = 187		Cefaclor N = 186	
	Cure	Failure	Cure	Failure
Cure	80	0	91	0
Improvement	70	16	56	13
Failure	0	21	0	23
Not Assessable	0	0	0	3
Same Clinical Response for both Applicant & Investigator	101/187(54%)		114/186(61%)	
Investigator called improved, <50% improved by Applicant's score (Clinical Failure by score)	16/86(19%)		13/69(19%)	

Table 22: Clinical Patient Outcomes Investigator vs. Applicant at TOC

Patient Outcome	Investigator	Applicant
<u>Cefdinir</u>	n=187	n=187
Success*	166	150
Failure	21	37
Not Assessable	0	0
<u>Cefaclor</u>	n=186	n=186
Success*	160	147
Failure	23	39
Not Assessable	3	0

* For investigator, "success"= cure + improvement. For Applicant, success is based on the clinical scoring system described above.

Medical and statistical officer's note: Unless otherwise noted, all confidence intervals presented in the following review will be double-sided, 95% confidence intervals about the difference between test and comparator drug with continuity correction and no correction for center effect.

95% CI for Investigator Determination of Clinical Outcome at TOC is (-4.52, 10.02).

95% CI for Applicant Determination of Clinical Outcome at TOC is (-7.53, 9.89).

Medical and statistical reviewer's note: The clinical outcome at test-of-cure, which is a primary endpoint, met DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.

Long-Term Follow Up, Clinical Cure

Table 23. Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the Long-Term Follow-Up Visit - Qualified Patients

Investigator Determination	Cefdinir BID N = 137		Cefaclor N = 139	
	Cure	Failure/Recurrence	Cure	Failure/Recurrence
Cure	109	10	117	3
Improvement	9	3	5	8
Failure/Recurrence	0	6	0	5
Not Assessable	0	0	0	1
Same Clinical				
Response for both	115/137		122/139	
Investigator & Applicant	(84%)		(88%)	
Investigator called				
improved, <50%	3/13		8/13	
improved by	(23%)		(35%)	
Applicant's score				
(Clinical Failure)				
Failure carried				
forward as Failure	12		7	
Assigned at TOC				

Table 24: Clinical Patient Outcomes Investigator vs. Applicant at LTFU

Patient Outcome	Investigator	Applicant
Cefdinir	n=137	n=137
Success ^a	131	118
Failure	6	19
Not Assessable	0	0
Cefaclor	n=139	n=139
Success ^a	133	122
Failure	5	17
Not Assessable	1	0

^a For investigator, "success"= cure +improvement. For Applicant, success is based on the clinical scoring system described above.

95% CI for Investigator Determination of Clinical Outcome at LTFU is (-5.60, 5.47).

95% CI for Applicant Determination for Clinical Outcome at LTFU is (-1.03, 7.03).

Medical officer's and statistical reviewer's note: The clinical outcome at long-term follow up, although not a primary endpoint, met DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.

Medical officer's note: The rates of agreement between Applicant and Investigator clinical outcome assignment based on the clinical score system differed somewhat between TOC and Long-Term Follow Up (54% and 84% agreement on cefdinir, and 61% and 88% agreement on cefaclor, respectively). Those assigned failure by Applicant's clinical score that were improved by Investigator's assessment was more similar (19% and 23% on cefdinir, and 19% and 35% on cefaclor, respectively). As the singular major outcome of interest is TOC, the differences matter little. In addition, most of the reassignment involved increasing clinical failures in a manner unbiased to treatment arm.

Test of Cure and Long-Term Follow Up Visits, ITT and MITT Analysis**Table 25. Clinical Efficacy at TOC and LTFU – ITT and MITT Populations by Clinical Cure, Microbiologic Eradication by Patient and Clinical Cure Among Clinically Evaluable Patients**

Parameter	Cefdinir BID		Cefaclor	
	n/N	%	n/N	%
TOC/ITT: Microbiologic Eradication by Patient ^a	234/347	67.4	221/343	64.4
TOC/ITT: Clinical Cure ^b	265/347	76.4	237/343	69.1
TOC/ITT: Microbiologic Eradication by Patient ^c	228/256	89.1	215/240	89.6
LTFU/ITT: Microbiologic Eradication by Patient ^d	177/347	51.0	166/343	48.4
LTFU/ITT: Clinical Cure ^e	187/347	53.9	170/343	49.6
Clinical Cure Rate ^f Among Clinically Evaluable Patients	164/222	73.8	163/227	71.8

^a n/N = Number of patients with eradication/total number of patients.

^b n/N = Number of patients with combined determination of cure/total number of patients.

^c n/N = Number of patients with eradication/total number of patients.

^d n/N = Number of patients with continued microbiologic eradication (ie, no relapse)/total number of patients.

^e n/N = Number of patients with combined determination of cure/total number of patients.

^f n/N = Number of patients with clinical cures divided by all clinically evaluable patients (microbiologic status irrelevant). See footnote 2 on page 54 for more detailed description.

95% CI for TOC/ITT, microbiologic eradication rate by patient is (-4.36, 10.36).

95% CI for TOC/ITT, clinical cure rate is (-0.36, 14.19).

95% CI for TOC/ITT, microbiologic eradication rate by patient is (-6.36, +5.32).

95% CI for LTFU/ITT, microbiologic eradication rate by patient is (-5.14, 10.36).

95% CI for LTFU/ITT, clinical cure rate, is (-3.41, 12.07).

95% CI for clinical cure rate among clinically evaluable patients is (-6.60, +10.74).

Medical officer's note: *The clinical outcomes above, which are not primary endpoints but evaluate several clinical populations (intent-to-treat and modified-intent-to-treat for clinical*

cure and microbiologic eradication by patient at both test of cure and long-term follow up) , all meet DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.

Test-of-Cure. Clinical Cure Rate by Patient according to Baseline Pathogens

Table 26. Clinical Cure Rate* by Patient (According to Their Baseline Pathogens) at the TOC Visit - Evaluable Patients

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir BID		Cefaclor		Cefdinir BID		Cefaclor	
	n/N	%	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	5/7	71.4	0/1	0	6/7	85.7	12/14	85.7
<i>Streptococcus pneumoniae</i>	9/9	100.0	13/16	81.3	20/23	87.0	17/19	89.4
<i>Haemophilus influenzae</i>	35/42	83.3	31/44	70.5	25/29	86.2	21/27	77.8
<i>Haemophilus parainfluenzae</i>	40/53	75.5	40/46	87.0	24/31	77.4	29/39	74.4
<i>Escherichia coli</i>	1/1	100.0	3/4	75.0	5/8	62.5	6/7	85.7
<i>Klebsiella pneumoniae</i>	1/2	50.0	1/1	100.0	5/7	71.4	11/13	84.6
<i>Moraxella catarrhalis</i>	4/4	100.0	3/3	100.0	5/6	83.3	5/8	62.5
Total	95/118	80.5	91/115	79.1	87/108	80.6	101/127	79.5
Total, single & multiple isolates	182/226	80.5	192/242	79.3				

n/N = Number of patients who were cured/total number of patients.

* Based on combined investigator/sponsor clinical assessments.

95% CI for Clinical Cure Rate at TOC by Patient according to baseline pathogens (single isolates) is (-9.79, +12.54).

Medical officer's note: The clinical cure rate at test of cure by patient according to baseline pathogens meets DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia. The applicant has by this data demonstrated provided enough clinical outcome and microbiologic information to be granted approval for the following pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Haemophilus parainfluenzae*.

Long-Term Follow Up, Clinical Cure by Patient according to Baseline Pathogens**Table 27. Clinical Cure Rate by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients (Classified as Cures at TOC)**

Baseline Pathogen	Single isolate		Multiple isolates	
	Cefdinir BID	Cefaclor	Cefdinir BID	Cefaclor
	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	3/3	100.0	0/0	—
<i>Streptococcus pneumoniae</i>	6/6	100.0	11/13	84.6
<i>Escherichia coli</i>	0/0	—	3/3	100.0
<i>Haemophilus influenzae</i>	29/32	90.6	28/29	96.6
<i>Haemophilus parainfluenzae</i>	35/36	97.2	30/34	88.2
<i>Klebsiella pneumoniae</i>	1/1	100.0	1/1	100.0
<i>Moraxella catarrhalis</i>	4/4	100.0	3/3	100.0
Total	112/118	94.9	119/129	92.2
Total, single & multiple isolates	177/185	95.7	202/216	93.5

n/N = Number of patients who were cured/total number of patients.

* Based on combined investigator/sponsor clinical assessments

95% CI for Clinical Cure Rate at LTFU by Patient (single isolate) is (-4.23, 9.56).

Medical officer's note: The clinical cure rate at long-term follow up by patient according to baseline pathogens meets DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.

Microbiologic Efficacy**Test-Of-Cure. Microbiologic Eradication by Pathogen****Table 28. Microbiologic Eradication Rate by Baseline Pathogen at the TOC Visit - Pathogens From Evaluable Patients**

Baseline Pathogen	Cefdinir BID		Cefaclor	
	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	16/17	94.1	14/15	93.3
<i>Streptococcus pneumoniae</i>	31/31	100.0	35/35	100.0
<i>Escherichia coli</i>	7/9	77.8	9/10	90.0
<i>Haemophilus influenzae</i> , β -lactamase +	11/14	78.6	12/15	80.0
<i>Haemophilus influenzae</i> , β -lactamase -	44/51	86.3	48/57	84.2
<i>Haemophilus parainfluenzae</i> , β -lactamase +	7/8	87.5	4/5	80.0
<i>Haemophilus parainfluenzae</i> , β -lactamase -	74/81	91.4	74/77	96.1
<i>Klebsiella pneumoniae</i>	8/9	88.9	11/11	100.0
<i>Moraxella catarrhalis</i> , β -lactamase +	10/10	100.0	10/10	100.0
<i>Moraxella catarrhalis</i> , β -lactamase -	0/0	—	1/1	100.0
Total	208/230	90.4	218/236	92.3

n/N = Number of pathogens eradicated/total number of pathogens.

95% CI test of cure the microbiologic eradication rate by pathogen is (-7.46, +3.58).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by pathogen at the test-of-cure visit (6 to 14 days posttherapy).

Long Term Follow Up Visit. Microbiologic Eradication by Pathogen

Qualified patients who had persistent pathogens at the TOC were automatically considered to have persistent pathogens at LTFU.

Table 29. Microbiologic Eradication Rate by Baseline Pathogen at the LTFU Visit - Pathogens From Qualified Patients (Classified as Patients With Eradication at TOC)

Baseline Pathogen	Cefdinir BID		Cefaclor	
	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	7/7	100.0	12/12	100.0
<i>Streptococcus pneumoniae</i>	20/20	100.0	27/27	100.0
<i>Escherichia coli</i>	4/4	100.0	7/7	100.0
<i>Haemophilus influenzae</i> , β -lactamase +	11/11	100.0	11/11	100.0
<i>Haemophilus influenzae</i> , β -lactamase -	34/34	100.0	40/40	100.0
<i>Haemophilus parainfluenzae</i> , β -lactamase+	6/6	100.0	4/4	100.0
<i>Haemophilus parainfluenzae</i> , β -lactamase-	50/51	98.0	51/51	100.0
<i>Klebsiella pneumoniae</i>	3/3	100.0	9/9	100.0
<i>Moraxella catarrhalis</i> , β -lactamase +	8/8	100.0	7/7	100.0
<i>Moraxella catarrhalis</i> , β -lactamase -	0/0	—	1/1	100.0
Total	143/144	99.3	169/169	100.0

n/N = Number of pathogens eradicated/total number of pathogens.

95% CI for the Microbiologic Eradication Rate by Pathogen at LTFU is (7.93, +20.26).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by pathogen at long-term follow-up.

Test-Of-Cure, Microbiologic Eradication by Patient**Table 30. Microbiologic Eradication Rate by Patient (According to Their Baseline Pathogens at the TOC Visit - Evaluable Patients)**

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir BID		Cefaclor		Cefdinir BID		Cefaclor	
	n/N	%	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	7/7	100.0	1/1	100.0	8/10	80.0	13/14	92.9
<i>Streptococcus pneumoniae</i>	9/9	100.0	16/16	100.0	20/22	90.9	19/19	100.0
<i>Escherichia coli</i>	1/1	100.0	3/4	75.0	6/8	75.0	5/5	100.0
<i>Haemophilus influenzae</i>	36/42	85.7	35/44	79.5	20/21	95.2	24/27	88.9
<i>Haemophilus parainfluenzae</i>	46/53	86.8	43/46	93.5	34/36	94.4	34/36	94.4
<i>Klebsiella pneumoniae</i>	2/2	100.0	1/1	100.0	4/7	57.1	9/10	90.0
<i>Moraxella catarrhalis</i>	4/4	100.0	3/3	100.0	6/6	100.0	8/8	100.0
Total	159/179	88.8	162/180	90.0	98/112	87.5	112/119	94.1
Total, single	257/291	88.3	274/299	91.6				
& multiple isolates								

n/N = Number of patients with eradication/total number of patients.

95% CI for the Microbiologic Eradication Rate by Patient (single isolate) at TOC is (-8.09, +5.75).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by patient at the test-of-cure visit (6 to 14 days posttherapy).

At the TOC visit, 20 evaluable cefdinir BID-treated patients had 22 persistent pathogens and 19 evaluable cefaclor-treated patients had 19 persistent pathogens. All persistent pathogens were susceptible to study medication at baseline and most (39/41) remained susceptible at TOC. Two isolates of *H. influenzae* that were susceptible at baseline were intermediately susceptible at TOC; one came from a cefdinir BID-treated patient and the other from a cefaclor-treated patient.

Long Term Follow Up Visit, Microbiologic Eradication by Patient**Table 31. Microbiologic Eradication by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients (Classified as Patients With Eradication at TOC)**

Baseline Pathogen	<u>Single isolate</u>				<u>Multiple isolates</u>			
	Cefdinir BID		Cefaclor		Cefdinir BID		Cefaclor	
	n/N	%	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	4/4	100.0	0/0	--	3/3	100.0	12/12	100.0
<i>Streptococcus pneumoniae</i>	6/6	100.0	13/13	100.0	14/14	100.0	15/15	100.0
<i>Escherichia coli</i>	0/0	--	2/2	100.0	13/13	100.0	19/19	100.0
<i>Haemophilus influenzae</i>	33/33	100.0	29/29	100.0	20/20	100.0	22/22	100.0
<i>Haemophilus parainfluenzae</i>	35/36	97.2	31/31	100.0	4/4	100.0	3/3	100.0
<i>Klebsiella pneumoniae</i>	1/1	100.0	1/1	100.0	2/2	100.0	6/6	100.0
<i>Moraxella catarrhalis</i>	4/4	100.0	3/3	100.0	4/4	100.0	4/4	100.0
Total	116/117	99.1	126/126	100.0	60/60	100.0	89/89	100.0
Total, single								
& multiple isolates	176/177	99.4	215/215	100.0				

n/N = Number of patients with eradication/total number of patients.

95% CI for Microbiologic Eradication Rate by Patient (single isolate) at LTFU is (-3.35, +1.64).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by patient at the long-term follow up.

Test of Cure and Long-Term Follow Up Visit, Modified Intent-to-Treat Analysis**Table 32. Microbiologic Efficacy at TOC and LTFU -- MITT and ITT Populations**

Parameter	Cefdinir BID		Cefaclor	
	n/N	%	n/N	%
TOC/MITT: Microbiologic Eradication by Pathogen ^a	339/369	91.9	313/338	92.6
TOC/ITT: Microbiologic Eradication by Pathogen ^a	347/387	89.7	323/385	83.9
LTFU/ITT Microbiologic Eradication by Pathogen ^a	263/387	68.0	252/385	65.5

^a n/N = Number of pathogens eradicated/total number of pathogens.

95% CI for microbiologic eradication rate by pathogen at TOC/MITT is (-4.96, +3.49).

95% CI for microbiologic eradication rate by pathogen at TOC/ITT is (-0.75, +10.79).

95% CI for microbiologic eradication rate by pathogen at LTFU/ITT is (-4.40, 9.41).

Medical officer's note: *Equivalence is demonstrated for microbiologic eradication rates by pathogen for modified intent to treat at test of cure and for intent to treat at test of cure and long term follow up.*

Test of Cure, Microbiologic versus Clinical Response Rates

Table 33. Microbiologic Versus Clinical Response at the Test-of-Cure
Visit - Evaluable Patients (%)

Microbiologic Response	Clinical Response	
	Cure ^a	Failure
Cefdinir BID, N = 187		
Patients With Eradication	142 (75.9)	25 (13.4)
Patients With Persistence	8 (4.3)	12 (6.4)
Cefaclor, N = 186		
Patients With Eradication	140 (75.2)	27 (14.5)
Patients With Persistence	7 (3.8)	12 (6.4)

^a Combined investigator/sponsor clinical determination

Medical officer's note: The rates of microbial persistence despite clinical cure, clinical failure with microbial eradication, clinical cure with microbial eradication, and clinical failure with microbial persistence are similar across both treatment arms.

At baseline, eight cefdinir BID- and six cefaclor-treated patients had *S. pneumoniae* isolates that were resistant (or intermediately susceptible) to penicillin (MIC ≥ 0.1 $\mu\text{g/mL}$). Despite this fact, all of the cefdinir BID- and cefaclor-treated patients had *S. pneumoniae* eradicated, and most (6/8) cefdinir BID- and all cefaclor-treated patients were assessed as clinical cures at TOC.

Medical officer's note: The numbers of resistant or intermediately resistant *S. pneumoniae* are very small and conclusions cannot be drawn. However, the applicant is not seeking labeling for resistant or intermediately resistant *S. pneumoniae* and the issue requires no further consideration here.

Superinfections. In this study, 3% (12) of cefdinir BID-treated and 6% (20) of cefaclor-treated patients had one or more superinfecting pathogens at the TOC visit. Most superinfecting pathogens were susceptible or intermediately susceptible to cefdinir (12 of 14 isolates) and cefaclor (23 of 29). Those isolates that were resistant to cefdinir included *Enterobacter cloacae* and *Pseudomonas aeruginosa*, while those resistant to cefaclor included *Acinetobacter calcoaceticus* var *anitratus*, *Enterobacter agglomerans*, *E. cloacae*, *P. aeruginosa*, *Pseudomonas fluorescens*, and *Pseudomonas putida*.

Table 34. Patients With Superinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir BID N = 347	Cefaclor N = 343
Gram-Positive^a		
<i>Streptococcus pneumoniae</i>	0	1
Gram-Negative^a		
<i>Acinetobacter calcoaceticus</i> var <i>lwoffii</i>	1	0
<i>Haemophilus haemolyticus</i>	0	1
<i>Haemophilus influenzae</i>	1	1
<i>Haemophilus parainfluenzae</i>	6	7
<i>Klebsiella pneumoniae</i>	0	1
<i>Pseudomonas aeruginosa</i>	1	0
<i>Pseudomonas fluorescens</i>	0	1
<i>Proteus mirabilis</i>	1	0
Multiple^b	2	8
Total	12 (3.5%)	20 (5.8%)

^a Pathogens appearing as sole superinfecting pathogens

^b Applicant's Appendix C.73 has complete summary of patients with multiple pathogens.

Medical officer's note: Development of superinfection was not a common event and similar across both arms.

Reinfections. Two patients in the cefdinir BID treatment group and one patient in the cefaclor treatment group had reinfections. For the cefdinir BID group, reinfecting pathogens included *M. catarrhalis* and *S. pneumoniae* plus *H. parainfluenzae*; for cefaclor they included *S. agalactiae* plus *M. catarrhalis*.

Medical officer's note: Development of reinfection was uncommon event and similar across both arms.

Safety

The safety of each study medication was assessed using adverse event data and the results from physical examinations and clinical laboratory tests (hematology, blood chemistry, and urinalysis). All patients randomized to treatment who received study medication were evaluated for safety.

Adverse Events. Any symptom (except those related to community-acquired pneumonia) or clinically significant concurrent illness not present at baseline which was reported by the patient/guardian or noted by the investigator was recorded as an adverse event. Worsening of pneumonia was also considered an adverse event if hospitalization was required, and abnormal clinical laboratory values could be designated as adverse events at the discretion of the

investigator.

Each adverse event reported by a patient or noted by an investigator was recorded on a CRF. Adverse events were evaluated by the investigator for relationship to drug (definitely, probably, possibly, unlikely, definitely not, or insufficient information); intensity (mild, moderate, or severe); duration; frequency; management of study medication; patient outcome (at last visit); and presence, frequency, and intensity relative to baseline. Drug-associated adverse events were those considered definitely, probably, or possibly related to study medication by the investigator.

Adverse events were considered serious if they were fatal, immediately life-threatening, severely or permanently disabling, required or prolonged hospitalization, or were an intentional or accidental overdose, a congenital anomaly, or cancer. Unexpected or serious adverse events were reported to the study manager throughout the study. During the medical review, other events could be identified as serious even if they did not meet the above definition. These other events could include:

- Anaphylaxis,
- Blood dyscrasias,
- Cardiac arrhythmias,
- Collagen disorders (e.g., LE syndrome, retroperitoneal fibrosis),
- Deafness,
- Hemorrhage from any site,
- Jaundice of any degree,
- Myopathy,
- Ophthalmic disorders (e.g., blindness, cataract, keratitis, glaucoma, optic atrophy, retinal disorder),
- Pseudomembranous colitis,
- Severe CNS/PNS disorders (e.g., coma, seizures, dyskinesia, encephalopathy, neuropathy, paralysis),
- Severe dermatologic disorders (e.g., exfoliative, desquamative, or vesiculobullous rashes; photosensitivity),
- Severe psychiatric disorders (e.g., psychosis, drug dependence), or
- Vasculitis.

Beginning December 1, 1992 (approximately 11 months after the study started), patients who discontinued treatment due to diarrhea were to be tested for *Clostridium difficile*.

Medical officer's note: The above description of safety evaluation is acceptable and should be capable of capturing ADRs of interest, particularly those associated with other cephalosporins which would also be expected with cefdinir.

Safety data were summarized for all patients who received study medication. For the cefdinir BID and cefaclor treatment groups, a CMH analysis, adjusting for center, was used to compare the rates (i.e., incidence) of all adverse events, drug-associated adverse events, diarrhea, and treatment discontinuations due to adverse events. Results of the Breslow-Day test were reviewed

in evaluating the consistency of the relationship between adverse events and treatment among centers.

The most frequently reported adverse events for patients treated with cefdinir BID included diarrhea (15%), headache (8%), nausea (3%), and rash (3%); and with cefaclor, diarrhea (6%), headache (5%), and rash (3%). When the incidence of diarrhea was not included in the analyses, there was no statistical difference between the two treatment groups in the numbers of patients experiencing adverse events ($p = 0.129$) or drug-associated adverse events ($p = 0.598$).

Twenty (6%) patients treated with cefdinir BID and 15 (4%) treated with cefaclor discontinued treatment due to an adverse event. After completing treatment, an additional four cefdinir BID- and four cefaclor-treated patients withdrew due to an adverse event. There was no statistical difference in the rates of treatment discontinuation between the two treatment groups ($p = 0.334$).

Seventeen (5%) cefdinir BID-treated patients and 15 (4%) cefaclor-treated patients experienced a serious adverse event. An additional patient in each of these treatment groups experienced a serious adverse event without ever receiving study medication; these two patients experienced worsening pneumonia that required hospitalization, a serious adverse event in this study. Six deaths occurred, three each in the cefdinir BID and cefaclor treatment groups.

Clinical laboratory abnormalities were transient and sporadic, and many of the markedly abnormal laboratory values were those commonly seen in patients treated with other β -lactam antibacterials. There were more cefdinir BID-treated patients who had markedly abnormal laboratory values than cefaclor-treated patients, but the overall rate at which markedly abnormal laboratory values occurred was similar for both groups (16% versus 13%).

Table 35. Summary of Adverse Events -- All Patients
[Number (%) of Patients]

	Cefdinir QD N = 14		Cefdinir BID N = 344		Cefaclor N = 340	
Adverse Events During Study						
All Adverse Events	5	(35.7)	168	(48.8)	130	(38.2)
Associated ^a Adverse Events	3	(21.4)	80	(23.3)	55	(16.2)
Adverse Events by Sex^b						
All Adverse Events						
Male	3	(42.9)	98	(51.0)	83	(43.7)
Female	2	(28.6)	70	(46.1)	47	(31.3)
Associated Adverse Events						
Male	3	(42.9)	46	(24.0)	35	(18.4)
Female	0	(0.0)	34	(22.4)	20	(13.3)
Adverse Events by Race^c						
All Adverse Events						
White	4	(33.3)	145	(48.8)	114	(39.9)
Black	1	(50.0)	13	(43.3)	13	(29.5)
Asian	0	(0.0)	3	(100.0)	0	(0.0)
Hispanic	0	(0.0)	5	(41.7)	2	(25.0)
Other	0	(0.0)	2	(100.0)	1	(100.0)
Associated Adverse Events						
White	2	(16.7)	73	(24.6)	51	(17.8)
Black	1	(50.0)	4	(13.3)	3	(6.8)
Asian	0	(0.0)	2	(66.7)	0	(0.0)
Hispanic	0	(0.0)	0	(0.0)	0	(0.0)
Other	0	(0.0)	1	(50.0)	1	(100.0)
Adverse Events by Age^d						
All Adverse Events						
13 to <18 yr	0	(0.0)	4	(40.0)	3	(37.5)
18 to <65 yr	5	(50.0)	126	(50.0)	92	(35.2)
≥65 yr	0	(0.0)	38	(46.3)	35	(49.3)
Associated Adverse Events						
13 to <18 yr	0	(0.0)	3	(30.0)	1	(12.5)
18 to <65 yr	3	(30.0)	63	(25.0)	43	(16.5)
≥65 yr	0	(0.0)	14	(17.1)	11	(15.5)
Adverse Events by Maximum Intensity^e						
All Adverse Events						
Mild	4	(28.6)	107	(31.1)	90	(26.5)
Moderate	1	(7.1)	76	(22.1)	54	(15.9)
Severe	0	(0.0)	21	(6.1)	10	(2.9)
Associated Adverse Events						
Mild	2	(14.3)	58	(16.9)	41	(12.1)
Moderate	1	(7.1)	30	(8.7)	17	(5.0)
Severe	0	(0.0)	5	(1.5)	1	(0.3)
Serious Adverse Events ^f	0	(0.0)	17	(4.9)	15	(4.4)

Deaths	0	(0.0)	3	(0.9)	3	(0.9)
Discontinuation of Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	20	(5.8)	15 ^a	(4.4)
Associated Adverse Events	0	(0.0)	10	(2.9)	6	(1.8)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	4	(1.2)	4	(1.2)
Associated Adverse Events	0	(0.0)	1	(0.3)	0	(0.0)
Associated Adverse Events	0	(0.0)	10	(2.9)	6	(1.8)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	4	(1.2)	4	(1.2)
Associated Adverse Events	0	(0.0)	1	(0.3)	0	(0.0)

^a Considered by the investigator to be possibly, probably, or definitely related to study medication.

^b Percentages based on total numbers of males or females in a treatment group

^c Percentages based on total numbers of patients of each race in a treatment group

^d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.

^e Patients with multiple adverse events were counted once in each applicable category.

^f Two additional patients (one cefdinir BID- and one cefaclor-treated) who did not receive study medication experienced a serious adverse event and are not included in the safety summary tables.

^g One patient discontinued due to a non-TESS adverse event.

Regardless of whether patients received cefdinir or cefaclor, most adverse events were related to the digestive system, body as a whole, the respiratory system, skin and appendages, and the nervous system. Most of the adverse events related to the digestive system were considered drug-associated by the investigator. Significantly more cefdinir BID-treated patients experienced adverse events ($p = 0.004$) and drug-associated adverse events ($p = 0.011$) than cefaclor-treated patients.

The most frequently reported adverse events for patients treated with cefdinir BID included diarrhea (15%), headache (8%), nausea (3%), and rash (3%); and with cefaclor, diarrhea (6%), headache (5%), and rash (3%).

Statistically, there was a significant difference in the rates of diarrhea when the cefdinir BID and cefaclor treatment groups were compared ($p < 0.001$). However, when diarrhea was not included in the analyses, there was no significant difference between the treatment groups in the numbers of patients experiencing adverse events ($p = 0.129$) or drug-associated adverse events ($p = 0.598$).

Medical officer's note: The side effect profile of cefdinir is not unexpected. Other newer cephalosporins have also been observed to have higher rates of diarrhea and gastrointestinal effects. The Applicant proposed to evaluate all patients withdrawn from study for diarrhea for Clostridium difficile-associated diarrhea beginning 12/1/92. Three patients were withdrawn but

the investigators failed to perform such testing. Among those patients reporting diarrhea as an ADR, the investigator consider the event mild in 75% of cases and only 2% were characterized as severe. Age and sex did not appear to be related to the occurrence of diarrhea. The remaining ADR profile resembles other cephalosporins, including the comparator arm.

Table 36. All and Associated^a Adverse Events by Body System - Patients Receiving Study Medication [Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 14		Cefdinir BID ^a N = 344		Cefaclor N = 340	
	All	Associated	All	Associated	All	Associated
DIGESTIVE SYSTEM	3 [*] (21.4)	3 [*] (21.4)	77 [*] (22.4)	60 [*] (17.4)	41 [*] (12.1)	33 (9.7)
Diarrhea	3 (21.4)	3 (21.4)	52 (15.1)	46 (13.4)	20 (5.9)	1 (5.6)
Nausea	1 (7.1)	1 (7.1)	11 (3.2)	10 (2.9)	7 (2.1)	5 (1.5)
Vomiting	0 (0.0)	0 (0.0)	8 (2.3)	5 (1.5)	5 (1.5)	4 (1.2)
Flatulence	0 (0.0)	0 (0.0)	5 (1.5)	2 (0.6)	1 (0.3)	1 (0.3)
Anorexia	0 (0.0)	0 (0.0)	4 (1.2)	3 (0.9)	4 (1.2)	3 (0.9)
Dyspepsia	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.6)	4 (1.2)	3 (0.9)
Gastroenteritis	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Liver Function Tests Abnormal	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Melena	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Rectal Hemorrhage	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	1 (0.3)
Jaundice	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Mouth Ulceration	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal Disorder	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)
Aphthous Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Dry Mouth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)
Eruclation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
BODY AS A WHOLE	1 (7.1)	0 (0.0)	59 [*] (17.2)	16 (4.7)	41 [*] (12.1)	12 [*] (3.5)
Headache	1 (7.1)	0 (0.0)	26 (7.6)	13 (3.8)	17 (5.0)	7 (2.1)
Back Pain	0 (0.0)	0 (0.0)	6 (1.7)	1 (0.3)	5 (1.5)	1 (0.3)
Infection	0 (0.0)	0 (0.0)	6 (1.7)	0 (0.0)	5 (1.5)	0 (0.0)
Abdominal Pain	0 (0.0)	0 (0.0)	5 (1.5)	2 (0.6)	4 (1.2)	3 (0.9)
Chest Pain	0 (0.0)	0 (0.0)	4 (1.2)	0 (0.0)	2 (0.6)	0 (0.0)
Neck Pain	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)	2 (0.6)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)	4 (1.2)	0 (0.0)
Abscess	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)
Accidental Injury	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	3 (0.9)	0 (0.0)
Allergic Reaction	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)
Cellulitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cyst	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Face Edema	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)
Fever	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Hernia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Photosensitivity Reaction	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Generalized Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
RESPIRATORY SYSTEM	1 (7.1)	0 (0.0)	32 [*] (9.3)	0 (0.0)	35 (10.3)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	8 (2.3)	0 (0.0)	9 (2.6)	0 (0.0)

Sinusitis	1	(7.1)	0	(0.0)	7	(2.0)	0	(0.0)	3	(0.9)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	4	(1.2)	0	(0.0)	3	(0.9)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	4	(1.2)	0	(0.0)	5	(1.5)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	3	(0.9)	0	(0.0)	3	(0.9)	0	(0.0)
Carcinoma of Lung	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	2	(0.6)	0	(0.0)
Epistaxis	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Asthma	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	5	(1.5)	0	(0.0)
Dyspnea	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Lung Disorder	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Sputum Increased	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cough Increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Pleural Effusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Voice Alteration	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
SKIN AND APPENDAGES	0	(0.0)	0	(0.0)	19	(5.5)	10	(2.9)	12^c	(3.5)	6	(1.8)
Rash	0	(0.0)	0	(0.0)	10	(2.9)	6	(1.7)	10	(2.9)	5	(1.5)
Sweating	0	(0.0)	0	(0.0)	4	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	3	(0.9)	3	(0.9)	1	(0.3)	0	(0.0)
Urticaria	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)
Acne	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Contact Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
NERVOUS SYSTEM	0	(0.0)	0	(0.0)	15^c	(4.4)	4^c	(1.2)	13^c	(3.8)	2	(0.6)
Dizziness	0	(0.0)	0	(0.0)	3	(0.9)	2	(0.6)	7	(2.1)	2	(0.6)
Insomnia	0	(0.0)	0	(0.0)	3	(0.9)	1	(0.3)	2	(0.6)	0	(0.0)
Abnormal Dreams	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Acute Brain Syndrome	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Confusion	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Depersonalization	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Hallucinations	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hemiplegia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertonia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Hypesthesia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Anxiety	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Tremor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
SPECIAL SENSES	0	(0.0)	0	(0.0)	9^c	(2.6)	1	(0.3)	15	(4.4)	3	(0.9)
Ear Disorder	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Eye Pain	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis Media	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)	2	(0.6)	0	(0.0)
Abnormal Vision	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Amblyopia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Pain	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	6	(1.8)	0	(0.0)
Tinnitus	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)
Eye Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Otitis Externa	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Taste Perversion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
METABOLIC AND NUTRITIONAL DISORDERS	0	(0.0)	0	(0.0)	8^c	(2.3)	2^c	(0.6)	6	(1.8)	3	(0.9)
Dehydration	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral Edema	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood Urea Nitrogen Increased	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Hyperglycemia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
AST Increased	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)

ALT Increased	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	1	(0.3)	1	(0.3)
Weight Gain	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Edema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Gout	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Hypoglycemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
UROGENITAL SYSTEM	1*	(7.1)	0	(0.0)	8*	(2.3)	2	(0.6)	6	(1.8)	3	(0.9)
Urinary Tract Infection	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Vaginal Moniliasis	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.6)	3	(0.9)	3	(0.9)
Kidney Calculus	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Prostatic Disorder	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary Frequency	1	(7.1)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Urination Impaired	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dysmenorrhea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Polyuria	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR SYSTEM	1	(7.1)	0	(0.0)	5*	(1.5)	0	(0.0)	9*	(2.6)	3	(0.9)
Atrial Fibrillation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)
Hypotension	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial Infarct	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial Ischemia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Palpitation	1	(7.1)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Cardiomyopathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Congestive Heart Failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Heart Arrest	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Heart Failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Vasodilation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
HEMIC AND LYMPHATIC SYSTEM	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	3	(0.9)	1	(0.3)
Lymphadenopathy	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cyanosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Ecchymosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Thrombocythemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
MUSCULOSKELETAL SYSTEM	0	(0.0)	0	(0.0)	1*	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)
Arthralgia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Myopathy	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Bone Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)

* Possibly, probably, or definitely related to treatment

† All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.

‡ The total number for each body system may be less than the number of patients in that body system because a patient can have ≥1 adverse event per system.

Deaths: Six deaths occurred in the study; three in each arm. All were believed definitely unrelated to treatment by the investigators.

Table 37. Deaths - All Patients

Treatment	Center	Patient Number	Age (yr), Sex	Cause of Death ^a	Relationship to Study Medication ^b	Study Day Drug Discontinued	Study Day Patient Died
Cefdinir BID	7	12	29, M	Left Upper Lobe Pneumonia (Pneumonia)	Definitely Not	10	49
	13	2	69, M	Adenocarcinoma of the Lung (Carcinoma of Lung)	Definitely Not	11	212
	27	58	75, M	Jakob-Creutzfeldt Disease (Acute Brain Syndrome)	Definitely Not	10	41
Cefaclor	13	7	78, M	Pulmonary Edema (Lung Edema)	Definitely Not	— ^c	— ^c
	27	5	86, M	Cardiopulmonary Arrest (Heart Arrest)	Definitely Not	11	15
	63	85	68, M	Lung Cancer (Carcinoma of Lung)	Definitely Not	3	3

^a When the investigator term and COSTART term differ, the COSTART adverse event term appears in parentheses.

^b As determined by the investigator

^c Patient died before receiving study medication.

Medical officer's note: The only death of concern is patient 12 at center 7. The patient had an uncomplicated medical history and review of the CRF suggests patient presented with a LLL pneumonia due to *Haemophilus influenzae* which responded to therapy. About 29 days after discharge, patient presented with a LUL pneumonia and died 10 days later. It appears the events are entirely unrelated.

Serious Adverse Events. Seventeen (5%) patients receiving cefdinir BID and 15 (4%) receiving cefaclor experienced serious adverse events. Only was one patient believed to have a serious adverse event related due to cefdinir; this was a patient with multiple other medical problems who experienced abdominal pain, diarrhea, nausea and vomiting characterized by the investigator as "mild". No serious adverse events were attributed to cefaclor.

Withdrawals due to Adverse Events. The following table summarizes adverse events leading to study discontinuations and withdrawals. Diarrhea, nausea, vomiting and pneumonia were the most common reasons for discontinuing treatment with cefdinir; pneumonia and rash were the most common reasons for discontinuing cefaclor. Overall, 20 (6%) of patients on cefdinir withdrew due to an adverse event and 14 (4%) on cefaclor withdrew due to an adverse event. Four patients in each treatment arm with between end of therapy and LTFU; half of these patients required additional antibiotics for respiratory infection.

Table 38. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Receiving Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir BID N = 344	Cefaclor N = 340
DIGESTIVE SYSTEM	7* (2.0)	3* (0.9)
Diarrhea	3 (0.9)	0 (0.0)
Nausea	3 (0.9)	2 (0.6)
Vomiting	3 (0.9)	2 (0.6)
Dyspepsia	1 (0.3)	0 (0.0)
Liver Function Tests Abnormal	1 (0.3)	0 (0.0)
RESPIRATORY SYSTEM	6* (1.7)	8 (2.4)
Pneumonia	3 (0.9)	3 (0.9)
Carcinoma of Lung	1 (0.3)	1 (0.3)
Dyspnea	1 (0.3)	0 (0.0)
Lung Disorder	1 (0.3)	1 (0.3)
Sinusitis	1 (0.3)	1 (0.3)
Bronchitis	0 (0.0)	1 (0.3)
Pleural Effusion	0 (0.0)	1 (0.3)
BODY AS A WHOLE	4 (1.2)	2 (0.6)
Abdominal Pain	2 (0.6)	0 (0.0)
Accidental Injury	1 (0.3)	0 (0.0)
Hernia	1 (0.3)	0 (0.0)
Abscess	0 (0.0)	1 (0.3)
Infection	0 (0.0)	1 (0.3)
CARDIOVASCULAR SYSTEM	3 (0.9)	1 (0.3)
Atrial Fibrillation	1 (0.3)	0 (0.0)
Myocardial Infarct	1 (0.3)	0 (0.0)
Myocardial Ischemia	1 (0.3)	0 (0.0)
Heart Arrest	0 (0.0)	1 (0.3)
METABOLIC AND NUTRITIONAL	3 (0.9)	1 (0.3)
Dehydration	1 (0.3)	0 (0.0)
Hyperglycemia	1 (0.3)	0 (0.0)
Weight Gain	1 (0.3)	0 (0.0)
Gout	0 (0.0)	1 (0.3)
NERVOUS SYSTEM	3 (0.9)	0 (0.0)
Confusion	1 (0.3)	0 (0.0)
Hallucinations	1 (0.3)	0 (0.0)
Somnolence	1 (0.3)	0 (0.0)
SKIN AND APPENDAGES	2 (0.6)	4 (1.2)
Rash	2 (0.6)	3 (0.9)

Contact Dermatitis

0 (0.0)

1 (0.3)

- The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Medical officer's note: *There are no unexpected findings here; abdominal complaints are again prominent in the cefdinir arm.*

Clinical Laboratory Values. Baseline specimens for each patient's clinical laboratory parameters (hematology, blood chemistry, and urinalysis) were to be collected prior to the receipt of study medication. At the TOC visit, clinical laboratory tests were repeated and these values were compared to standard normal values and the patient's baseline values. Significantly abnormal values at TOC visit were repeated until the abnormality resolved or a reason for the abnormality was determined.

Clinical laboratory test results were examined by three methods: median changes from baseline, category shift changes, and markedly abnormal values at the first posttherapy visit (i.e., typically the TOC visit).

Medical officer's note: *No clinically significant changes were noted that were attributed to cefdinir alone; there were slightly more increases and decreases in platelet counts and bicarbonate levels and more decreases than increases in bacterial urine count. Most changes observed in this analysis related to resolution of infection, such as decreases in white blood cell count and PMNs and were seen across both arms. Although all patients who received medication were evaluated for safety in this study, the total number enrolled is only 704. There are no safety signals detectable upon review of this study. This reviewer will perform an integrated safety for this formulation on all submitted studies which will offer more ability to detect smaller changes.*

Reviewers' conclusions regarding NDA 50-739, Protocol 983-4, Pivotal Study submitted in support of approval for community acquired pneumonia indication.

Multiple methods and outcomes were evaluated, and with respect to both clinical and microbiologic efficacy, cefdinir 300 milligrams po BID is equivalent to cefaclor 500 milligrams po TID in the treatment of community acquired pneumonia.

Study 983-4 alone provides enough microbiologic support the the approval cefdinir to treat community acquired pneumonia caused by *Streptococcus pneumoniae*, β -lactamase (-) *Haemophilus influenzae* and β -lactamase (-) *Haemophilus parainfluenzae*. Insufficient evidence is available to support claims of efficacy against *Staphylococcus aureus* and *Streptococcus pyogenes*. Numbers were entirely insufficient for *Streptococcus pyogenes*; only one patient with *Streptococcus pyogenes* was treated with cefdinir in this study. There is little evidence to solidly support *Staphylococcus aureus* as the sole etiologic agent in the 17 patients from whom this pathogen was isolated.

The safety profile of both treatment arms also is very similar and not unlike other cephalosporins. The singular difference which appears is the greater occurrence of diarrhea in patients treated with cefdinir. A more powerful analysis of safety issues will be offered by an integrated safety analysis which will conclude the review of this NDA. Diarrhea will be evaluated there.

APPEARS THIS WAY
ON ORIGINAL

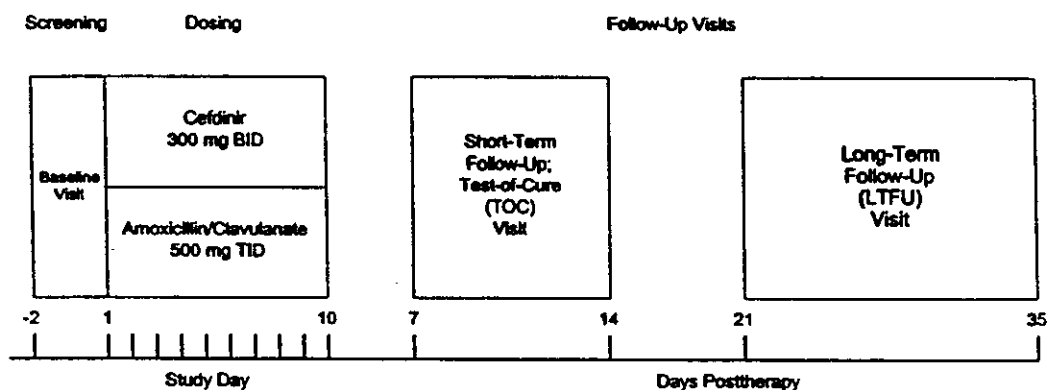
Medical officer's note: Most of the following text has been duplicated from the Applicant's submission as the CANDA allow for copying pieces of the submission. The medical officer's comments appear in the notes. This is the second and final pivotal study supporting the Applicant's community acquired pneumonia submission.

Indication: Community Acquired Pneumonia

Title and Study Number: A Phase 3, 10-day, investigator-blind, randomized, comparative, multi center study of cefdinir (CI-983) versus amoxicillin/clavulanate in the treatment of community-acquired bacterial pneumonia (Protocol 983-26)

Objective: The objective of this study was to evaluate the efficacy and safety of cefdinir (300 mg BID) versus amoxicillin/clavulanate (Augmentin®) (500 mg TID) in the treatment of patients with community-acquired bacterial pneumonia.

Study Design: This study was conducted at 35 centers in 9 countries including Canada, Australia and South Africa in addition to centers in western Europe. All centers used similarly amended protocols and identical case report forms (CRFs). This study was conducted in compliance with the Good Clinical Practice Guidelines of the United States Food and Drug Administration (FDA) and European Community Good Clinical Practice Guidelines, and according to the Declaration of Helsinki. An ethics committee or institutional review board (IRB) approval was obtained at each center before the study began. Before enrollment, each patient or guardian was informed of the study objectives and was required to provide written informed consent.



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Figure 3. Protocol 983-26 Study Design

Medical officer's note: Protocol 983-26, submitted as the Applicant's second pivotal study, is identical to the preceding domestic study in design. There are only three differences: (1) protocol 983-26 took place at centers in Europe, South Africa, Australia and Canada; (2) protocol 983-26 was investigator blinded, whereas protocol 983-4 was double dummy blinded; and (3) protocol 983-26 used amoxicillin/clavulanate 500 mg po TID was used as the comparator arm and protocol 983-4 used cefaclor 300 mg po BID.

An independent randomization schedule was prepared for each study center. The planned treatment group ratio at each site was 1:1 for cefdinir (300 mg BID) and amoxicillin/clavulanate (500 mg TID). A block size of 4 patients was used, with 2 treatment replicates per block.

Medical officer's note: Unlike protocol 983-4, protocol 983-26 adhered to original randomization schedule because it was originally designed as a two-armed study, not a three armed study including cefdinir 600 mg po qd.

Population and Inclusion/Exclusion Criteria: The population is identical to that of protocol 983-4; see review of study 983-4 preceding this review..

The following were the exclusion criteria for protocol 983-26 that differed from the exclusion criteria for protocol 983-4. See review of study 983-4 preceding this review.

Patients with acute pseudomembranous colitis or a history of pseudomembranous colitis;

- ▶ **Hospitalized or institutionalized patients, as well as patients who had been hospitalized within the preceding 4 weeks;**
- ▶ **Patients who had received another systemic antibacterial agent within a specified time period prior to the anticipated first dose of study medication. The specified period was 48 hours, or 5 half-lives of the antibacterial agent, whichever was longer.**

Medical officer's note: With respect to population evaluated, inclusion and exclusion criteria, protocol 983-26 is identical to protocol 983-4 with the exception of the minor items which are detailed above. Protocol 983-4 did not exclude patients with acute pseudomembranous colitis or a history of pseudomembranous colitis; or hospitalized or institutionalized patients, as well as patients who had been hospitalized within the preceding 4 weeks. In addition, rather than the excluding duration of another systemic antibacterial being less than 48 hours, it was less than 7 days. However, both protocols were amended to include the 5 half-lives and conformed that way. The medical reviewer sees these differences as extremely minor, and the two trials entirely comparable and population studied and inclusion/exclusion criteria are acceptable.

Evaluability Criteria:

When patients were discontinued early, the following were to be completed: sputum culture and susceptibility testing, chest x-ray, clinical evaluation (i.e., assessment of signs and symptoms as well as an overall assessment of clinical efficacy), physical examination, clinical laboratory tests, as well as records of adverse events.

Medical officer's note: *The evaluability criteria for protocol 983-26 are identical to those for protocol 983-4 with the exception of obtaining a chest x-ray on discontinued patients in protocol 983-26 (as bolded and underlined above). On these grounds, the two studies are again directly comparable and evaluability criteria are acceptable.*

Laboratories were instructed to use testing procedures that conformed with National Committee for Clinical Laboratory Standards (NCCLS) guidelines. **However, use of other appropriate local guidelines was acceptable, as culture and susceptibility test results from European clinical laboratories have been shown to be similar to those produced with NCCLS reference methods.** MIC trays and discs for cefdinir were supplied by Parke-Davis.

Medical officer's note: *The microbiologic breakpoints, by both dilution and diffusion techniques, conform to those adhered to in protocol 983-4. No mention is made in this report of the special case of susceptibility testing for S. pneumoniae (i.e., whether oxacillin disc testing for a zone size of ≥ 20 mm or oxacillin diffusion inhibitory concentration of ≤ 0.06 $\mu\text{g/mL}$ is construed as penicillin susceptible and therefore cefdinir susceptible). Inquiry was made from Dr. Altaie (DAIDP microbiology reviewer) as to the adequacy of the microbiologic evaluation in this protocol. She reviewed the testing, including the susceptibility testing of S. pneumoniae, and believes that the techniques used were adequate and comparable to the studies performed in the United States. Hence, pathogen eradication in 983-26 is comparable to 983-4 and isolates can be used to count for numbers of critical pathogens evaluated.*

Endpoints Defined (Clinical and Microbiological): The following table, duplicated from the Applicant's submission, described what data was collected and at what visits.

Table 38. Schedule of Clinical Observations and Laboratory Measurements

Procedure/Observation	Baseline ^a	Day 1	Days 3-5	Day 10	Posttherapy Visits	
					7-14 Days ^b	21-35 Days
Medical History	X					
Physical Examination	X				X	X
Clinical Assessment of Signs and Symptoms	X		X		X	X
Gram Stain, Sputum Culture, and Susceptibility Testing	X		X		X	X
Blood Culture and Susceptibility Testing (optional)	X		X			
Chest X-ray	X				X	X ^c
Adverse Events		X			X	X
Clinical Laboratory Testing ^d	X				X	X ^e
Assessment of Clinical Efficacy					X	X
Dosing		X		X		

^a Prior to treatment (within 48 hours of therapy initiation)

^b Also to be performed whenever therapy was discontinued early.

^c Not required for patients showing significant radiologic improvement at previous visit

^d Parameters to be assessed are listed in the protocol.

^e Performed only if abnormalities were detected at the previous visit.

Medical officer's note: See similar schedule for protocol 983-4 on page 45 of this review. The only differences, which are quite minor, present in this schedule are: (1) chest x-ray at LTFU visit was not required among those patients demonstrating significant improvement at TOC in protocol 983-26; and (2) blood cultures could be drawn in 983-26 at the discretion of the investigator; no blood culture data was obtained in protocol 983-26. This reviewer considers these differences to be so minor as to be inconsequential.

Specimens were collected for culture at the baseline, **Days 3 through 5**, TOC, and LTFU visits.

Medical officer's note: With respect to microbiologic endpoints, protocol 983-4 is identical to 983-26 except for the additional culture noted above. As this is not an endpoint for analysis, it is of no consequence to outcome.

Clinical Outcomes.

Medical officer's note: Protocol 983-26 is similar to protocol 983-4 with respect to the investigator's assessment of clinical endpoints. However, there is a single major difference in

that protocol 983-26 does not include an "improvement" category assigned by the investigator. Thus, the patient assignment by investigator has no ambiguous clinical outcome between "cure" and "failure". In many ways this is an improvement. However, because the major clinical outcome of interest is the same scoring algorithm employed by the Applicant in protocol 983-4, the studies are directly comparable based on Applicant's use of this clinical scoring system (see protocol 983-4, page 48, Medical officer's note and text following the note up to page 49).

As stated in description of protocol 983-4, the medical reviewer believes this to be a fair and unbiased method with which to assign clinical outcome. Review of protocol 983-4 demonstrated consistent adherence to this clinical algorithm. Thus, the medical reviewer believes this to be an entirely acceptable method. The difference in use of the algorithm is clarified below: there is no category for "improvement" assigned by the investigator. For comparison, see table on page 49 of review for protocol 983-4.

TABLE 39. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU^{ab}

Sponsor Assessment at TOC	Investigator Assessment at TOC		
	Cure	Failure	Not Assessable
Cure	Cure	Failure	Cure
Failure	Cure	Failure	Failure
Not Assessable	Cure	Failure	Not Assessable

Sponsor Assessment at LTFU	Investigator Assessment at LTFU		
	Cure	Failure/ Recurrence	Not Assessable
Cure	Cure	Recurrence	Cure
Failure	Cure	Recurrence	Failure
Recurrence	Cure	Recurrence	Recurrence
Not Assessable	Cure	Recurrence	Not Assessable

^a The combined assessments are shown in bold typeface.

^b Note: If a patient had a combined clinical assessment of failure at the TOC visit, the patient was automatically a failure on the combined assessment scale at the LTFU visit.

The clinical cure rate was the percentage of patients rated as Cure on the combined assessment scale. Each patient provided one observation. Clinical cure rates were calculated separately for TOC and LTFU.

Medical officer's note: *Protocol 983-26 is almost identical to protocol 983-4 with respect to the clinical endpoints. The singular difference being the elimination of an investigator assigned "improvement" category. However, use of the clinical algorithm is the same and consistent, and this medical reviewer believes these the two protocols are comparable.*

Statistical Considerations: This investigator-blind, comparative study of cefdinir versus amoxicillin/clavulanate was designed with a sample size of 112 evaluable patients per randomized treatment group for a total of 224 evaluable patients based on an assumed 90% microbiologic eradication rate for each randomized group. Equivalence was to be assessed by comparing a one-tailed 95% confidence interval (CI) for the difference (cefdinir minus amoxicillin/clavulanate) in microbiologic eradication rates to a set of predetermined, fixed criteria for equivalence. Sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and amoxicillin/clavulanate microbiologic eradication rates at TOC.

Study centers contributing 8 or fewer patients, or 2 or fewer patients in any treatment group, were pooled for center-adjusted analyses (except that for the ITT analysis by pathogen, the same pooling rule applied to the number of available pathogens).

Medical officer's note: *Statistical treatment for protocol 983-26 was identical to protocol 983-4. The only difference is the smaller size of protocol 983-26.*

Analysis populations for efficacy examined in this report include the evaluable (defined as patients who were microbiologically and clinically evaluable), the clinically evaluable, the modified intent-to-treat (MITT), and the intent-to-treat (ITT).

Study Results

Investigators and Numbers Enrolled

Table 40. List of Investigators

Center	Investigator	Country	Number of Patients		
			Randomized to Treatment (N)	Completed TOC Visit (% of N)	Evaluable at TOC (% of N)
1	P. Aldons	Australia	40	30(75)	19(47.5)
2	M. Phillips	Australia	16	15(93.8)	5(31.3)
3	K. Y. Yan	Australia	1	1(100)	0(0)
4	P. Veyssier	France	18	18(100)	9(50)
5	P. Vinceneux	France	7	7(100)	3(42.9)
6	P. Zuck	France	4	4(100)	3(75)
7	D. Le Roux	South Africa	20	15(75)	13(65)
8	P. Frith	Australia	5	5(100)	2(40)
9	P. J. Arens	Germany	5	4(80)	2(40)
10	M. Kunze	Germany	15	15(100)	5(33.3)
12	F. Vogel	Germany	40	30(75)	17(42.5)
13	C. Schoch	Germany	4	4(100)	2(50)
14	G. Dunkhase	Germany	14	14(100)	6(42.9)
16	P. Krupp	Germany	1	1(100)	1(100)
18	C. van Herwaarden	Netherlands	11	11(100)	9(81.8)
19	G. Siemon	Germany	16	16(100)	5(31.3)
20	G. Palmieri	Italy	41	39(95.1)	8(19.5)
21	J. Muir	France	12	10(83.3)	2(16.7)
22	W. Petermann	Germany	37	36(97.3)	15(40.5)
23	S. Fontana	Italy	4	4(100)	0(0)
26	C. K. Chan	Canada	1	1(100)	0(0)
27	C. Laroche	Canada	7	6(85.7)	2(28.6)
28	G. Achyuthan	Canada	9	8(88.9)	5(55.6)
29	L. Latulippe	Canada	6	6(100)	2(33.3)
32	C. St-Pierre	Canada	12	9(75)	3(25)
33	D. Makinen	Canada	41	38(92.7)	10(24.3)
36	J. S. S. Marx	South Africa	31	22(71)	10(32.3)
37	H. P. Meyer	South Africa	49	42(85.7)	18(36.7)
38	R. Henzgen	Germany	49	46(93.9)	10(20.4)
39	L. Van Schil	Belgium	16	12(75)	10(62.5)
40	A. Volckaert	Belgium	1	0(0)	0(0)
45	J. P. Ducroix	France	8	8(100)	2(25)
47	R. Rimoldi	Italy	4	4(100)	0(0)
51	T. Wanke	Austria	6	4(66.7)	2(33.3)
Total			554	488(88.1)	201(36.3)

Table 41. Patient Recruitment by Country

Country	Number of Centers That Enrolled Patients	Number of Patients Randomized
Australia	4	62
Austria	2	9
Belgium	2	17
Canada	6	76
France	5	49
Germany	9	181
Italy	3	49
Netherlands	1	11
South Africa	3	100
Total	35	554

Medical officer's note: There are a large number of centers in different countries with no one center having a huge number of enrollees. The Applicant is providing us with numbers of enrollees that are clinically evaluable, microbiologically and clinically evaluable by treatment arm and investigator.

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Demographics

Table 42. Patient Characteristics - All Patients
(Number (%) of Patients)

Variable	Cefdinir N = 277	AmoxClav N = 277	Total N = 554
Sex			
Male	173 (62.5)	172 (62.1)	345 (62.3)
Female	104 (37.5)	105 (37.9)	209 (37.7)
Race			
White	222 (80.1)	222 (80.1)	444 (80.1)
Black	50 (18.1)	50 (18.1)	100 (18.1)
Asian	2 (0.7)	2 (0.7)	4 (0.7)
Other ^a	3 (1.1)	3 (1.1)	6 (1.1)
Age, yr			
Median	57.0	55.0	56.0
Range	14 - 94	16 - 99	14 - 99
Distribution			
13 to <18	5 (1.8)	2 (0.7)	7 (1.3)
18 to <65	161 (58.1)	164 (59.2)	325 (58.7)
≥65	111 (40.1)	111 (40.1)	222 (40.1)

^a Other = Mixed (3 patients); Metis, North African, Spanish (1 patient each).TABLE 43. Patient Characteristics - Evaluable Patients
(Number (%) of Patients)

Variable	Cefdinir N = 104	Amox/Clav N = 97	Total N = 201
Sex			
Male	63 (60.6)	66 (68.0)	129 (64.2)
Female	41 (39.4)	31 (32.0)	72 (35.8)
Race			
White	82 (78.8)	74 (76.3)	156 (77.6)
Black	20 (19.2)	21 (21.6)	41 (20.4)
Asian	1 (1.0)	0 (0.0)	1 (0.5)
Other ^a	1 (1.0)	2 (2.1)	3 (1.5)
Age, yr			
Median	55.5	56.0	56.0
Range	14 - 92	16 - 95	14 - 95
Distribution			
13 to <18	2 (1.9)	1 (1.0)	3 (1.5)
18 to <65	63 (60.6)	59 (60.8)	122 (60.7)
≥65	39 (37.5)	37 (38.1)	76 (37.8)

^a Other = Mixed (2 patients), North African (1 patient).

Among all randomized patients, the presence and severity of clinical signs and symptoms were similar for both treatment groups. Most patients presented with cough (100%), sputum production (99%), shortness of breath (86%), and rales (82%). Mean baseline clinical score was 15.0 in the cefdinir treatment group and 14.9 in the amoxicillin/clavulanate treatment group (maximum possible score was 31.5). Among the evaluable and clinically evaluable patients,

mean baseline clinical score was 15.8 for patients randomized to cefdinir and 15.3 for patients randomized to amoxicillin/clavulanate and 14.9 for the cefdinir treatment group and 14.7 for amoxicillin/clavulanate treatment group. Twenty-nine patients (10%) randomized to cefdinir and 26 (9%) randomized to amoxicillin/clavulanate had 1 or more episodes of LRTI within 6 months prior to the start of the study. Seventy-six (27%) patients in the cefdinir group and 83 (30%) patients in the amoxicillin/clavulanate group had a prior or concurrent history of other respiratory ailments that might have predisposed the patient to pneumonia (e.g., asthma, chronic obstructive pulmonary disease, bronchiectasis, emphysema).

***Medical officer's note:** The demographic characteristics are fairly evenly distributed by treatment arm among those enrolled and those evaluable.*

Smoking and Past Medical History: Smoking or tobacco use history was obtained in this study. The following Table demonstrates the distribution of this important variable:

Table 44: Smoking Status for All Enrolled Patients

Smoking Status	cefdinir N (%)	amox/clav N (%)
Never	120 (43.3)	116 (41.9)
Past	64 (23.1)	70 (25.3)
Current	93 (33.6)	90 (32.5)
Unknown	0 (0)	1 (0.4)
Total	277 (100.0)	277 (100.0)

Table 45: Years of Smoking for All Enrolled Patients
Reporting Past or Present Smoking History

Smoking Status	cefdinir (years)	amox/clav (years)
Past	30.4	23.6
Current	22.9	21.7
Total	25.9	22.5

**Table 46: Number of Cigarettes Smoked for All Enrolled Patients
Reporting Past or Present Smoking History**

Smoking Status	Average number of cigarettes smoked/day	cefdinir N (%)	amox/clav N (%)
Past	light (1-10 per day)	16 (25)	15 (21.4)
	moderate (11-20 per day)	26 (40.6)	34 (48.6)
	heavy (≥ 21 per day)	21 (32.8)	20 (28.6)
	unknown	1 (1.6)	1 (1.4)
Current	light (1-10 per day)	25 (26.9)	26 (28.9)
	moderate (11-20 per day)	44 (47.3)	41 (45.6)
	heavy (≥ 21 per day)	22 (23.7)	22 (22.4)
	unknown	2 (2.2)	1 (1.1)
Total	light (1-10 per day)	41 (26.1)	41 (25.6)
	moderate (11-20 per day)	70 (44.6)	75 (46.9)
	heavy (≥ 21 per day)	43 (27.4)	42 (26.3)
	unknown	3 (1.9)	2 (1.3)

History of existing or prior pulmonary disease was in an open ended inquiry regarding "Past Medical History" which appeared in the questionnaire. That question provided the following results for clinically evaluable patients:

Table 47: Prior Pulmonary Diagnoses & Conditions Predisposing to Community Acquired Pneumonia for All Clinically Evaluable Patients

Pulmonary Diagnosis	cefdinir	amox/clav
COPD	29	34
Asthma	38	39
Pneumonia	0	0
Bronchitis	13	9
Lung cancer	0	5
Bronchiectasis	5	6
Pulmonary fibrosis	1	0
Cor pulmonale	2	2
Allergic bronchopulmonary aspergillosis	0	0
Total	88	96

Medical officer's note: The Applicant is currently evaluating the "past medical history" section of the study questionnaire to determine whether pulmonary diagnoses (i.e., COPD, smoking history, bronchiectasis, prior pneumonia, etc.) are also evenly distributed by treatment arm. The statement above suggests that past medical history is evenly distributed by treatment arm. In addition, the scoring assigned to patients at enrollment for the purposes of assigning the combined investigator-applicant outcome did not differ significantly at enrollment, among evaluable or clinically evaluable patients or by treatment arm. It does look like randomization effectively distributed these potential confounders of pneumonia outcome

Table 48. Patient Exposure to Study Medication - All Patients
[Number of Patients]

Days on Study Medication	Cefdinir N = 277	Amox/clav N = 277
1	2	5
2	3	2
3	8	3
4	10	5
5	7	6
6	2	5
7	3	6
8	5	9
9	3	4
10	148	99
11	76	123
12	1	2
Median	10.0	10.0

* In each treatment group, 1 patient with "unknown" exposure actually took no study medication (0 days).

Medical officer's note: Given the chart above, one can conclude that compliance with medication was good and most patients enrolled were exposed to the appropriate amount of treatment assigned by the study.

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Efficacy

The numbers of patients randomized to treatment are compared to other patients populations in Table 12 as follows:

Table 49. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	N	Cefdinir	Amox/clav
ITT ¹	554 (100.0)	277 (100.0)	277 (100.0)
MITT	263 (47.5)	137 (49.5)	126 (45.5)
Clinically Evaluable	396 (71.5)	201 (72.6)	195 (70.4)
Evaluable	201 (36.3)	104 (37.5)	97 (35.0)
Qualified ^a	123 (22.2)	63 (60.6)	60 (61.9)

^a As a percentage of the evaluable patient population

¹ Evaluable patients had no known protocol violations that might have affected the efficacy assessments at TOC. Patients became unevaluable if they had no baseline pathogen, had a resistant baseline pathogen, failed to take study drug as prescribed, had off-schedule cultures or clinical assessments, had missing microbiologic or clinical signs/symptoms data at baseline or follow-up, took a concurrent systemic antibacterial therapy not for disease under study, had a concurrent infection, or lacked the required baseline diagnosis. However, patients whose assessments were done early (i.e., before the follow-up visit window) or who took a concurrent antibacterial due to early failure did not become unevaluable for these reasons.

Patients in the clinically evaluable population had the correct indication documented by a baseline chest x-ray and the minimum required clinical signs and symptoms (cough and sputum production) at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy for other concurrent infections; and had their clinical evaluations performed within the range of days specified in the protocol. Patients were not excluded from this data set due to having no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

Data were examined at LTFU for qualified patients. Qualified patients were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits (e.g., qualified patients did not take any concurrent systemic antibacterial agents).

Patients in the MITT population had the correct indication, received study medication, had at least 1 baseline pathogen, and had a follow-up culture. The MITT population was the same at TOC and LTFU.

Patients in the ITT population were those randomized to treatment. Patients who had no baseline pathogen or no follow-up culture were considered to have microbiologic persistence in the ITT analyses. Similarly, patients who had no follow-up clinical assessment were categorized as failures in the ITT analyses.

Medical officer's note: The medical officer agrees with this evaluable populations which are identical to those defined in protocol 983-4.

Medical officer's note: As compared to protocol 983-4, the percentages of enrollees that are part of the MITT, Evaluable and Qualified population are smaller (see page 57 of this review). The Clinically evaluable population here is a bit larger. These differences are consistent with more patients having microbiologic information. It is unclear how this affects comparability of trials, if at all.

TABLE 50. Patient Disposition - All Patients
[Number (%) of Patients]

Patient Disposition	Cefdinir	Amox/clav	Total
Randomized to Treatment	277	277	554
Withdrawn Prior to End of Treatment			
Lack of Efficacy	21 (7.6)	14 (5.1)	35 (6.3)
Adverse Event	9 (3.2)	14 (5.1)	23 (4.2)
Other/Administrative	9 ^a (3.2)	7 ^b (2.5)	16 (2.9)
No Baseline Pathogen	4 (1.4)	9 (3.2)	13 (2.3)
Lack of Compliance	6 (2.2)	14 (5.1)	20 (3.6)
Resistant Baseline Pathogen	4 (1.4)	0 (0.0)	4 (0.7)
Completed Treatment	224 (80.9)	219 (79.1)	443 (80.0)
Completed Follow-Up Visits			
TOC	244 (88.1)	244 (88.1)	488 (88.1)
LTFU	160 (57.8)	181 (65.3)	341 (61.6)

^a Reasons include: Patient discharged without study medication (3 patients); wrong indication (2 patients); and concurrent antibacterial, study drug dosing error, history of hepatic disease, patient not enrolled (1 patient each).

^b Reasons include: Wrong indication (4 patients); and inability to swallow capsules, patient request, patient not enrolled (1 patient each).

Medical officer's note: In this study and study 983-4, disposition of patients between cefdinir and comparator are fairly even. Follow-up at TOC is greater here. Withdrawal prior to end of treatment is not dominated by one reason. No important differences between treatment arms are discernable in this study with respect to patient disposition.

TABLE 51. Reasons Patients Were Not Evaluable at TOC or Disqualified at LTFU
(Number of Patients)

	Cefdinir	Amox/clav
Randomized to Treatment	277	277
Reasons Patients Were Not Evaluable for TOC Analyses		
Baseline X-Ray Missed	8	4
Clinical Assessment Missed	12	11
Clinical Evaluation Out-of-Date Range ^a	23	30
Concurrent Antibacterial ^a	5	16
Medication Not as Prescribed	19	24
Prior Antibacterial	21	11
Resistant Baseline Pathogen(s)	11	12
Wrong Indication	6	12
Culture ^b Out-of-Date Range ^a	27	33
Culture ^b Missed	26	26
No Baseline Susceptibility Tests	7	6
No Proven Baseline Pathogen	128	139
Total Not Evaluable	173	180
Patients Who Were Evaluable at TOC^c	104	97
Reasons Patients Were Disqualified for LTFU Analyses		
Clinical Assessment Missed	26	18
Clinical Evaluation Out-of-Date Range ^a	3	8
Concurrent Antibacterial ^a	6	4
Culture ^d Out of Date Range ^a	3	8
Culture ^d Missed	33	27
Total Disqualified	41	37
Patients Who Were Qualified at LTFU	63	60

^a Patients who had microbiologic and/or clinical assessments done early or who took a concurrent antibacterial because they were early failures were not removed from the evaluable analyses for these reasons.

^b Baseline or TOC culture

^c Only these patients were candidates for qualified analyses at LTFU.

^d LTFU culture

Medical officer's note: Although reasons patients were not evaluable are justifiable by review of the protocol and appear fairly evenly distributed between treatment arms, the large numbers of patients not evaluable is extremely disappointing. It is fortunate that analysis of patients clinically evaluable does not require a proven baseline pathogen, a very large group among those nonevaluable. Many cases of CAP may be due to pathogens not routinely isolated (i.e., Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, etc.) which would not be expected to be responsive to either treatment arm and it is uncertain how many such

individuals are enrolled here.

Thirteen (4%) of the 333 baseline pathogens with determined susceptibility to cefdinir were resistant to cefdinir, and 13 (4%) of the 332 baseline pathogens with determined susceptibility to amoxicillin/clavulanate were resistant to amoxicillin/clavulanate (Table 11). There were no significant differences between the number of isolates resistant to cefdinir and the number of isolates resistant to amoxicillin/clavulanate for all pathogens combined ($p = 1.0$), nor for the individual species *H. influenzae*, *H. parainfluenzae*, *S. aureus*, *K. pneumoniae*, and *E. coli*. No *M. catarrhalis* isolates were resistant to either study medication.

Table 52: Distribution of Baseline Pathogens by Susceptibility to Study Medication - Pathogens From All Patients (only those requested in package insert)
(Number of Pathogens)

Baseline Pathogen	N	Cefdinir				Amoxicillin/Clavulanate			
		S	I	R	U	S	I	R	U
Gram-Positive									
<i>Staphylococcus aureus</i>	19	17	0	0	2	15	0	2	2
<i>Streptococcus pneumoniae</i>	117	110	3	1	3	113	0	1	3
Gram-Negative									
<i>Escherichia coli</i>	10	9	0	1	0	8	1	1	0
<i>Haemophilus influenzae</i>									
β-lactamase +	8	8	0	0	0	8	0	0	0
β-lactamase -	69	62	3	2	2	64	0	2	3
β-lactamase unknown	11	6	0	0	5	7	0	0	4
<i>Haemophilus parainfluenzae</i>									
β-lactamase +	2	2	0	0	0	1	0	1	0
β-lactamase -	25	23	1	1	0	25	0	0	0
β-lactamase unknown	8	7	0	0	1	6	0	1	1
<i>Klebsiella pneumoniae</i>	12	11	0	1	0	10	1	1	0
<i>Moraxella catarrhalis</i>									
β-lactamase +	12	10	2	0	0	12	0	0	0
β-lactamase -	2	1	1	0	0	2	0	0	0
β-lactamase unknown	4	4	0	0	0	4	0	0	0

N = Number of pathogens; S = Susceptible; I = Moderate or intermediate susceptibility; R = Resistant; U = Unknown susceptibility.

Medical officer's note: Once again, there does not appear to be any difference between treatment arms for this evaluation.

Clinical Efficacy**Test of Cure, Clinical Cure**

TABLE 53 Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the TOC Visit - Evaluable Patients [Number of Patients]

Investigator Determination	Combined Investigator/Sponsor Determination			
	Cefdinir N = 104		Amoxicillin/Clavulanate N = 97	
	Cure	Failure	Cure	Failure
Cure	83	0	86	0
Failure	0	18	0	9
Not Assessable	0	3	0	2
Cure rate	83/104(80%)		86/97(89%)	

For Clinical Cure Rate among Evaluable Patients at TOC, the lower limit of the one- tailed 95% CI about the difference with continuity correction is (-19.82, 2.11).

Medical officer's note: The changes made by applying the clinical algorithm resulted in reassigning the three investigator deemed "not assessable" patients to the combined sponsor-investigator failure arm in the cefdinir treated group and reassignment of two patients in the amoxicillin/clavulanate group in a similar manner. This would not impact outcome and would slightly favor the amoxicillin/clavulanate arm. Cefdinir failed to meet the predetermined criteria for equivalence against amoxicillin/clavulanate.

Long-Term Follow Up, Clinical Cure

TABLE 54 Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the LTFU Visit - Qualified Patients

Investigator Determination	Combined Investigator/Sponsor Determination					
	Cefdinir N = 63			Amoxicillin/clavulanate N = 60		
	Cure	Failure*	Recurrence	Cure	Failure*	Recurrence
Cure	57	2	0	58	0	0
Failure/Recurrence	0	2	2	0	1	1
Cure rate	57/63(90.4%)			58/60(96.7%)		

* The patients in this column were automatically clinical failures on the combined scale at LTFU because they had been clinical failures on the combined scale at TOC.

For Clinical Cure Rate among Evaluable Patients at LTFU, the lower limit of the 95% CI about the difference with continuity correction is (-16.37, 3.99).

Medical officer's note: This is not a primary outcome measure and the numbers are smaller.

Thus, the finding is of less significance that the comparison of clinical cure rate among evaluable patients at TOC.

Test of Cure and Long-Term Follow Up Visits, ITT and MITT Analysis

TABLE 55 Clinical Efficacy at TOC and LTFU – ITT and MITT Populations by Clinical Cure, Microbiologic Eradication by Patient and Clinical Cure Among Clinically Evaluable Patients

Parameter	Cefdinir BID		Amoxicillin/ Clavulanate	
	n/N	%	n/N	%
TOC/ITT: Microbiologic Eradication by Patient ^a	122/277	44.0	116/277	41.9
TOC/ITT: Clinical Cure ^b	198/277	71.5	221/277	79.8
TOC/MITT: Microbiologic Eradication by Patient ^c	119/137	86.9	115/126	91.3
LTFU/ITT: Microbiologic Eradication by Patient ^d	75/277	27.1	73/277	26.4
LTFU/ITT: Clinical Cure ^e	142/277	51.3	169/277	61.0
Clinical Cure Rate ^f Among Clinically Evaluable Patients	155/201	77.0	166/195	85.0

^a n/N = Number of patients with eradication/total number of patients.

^b n/N = Number of patients with combined determination of cure/total number of patients.

^c n/N = Number of patients with eradication/total number of patients.

^d n/N = Number of patients with continued microbiologic eradication (i.e., no relapse)/total number of patients.

^e n/N = Number of patients with combined determination of cure/total number of patients.

^f n/N = Number of patients with clinical cures divided by all clinically evaluable patients (microbiologic status irrelevant). See footnote on page 95 for more detailed description.

For TOC/ITT, microbiologic eradication rate by patient, the 95% CI about the difference with continuity correction is (-6.44, 10.77).

For TOC/ITT, clinical cure rate, the 95% CI about the difference with continuity correction is (-15.78, -0.83).

For TOC/MITT, microbiologic eradication rate by patient, the 95% CI about the difference with continuity correction is (-12.67, 3.86).

For LTFU/ITT, microbiologic eradication rate by patient, the 95% CI about the difference with continuity correction is (-7.01, 8.45).

For LTFU/ITT, clinical cure rate, the 95% CI about the difference with continuity correction is (-18.33, -1.16).

For Clinical Cure Rate among Clinically Evaluable Patients, the 95% CI about the difference with continuity correction is (-16.18, 0.15).

Medical officer's note: The clinical outcomes above, which are not primary endpoints but evaluate several clinical populations (intent to treat and modified intent to treat for clinical cure and microbiologic eradication by patient at both test of cure and long-term follow up), are marginal and disappointing. Clinical cure at both TOC and LTFU are failures (or near failures) and clinical cure among clinically evaluable patients is also disappointing. ITT microbiologic eradication rates by patient at TOC and LTFU are equivalent, and MITT microbiologic eradication rates by patient at TOC is also equivalent.

Test-of-Cure, Clinical Cure Rate by Patient according to Baseline Pathogens

Table 56. Clinical Cure Rate* by Patient (According to Their Baseline Pathogens) at the TOC Visit - Evaluable Patients

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	1/1	100.0	5/5	100.0	3/4	75.0	1/1	100.0
<i>Streptococcus pneumoniae</i>	29/36	80.6	32/36	88.9	6/7	85.7	7/8	87.5
<i>Haemophilus influenzae</i>	25/29	86.2	19/21	90.5	3/6	50.0	4/5	80.0
<i>Haemophilus parainfluenzae</i>	4/8	50.0	7/8	87.5	2/3	66.7	2/2	100.0
<i>Escherichia coli</i>	0/0	0	0/0	0	0/1	0	0/0	0
<i>Klebsiella pneumoniae</i>	3/4	75.0	1/1	100.0	1/1	100.0	0/0	0
<i>Moraxella catarrhalis</i>	6/6	100.0	3/3	100.0	0/0	0	5/5	100.0
Total	76/96	79.2	77/86	89.5	15/22	68.2	14/21	66.7
Total single & multiple isolates	91/118	77.1	91/107	85.0				

n/N = Number of patients who were cured/total number of patients.

* Based on combined investigator/sponsor clinical assessments.

For TOC, the Clinical Cure Rate by Patient (single isolate) according to Baseline Pathogens, the 95% CI about the difference with continuity correction is **(-21.86, 1.12)**.

Medical officer's note: Again, cefdinir does not meet equivalence against the comparator, amoxicillin/clavulanate. However, enough microbiologic evidence is available, when coupled with study 983-4, to provide support for *Moraxella catarrhalis* to be a pathogen labeled for pneumonia.

Long-Term Follow Up. Clinical Cure by Patient according to Baseline Pathogens

Table 57. Clinical Cure Rate^a by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients Who Were Classified as Cures at TOC

Baseline Pathogen	Single Isolate				Multiple Isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	1/1	100.0	5/5	100.0	1/1	100.0	0/0	0
<i>Streptococcus pneumoniae</i>	19/19	100.0	24/25	96.0	3/4	75.0	4/4	100.0
<i>Haemophilus influenzae</i>	21/21	100.0	11/11	100.0	1/2	50.0	3/3	100.0
<i>Haemophilus parainfluenzae</i>	4/4	100.0	6/6	100.0	1/1	100.0	1/1	100.0
<i>Escherichia coli</i>	0/0	0	0/0	0	0/0	0	0/0	0
<i>Klebsiella pneumoniae</i>	2/2	100.0	0/0	—	0/0	0	0/0	0
<i>Moraxella catarrhalis</i>	5/6	83.3	3/3	100.0	0/0	0	4/4	100.0
Total	56/57	98.2	55/56	98.2	6/8	75.0	12/12	100.0
Total, single & multiple isolates	62/65	95.3	77/78	98.7				

n/N = Number of patients who were cured/total number of patients.

a Based on combined investigator/sponsor clinical assessments.

For LTFU, the Clinical Cure Rate by Patient according to Baseline Pathogens (single isolate), the 95% CI about the difference with continuity correction is **(-10.42, 3.76)**.

Medical officer's note: Equivalence is demonstrated in this outcome, which is not primary.

Microbiologic Efficacy**Test-of-Cure. Microbiologic Eradication by Pathogen**

Table 58. Microbiologic Eradication Rate by Baseline Pathogen at the TOC Visit -
Pathogens From Evaluable Patients

Baseline Pathogen	Cefdinir		Amox/clav	
	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	3/4	75.0	5/6	83.3
<i>Streptococcus pneumoniae</i>	42/44	95.5	43/44	97.7
<i>Escherichia coli</i>	0/1	0.0	0/0	—
<i>Haemophilus influenzae</i>				
β -lactamase +	2/3	66.7	3/3	100.0
β -lactamase -	21/29	72.4	17/21	81.0
β -lactamase unknown	3/3	100.0	1/2	50.0
<i>Haemophilus parainfluenzae</i>				
β -lactamase -	10/10	100.0	11/11	100.0
β -lactamase unknown	1/1	100.0	1/1	100.0
<i>Klebsiella pneumoniae</i>	5/5	100.0	1/1	100.0
<i>Moraxella catarrhalis</i>				
β -lactamase +	4/4	100.0	6/6	100.0
β -lactamase -	1/1	100.0	1/1	100.0
β -lactamase unknown	1/1	100.0	1/1	100.0
Total	93/106	87.7	90/97	92.8

n/N = Number of pathogens eradicated/total number of pathogens.

For LTFU, the Microbiologic Eradication Rate by Baseline Pathogen, the 95% CI about the difference with continuity correction is (-14.13, 4.03).

Medical officer's note: Acceptable eradication rates are demonstrated in this nonprimary outcome measure.

Long-Term Follow Up. Microbiologic Eradication by Pathogen

TABLE 59. Microbiologic Eradication Rate by Baseline Pathogen at the LTFU Visit - Pathogens From Qualified Patients Who Were Classified as Patients With Eradication at TOC

Baseline Pathogen	Cefdinir		Amox/clav	
	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	1/1	100.0	4/4	100.0
<i>Streptococcus pneumoniae</i>	22/22	100.0	27/27	100.0
<i>Haemophilus influenzae</i>				
β -lactamase +	1/1	100.0	2/2	100.0
β -lactamase -	16/16	100.0	8/8	100.0
β -lactamase unknown	1/1	100.0	0/0	—
<i>Haemophilus parainfluenzae</i>				
β -lactamase -	6/6	100.0	7/7	100.0
<i>Klebsiella pneumoniae</i>	2/2	100.0	0/0	—
<i>Moraxella catarrhalis</i>				
β -lactamase +	4/4	100.0	5/5	100.0
β -lactamase -	1/1	100.0	1/1	100.0
β -lactamase unknown	1/1	100.0	0/0	—
Total	55/55	100.0	54/54	100.0

n/N = Number of pathogens eradicated/total number of pathogens.

Qualified patients who had persistent pathogens at the TOC visit were automatically considered to have persistent pathogens at LTFU.

Medical officer's note: Equivalence is clearly evident at this non-primary endpoint.

Test of Cure. Microbiologic Eradication by Patient**TABLE 60. Microbiologic Eradication Rate by Patient (According to Their Baseline Pathogens) at the TOC Visit - Evaluable Patients**

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	0/1	0	4/5	80.0	3/3	100.0	1/1	100.0
<i>Streptococcus pneumoniae</i>	35/36	97.2	35/36	97.2	5/8	62.5	7/8	87.5
<i>Haemophilus influenzae</i>	22/29	75.9	18/21	85.7	3/6	50.0	3/5	60.0
<i>Haemophilus parainfluenzae</i>	8/8	100.0	8/8	100.0	2/3	66.7	3/3	100.0
<i>Escherichia coli</i>	0/0	0	0/0	0	0/1	0	0/0	0
<i>Klebsiella pneumoniae</i>	4/4	100.0	1/1	100.0	1/1	100.0	0/0	0
<i>Moraxella catarrhalis</i>	6/6	100.0	3/3	100.0	0	0	4/5	80.0
Total	75/84	89.2	69/74	93.2	14/22	63.6	18/22	81.8
Total, single & multiple isolates 89/106 84.0 87/96 90.6								

n/N = Number of patients with eradication/total number of patients.

For TOC, the Microbiologic Eradication Rate by Patient, the 95% CI about the difference with continuity correction is (-13.97, 6.06).

At the TOC visit, 13 evaluable cefdinir-treated patients had 13 persistent pathogens, and 9 evaluable amoxicillin/clavulanate treated patients had 9 persistent pathogens. All of the persistent pathogens had been susceptible to study medication at baseline and 18/22 remained susceptible at TOC (Appendix E.2). Among cefdinir-treated patients, susceptibility at TOC was intermediate for one isolate of *H. influenzae* and unknown for two isolates of *H. influenzae*. One isolate of *H. influenzae* from an amoxicillin/clavulanate-treated patient was of unknown susceptibility at TOC.

Long-Term Follow Up Visit. Microbiologic Eradication by Patient

Table 61. Microbiologic Eradication by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients Who Were Classified as Patients with Eradication at TOC

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	0/0	—	4/4	100.0	1/1	100.0	0/0	0
<i>Streptococcus pneumoniae</i>	19/19	100.0	24/24	100.0	3/3	100.0	3/3	100.0
<i>Haemophilus influenzae</i>	17/17	100.0	9/9	100.0	1/1	100.0	1/1	100.0
<i>Haemophilus parainfluenzae</i>	5/5	100.0	6/6	100.0	1/1	100.0	1/1	100.0
<i>Escherichia coli</i>	0/0	0	0/0	0	0/0	0	0/0	0
<i>Klebsiella pneumoniae</i>	2/2	100.0	0/0	—	0/0	0	0/0	0
<i>Moraxella catarrhalis</i>	6/6	100.0	3/3	100.0	0/0	0	3/3	0
Total	49/49	100.0	46/46	100.0	6/6	100.0	8/8	100.0
Total, multiple & single isolates	55/55	100.0	54/54	100.0				

n/N = Number of patients with eradication/total number of patients.

Medical officer's note: Equivalence is demonstrated around this non-primary endpoint.

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ON ORIGINAL

Test of Cure and Long-Term Follow Up Visit Modified Intent-to-Treat Analysis**Table 62. Microbiologic Efficacy at TOC and LTFU – MITT and ITT Populations**

Parameter	Cefdinir BID		Amox/clav	
	n/N	%	n/N	%
TOC/MITT: Microbiologic Eradication by Pathogen*	151/182	83	140/165	84.8
TOC/ITT: Microbiologic Eradication by Pathogen*	146/164	89	139/150	92.7
LTFU/ITT Microbiologic Eradication by Pathogen*	93/182	51.1	94/165	57

* n/N = Number of pathogens eradicated/total number of pathogens.

For TOC/MITT, microbiologic eradication rate by pathogen, the 95% CI about the difference with continuity correction is (-10.19, 6.43).

For TOC/ITT, microbiologic eradication rate by pathogen, the 95% CI about the difference with continuity correction is (-10.63, 3.34).

For LTFU/ITT, microbiologic eradication rate by pathogen, the 95% CI about the difference with continuity correction is (-16.93, 5.19).

Medical officer's note: *The Applicant performed adequately in these comparisons, which are non-primary endpoints.*

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Test of Cure, Microbiologic Versus Clinical Response Rates

Table 63. Microbiologic Versus Clinical Response Rates at the TOC Visit - Evaluable Patients [Number (%) of Patients]

Microbiologic Response	Clinical Response*	
	Cure	Failure
Cefdinir, N = 104		
Patients With Eradication	77 (74.0)	14 (13.5)
Patients With Persistence	6 (5.8)	7 (6.7)
Amoxicillin/clavulanate, N = 97		
Patients With Eradication	79 (81.4)	9 (9.3)
Patients With Persistence	7 (7.2)	2 (2.1)

* Based on combined investigator/sponsor clinical assessment

Medical officer's note: These results demonstrate a trend of lower eradication and greater clinical response with cefdinir treatment.

Superinfections: At TOC, 32 (12%) cefdinir-treated patients and 28 (10%) amoxicillin/clavulanate-treated patients had one or more superinfecting pathogens. In patients treated with cefdinir, 23 of 38 (61%) superinfecting pathogens were susceptible to cefdinir, while among amoxicillin/clavulanate-treated patients, 23 of 41 (56%) superinfecting pathogens were susceptible to amoxicillin/clavulanate.

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Table 64. Patients With Superinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir N = 277	Amoxicillin/clavulanate N = 277
Gram-Positive		
Beta-hemolytic <i>streptococcus</i> (not group A, B, or D)	1	0
<i>Staphylococcus epidermidis</i>	0	1
<i>Streptococcus mitis</i>	1	1
<i>Streptococcus pneumoniae</i>	2	0
<i>Streptococcus</i> (viridans groups)	2	0
Group C <i>streptococcus</i>	1	0
Group F <i>streptococcus</i>	1	0
Gram-Negative		
<i>Citrobacter freundii</i>	0	1
<i>Enterobacter cloacae</i>	1	1
<i>Escherichia coli</i>	0	2
<i>Haemophilus influenzae</i>	6	1
<i>Haemophilus parainfluenzae</i>	5	6
<i>Klebsiella pneumoniae</i>	0	1
<i>Moraxella catarrhalis</i>	3	0
<i>Neisseria</i> species	0	2
<i>Pseudomonas aeruginosa</i>	2	2
<i>Proteus vulgaris</i>	1	0
Multiple	6	10
Total	32	28

Medical officer's note: Study 983-4 had superinfection rates of 3.5% and 5.8% for the cefdinir and cefaclor arms respectively. It is difficult to know what to make of the superinfection rates of 12% cefdinir and 10% for amoxicillin/clavulanate seen here. In addition, the pathogens identified by the studies are quite different. There is only one gram positive isolate (*S. pneumoniae*) identified as a superinfection in study 983-4. Here there are many more; some of questionable significance as pathogens in the setting of CAP without strong documentation. One wonders whether this points to differences in microbiologic judgements on the part of those interpreting culture results. What is evident is that superinfection rates appear to be equivalent across treatment and control arms in both studies. Thus, there seems to be no increased rate attributable to study drug.

Reinfections: One cefdinir-treated patient was reinfected with *H. influenzae*; and one patient in the amoxicillin/clavulanate treatment group was reinfected with Group C *Streptococcus*.

Medical officer's note: Reinfections rates are similar and unremarkable across both treatment arms.

Safety

Medical officer's note: With the exception of the following items, safety for protocol 983-27 was evaluated with the same methodology of safety for protocol 983-4. In protocol 983-4, abnormal laboratory values were designated as adverse events at the discretion of the investigator whereas in protocol 983-27, abnormal clinical laboratory values were designated as adverse events if they were confirmed by repeat testing, suggested a disease or organ toxicity, or required active management (e.g., discontinuation of drug, more frequent follow-up, diagnostic investigation, etc). It is noteworthy that both protocols required that patients discontinuing treatment due to diarrhea in protocol 983-4 were to be tested for *C. difficile* as well.

Safety data were evaluated for 276 patients who took cefdinir and 276 patients who took amoxicillin/clavulanate because one patient in each treatment group was randomized but did not take study drug. Forty-one (15%) cefdinir-treated patients and 43 (16%) amoxicillin/clavulanate-treated patients had one or more adverse events that the investigator considered drug-associated. Eleven (4%) patients who received cefdinir and 14 (5%) who received amoxicillin/clavulanate discontinued treatment due to adverse events; an additional three patients in the cefdinir group and one patient in the amoxicillin/clavulanate group withdrew from the study due to an adverse event after completing treatment. Fourteen (5%) patients who received cefdinir and 15 (5%) amoxicillin/clavulanate-treated patients experienced a serious adverse event. Seven patients died: four who received cefdinir, and three who received amoxicillin/clavulanate.

Medical officer's note: There appears to be no difference between rates of ADRs in the cefdinir and amoxicillin clavulanate arms with respect to overall rates of drug associated ADR, rates of patients discontinuing therapy due to an ADRs, rates of serious ADRs or overall death rate in study.

Table 65. Summary of Adverse Events - All Patients Who Received Study Medication
[Number (%) of Patients]

	cefdinir (n=276)	amox/clav (n=276)
Adverse Events During Study		
All Adverse Events	97 (31.5)	97 (35.1)
Associated ^a Adverse Events	41 (14.9)	43 (15.6)
Adverse Events During Treatment		
All Adverse Events	59 (21.4)	71 (25.7)
Adverse Events by Sex^b		
All Adverse Events		
Male	47 (27.3)	53 (30.8)
Female	40 (38.5)	44 (42.3)
Associated Adverse Events		
Male	23 (13.4)	20 (11.6)
Female	18 (17.3)	23 (22.1)
Adverse Events by Race^c		
All Adverse Events		
White	75 (33.9)	82 (37.1)
Black	11 (22.0)	13 (26.0)
Asian	1 (50.0)	0 (0.0)
Hispanic	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (66.7)
Associated Adverse Events		
White	40 (18.1)	41 (18.6)
Black	1 (2.0)	2 (4.0)
Asian	0 (0.0)	0 (0.0)
Hispanic	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Adverse Events by Age^d		
13 to <18 yr	0 (0.0)	1 (50.0)
18 to <65 yr	53 (33.1)	58 (35.4)
≥65 yr	34 (30.6)	38 (34.5)
Associated Adverse Events		
13 to <18 yr	0 (0.0)	1 (50.0)
18 to <65 yr	30 (18.8)	30 (18.3)
≥65 yr	11 (9.9)	12 (10.9)

^a Considered by the investigator to be possibly, probably, or definitely related to study medication.

^b Percentages based on total numbers of males or females in a treatment group

^c Percentages based on total numbers of patients of each race in a treatment group

^d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.

All and Drug-Associated Adverse Events

Table 66. All and Associated^a Adverse Events by Body System^b - Patients Who Received Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir N = 276				Amoxicillin/Clavulanate N = 276			
	All		Associated		All		Associated	
DIGESTIVE SYSTEM	40	(14.5)	31	(11.2)	47	(17.0)	31	(11.2)
Diarrhea	23	(8.3)	22	(8.0)	22	(8.0)	19	(6.9)
Dyspepsia	7	(2.5)	3	(1.1)	2	(0.7)	2	(0.7)
Constipation	3	(1.1)	0	(0.0)	3	(1.1)	0	(0.0)
Gastritis	3	(1.1)	2	(0.7)	4	(1.4)	1	(0.4)
Liver Function Tests Abnormal	3	(1.1)	3	(1.1)	1	(0.4)	1	(0.4)
Nausea	2	(0.7)	1	(0.4)	8	(2.9)	4	(1.4)
Vomiting	2	(0.7)	1	(0.4)	7	(2.5)	4	(1.4)
Abnormal Stools	1	(0.4)	1	(0.4)	1	(0.4)	1	(0.4)
Anorexia	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Dry Mouth	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenal Ulcer	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hemorrhagic Colitis	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Melena	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Rectal Disorder	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Stomach Ulcer	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Biliary Pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Dysphagia	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Flatulence	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Gastrointestinal Disorder	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Rectal Hemorrhage	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
BODY AS A WHOLE	28	(10.1)	6	(2.2)	28	(10.1)	6	(2.2)
Headache	11	(4.0)	0	(0.0)	10	(3.6)	3	(1.1)
Infection	7	(2.5)	2	(0.7)	1	(0.4)	1	(0.4)
Abdominal Pain	6	(2.2)	4	(1.4)	1	(0.4)	1	(0.4)
Accidental Injury	3	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Asthenia	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Back Pain	2	(0.7)	0	(0.0)	3	(1.1)	0	(0.0)
Flu Syndrome	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Abscess	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Chest Pain	1	(0.4)	0	(0.0)	2	(0.7)	0	(0.0)
Chest Pain Substernal	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sudden Death	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Allergic Reaction	0	(0.0)	0	(0.0)	2	(0.7)	1	(0.4)
Cellulitis	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Fever	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
HIV Test Positive	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	4	(1.4)	0	(0.0)
RESPIRATORY SYSTEM	16	(5.8)	2	(0.7)	14	(5.1)	0	(0.0)
Pharyngitis	3	(1.1)	0	(0.0)	2	(0.7)	0	(0.0)

Rhinitis	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
Dyspnea	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)

- * Associated adverse events are those considered possibly, probably, or definitely related to treatment.
 * The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have >1 adverse event per system.

Medical officer's note: The ADR rates are identical for cefdinir and amoxicillin/clavulanate. Of note, gastrointestinal complaints, particularly diarrhea, are prominent but equal across treatment arms. Interestingly, the incidence of adverse events, including diarrhea, was greater in certain groups in both treatment arms. See the following chart:

Table 67: Variation in Rates of Adverse Events among Different Groups

Demographic group	Overall Adverse Events		Diarrhea Rates	
	cefdinir	amox/clav	cefdinir	amox/clav
Sex				
Male	27%	31%	5%	6%
Female	39%	42%	14%	11%
Race				
Whites	34%	37%	10%	10%
Blacks	22%	26%	2%	0%

It will be interesting to see whether the integrated safety analysis supports higher overall rates of ADRs, and in particular diarrhea, among females and blacks.

Table 68. All and Associated^a Adverse Events by Body System^b - Patients Who Received Study Medication
 [Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir N = 276				Amox/Clav N = 276			
	All		Associated		All		Associated	
DIGESTIVE SYSTEM	40	(14.5)	31	(11.2)	47	(17.0)	31	(11.2)
Diarrhea	23	(8.3)	22	(8.0)	22	(8.0)	19	(6.9)
Dyspepsia	7	(2.5)	3	(1.1)	2	(0.7)	2	(0.7)
Constipation	3	(1.1)	0	(0.0)	3	(1.1)	0	(0.0)
Gastritis	3	(1.1)	2	(0.7)	4	(1.4)	1	(0.4)
Liver Function Tests Abnormal	3	(1.1)	3	(1.1)	1	(0.4)	1	(0.4)
Nausea	2	(0.7)	1	(0.4)	8	(2.9)	4	(1.4)
Vomiting	2	(0.7)	1	(0.4)	7	(2.5)	4	(1.4)
Abnormal Stools	1	(0.4)	1	(0.4)	1	(0.4)	1	(0.4)
Anorexia	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Dry Mouth	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenal Ulcer	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hemorrhagic Colitis	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Melena	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Rectal Disorder	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)

Stomach Ulcer	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Biliary Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dysphagia	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Flatulence	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Gastrointestinal Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Rectal Hemorrhage	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
BODY AS A WHOLE	28 (10.1)	6 (2.2)	28 (10.1)	6 (2.2)
Headache	11 (4.0)	0 (0.0)	10 (3.6)	3 (1.1)
Infection	7 (2.5)	2 (0.7)	1 (0.4)	1 (0.4)
Abdominal Pain	6 (2.2)	4 (1.4)	1 (0.4)	1 (0.4)
Accidental Injury	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Back Pain	2 (0.7)	0 (0.0)	3 (1.1)	0 (0.0)
Flu Syndrome	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Abscess	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Chest Pain	1 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)
Chest Pain Substernal	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden Death	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Allergic Reaction	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.4)
Cellulitis	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Fever	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
HIV Test Positive	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)
RESPIRATORY SYSTEM	16 (5.8)	2 (0.7)	14 (5.1)	0 (0.0)
Pharyngitis	3 (1.1)	0 (0.0)	2 (0.7)	0 (0.0)
Rhinitis	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
Dyspnea	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Pleural Disorder	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	2 (0.7)	2 (0.7)	1 (0.4)	0 (0.0)
Asthma	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Carcinoma of Lung	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Epistaxis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumothorax	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory Disorder	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Lung Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Lung Edema	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Pleural Effusion	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
NERVOUS SYSTEM	12 (4.3)	3 (1.1)	6 (2.2)	0 (0.0)
Insomnia	3 (1.1)	1 (0.4)	2 (0.7)	0 (0.0)
Dizziness	2 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)
Personality Disorder	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	2 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)
Convulsion	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Sleep Disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Twitching	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Agitation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Delirium	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Paresthesia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
CARDIOVASCULAR SYSTEM	10 (3.6)	1 (0.4)	6 (2.2)	0 (0.0)
Postural Hypotension	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial Fibrillation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial Flutter	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Arrest	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Failure	1 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)
Hypertension	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Palpitation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram Abnormal	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Phlebitis	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Thrombophlebitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
SKIN AND APPENDAGES	8 (2.9)	5 (1.8)	9 (3.3)	7 (2.5)
Herpes Simplex	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	2 (0.7)	2 (0.7)	1 (0.4)	0 (0.0)
Acne	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Dry Skin	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Maculopapular Rash	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Rash	1 (0.4)	1 (0.4)	7 (2.5)	6 (2.2)
Eczema	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Urticaria	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
UROGENITAL SYSTEM	6 (2.2)	2 (0.7)	9 (3.3)	3 (1.1)
Vaginitis	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)
Albuminuria	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hematuria	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Kidney Failure	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Orchitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary Tract Infection	1 (0.4)	0 (0.0)	4 (1.4)	1 (0.4)
Breast Carcinoma	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Urinary Retention	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Vaginal Moniliasis	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.7)
SPECIAL SENSES	4 (1.4)	2 (0.7)	4 (1.4)	0 (0.0)
Conjunctivitis	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Taste Perversion	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Uveitis	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Amblyopia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Ear Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Otitis Media	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
METABOLIC AND NUTRITIONAL	3 (1.1)	1 (0.4)	7 (2.5)	1 (0.4)
Hyperuricemia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Lactate Dehydrogenase Increase	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
NPN Increased	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Bilirubinemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hyperglycemia	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)

Peripheral Edema	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
SGPT Increased	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
MUSCULOSKELETAL SYSTEM	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)
Arthralgia	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid Arthritis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
ENDOCRINE SYSTEM	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Diabetes Mellitus	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

NPN = Nonprotein nitrogen

Associated adverse events are those considered possibly, probably, or definitely related to treatment.

The totals for each body system may be less than the number of patients with adverse events in that body system

verse event per system.

Deaths: Seven patients, four in the cefdinir treatment group and three in the amoxicillin/clavulanate group, died during the study. None of the deaths were considered related to study medication by the investigator.

Table 69. All Patient Deaths

Treatment	Center	Patient No.	Age (yr), Sex	Cause of Death ^a	Relationship to Study Medication	Study Day Drug Discontinued	Study Day Patient Died
Cefdinir							
	19	3	57, M	Respiratory Insufficiency (Respiratory Disorder)	Definitely Not	10	23
				Lung-Cancer (Carcinoma of Lung)	Definitely Not		
	21	1	87, M	Sudden Death of Probable Cardiac Origin (Sudden Death)	Unlikely	1	1
	38	44	85, F	Acute Cardiac Failure (Heart Failure)	Definitely Not	5	36
	39	4	80, F	Dyspnoea (Dyspnea)	Unlikely	11	38
Amox/Cla							
	33	2	39, F	Probable Metastatic Ca Breast (Breast Carcinoma)	Definitely Not	6	25
	38	1	84, M	Sudden Death	Definitely Not	11	38
	51	4	68, M	Cardiac Failure (Heart Failure)	Definitely Not	4	4

^a When the investigator term and COSTART term differ, the COSTART term appears in parentheses.^b Relationship to study medication of adverse event leading to death, in the opinion of the investigator

Medical officer's note: Review of case summaries for these patients, found in Applicant's Appendix B.2 does not suggest any deaths attributable to drug.

Serious Adverse Events: Twenty-nine patients, 14 (5%) treated with cefdinir and 15 (5%)

treated with amoxicillin/clavulanate, experienced serious adverse events during this study. Serious adverse events that the investigator considered related to cefdinir were exacerbation of pneumonia in two patients, and hemorrhagic colitis in one patient. No serious adverse events were considered to be related to amoxicillin/clavulanate. Eight cefdinir-treated patients and five amoxicillin/clavulanate-treated patients withdrew from the study due to these serious events.

Medical officer's note: Review of case summaries for these patients, found in Applicant's Appendix B.2 does not suggest that the drug was related to the outcomes.

Withdrawals Due to Adverse Events: Fourteen (5%) patients treated with cefdinir and 15 (5%) treated with amoxicillin/clavulanate withdrew from the study due to adverse events. Of these, 11 (4%) patients treated with cefdinir and 14 (5%) patients treated with amoxicillin/clavulanate discontinued treatment due to adverse events. The remaining three cefdinir-treated patients and one amoxicillin/clavulanate-treated patient withdrew after completing treatment but before the LTFU visit. There was no significant difference between the treatment groups in the number of patients discontinuing treatment due to adverse events ($p = 0.30$).

Diarrhea resulted in withdrawal of two patients in each treatment group; pneumonia and carcinoma of lung each resulted in withdrawal of two patients in the cefdinir treatment group; and rash led to withdrawal of two patients in the amoxicillin/clavulanate group. All other adverse events that led to withdrawal did so in only one patient each.

Medical officer's note: Review of case summaries for these patients, found in Applicant's Appendix B.2 does not differ with respect to withdrawal by treatment arm.

Table 69. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Who Received Study Medication [Number % of Patients]

BODY SYSTEM/ - Adverse Event	Cefdinir N = 276	Amox/Clav N = 276
RESPIRATORY SYSTEM	4 (1.4)	3 (1.1)
Pneumonia	2 (0.7)	0 (0.0)
Carcinoma of Lung	2 (0.7)	0 (0.0)
Lung Disorder	0 (0.0)	1 (0.4)
Lung Edema	0 (0.0)	1 (0.4)
Pleural Effusion	0 (0.0)	1 (0.4)
BODY AS A WHOLE	3 (1.1)	2 (0.7)
Abscess	1 (0.4)	0 (0.0)
Infection	1 (0.4)	0 (0.0)
Sudden Death	1 (0.4)	0 (0.0)
Cellulitis	0 (0.0)	1 (0.4)
Headache	0 (0.0)	1 (0.4)
DIGESTIVE SYSTEM	2 (0.7)	4 (1.4)
Diarrhea	2 (0.7)	2 (0.7)
Dysphagia	0 (0.0)	1 (0.4)

Vomiting	0 (0.0)	1 (0.4)
NERVOUS SYSTEM	2 (0.7)	0 (0.0)
Convulsion	1 (0.4)	0 (0.0)
Somnolence	1 (0.4)	0 (0.0)
SKIN AND APPENDAGES	2 (0.7)	3 (1.1)
Acne	1 (0.4)	0 (0.0)
Pruritus	1 (0.4)	0 (0.0)
Rash	0 (0.0)	2 (0.7)
Urticaria	0 (0.0)	1 (0.4)
CARDIOVASCULAR SYSTEM	1 (0.4)	1 (0.4)
Heart Arrest	1 (0.4)	0 (0.0)
Heart Failure	0 (0.0)	1 (0.4)
SPECIAL SENSES	1 (0.4)	0 (0.0)
Uveitis	1 (0.4)	0 (0.0)
UROGENITAL SYSTEM	0 (0.0)	3 (1.1)
Breast Carcinoma	0 (0.0)	1 (0.4)
Pyelonephritis	0 (0.0)	1 (0.4)
Urinary Tract Infection	0 (0.0)	1 (0.4)

Medical officer's note: Review of the above table suggests no important differences by treatment arm with respect to treatment discontinuations and study withdrawals.

Clostridium difficile-Associated Diarrhea: Although *Clostridium difficile* testing was to have been done for patients discontinuing study medication due to diarrhea, none of the four patients who discontinued therapy due to diarrhea were tested. One patient developed hemorrhagic colitis 17 days after completing the 10-day course of treatment with cefdinir but *Clostridium difficile* toxin tests conducted on stool samples collected Days 30 and 35 were negative.

Medical officer's note: Diarrhea rates are high among participants of protocol 983-27 in both study arms. Among patients receiving cefdinir in protocol 983-4, diarrhea rates were high. Testing for *C. difficile* toxin was intended but not carried through. All cephalosporins marketed in the United States currently bear labeling regarding pseudomembranous colitis. Although these two protocols provide little information, and the integrated safety summary may be helpful and will be completed at a later date, this reviewer believes the language found in the other cephalosporin package inserts regarding this ADR would be appropriate.

Clinical Laboratory Values.

Medical officer's note: Analysis of clinical laboratory values was identical to that performed in protocol 983-4 (median changes from baseline, category shift changes, and markedly abnormal values at first posttherapy visit). There were no abnormal values or changes associated with cefdinir therapy; abnormalities most typically were consistent with resolving infection.

(resolution of leukocytosis), and were similar across both treatment arms.

CONCLUSIONS

- Overall, cefdinir 300 mg BID for 10 days was not as effective as amoxicillin/clavulanate 500 mg TID for 10 days in treating adult patients with community-acquired bacterial pneumonia. Differences were observed in the clinical response rate. Although not equivalent, all responses were good. Microbiologic response rates were equivalent.
- Cefdinir demonstrated efficacy against *Streptococcus pneumoniae* (35/36, 97.2%), *Haemophilus influenzae* (22/29, 75.9%) and *Moraxella catarrhalis* (6/6, 100%). The additional isolates of *Moraxella catarrhalis* successfully treated in this study, when coupled with those from study 983-4 provide a requisite number to allow to efficacy labeling. Insufficient evidence is available to support claims of efficacy for CAP due to *Streptococcus pyogenes* or *Staphylococcus aureus*.
- No difference was observed between cefdinir and amoxicillin/clavulanate with respect to incidence of drug-associated adverse events, including diarrhea, during treatment. There was no difference between the treatments in the rate of treatment discontinuation due to adverse events.

RECOMMENDATIONS REGARDING TWO PIVOTAL CAP TRIALS (983-4 & 983-26)

- Cefdinir 300 mg po bid for 10 days be approved for the treatment of CAP.
- Cefdinir be approved for CAP due to *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta lactamase producing), *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*.

/S/

Holli Hamilton, MD, MPH
Medical Officer
HFD-520 FDA

Concurrences:

HFD-520/TL/Jan Soreth, MD
HFD-520/DivDir/Gary Chikamori, MD

cc: Orig NDAs 50-674 & 50-675

HFD-520/Division File
HFD-520/CSO BDuval-Miller
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague

HFD-40/DMAC/J. Spearman

/S/

Aloka Chakravarty, Ph.D. U
Statistician
HFD-520 FDA
725

Concurrence:

HFD-725/TL/DLin, PhD J.L.

HFD-520/Pharm/FPelsor
HFD-520/MO/HHamilton
HFD-520/TL/JSoreth
HFD-725/Stat/AChakravarty
HFD-725/Stat/TL/DLin

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Acute Exacerbation of Chronic Bronchitis

A double-blind, randomized, multicenter (N=36, U.S. and international sites) study of cefdinir (CI-983) versus cefuroxime axetil in the treatment of patients with acute exacerbations of chronic bronchitis (Protocol 983-5) .

Medical officer's note: This reviewer believes that the clinical outcome is the critical measure in this indication. Microbiological outcome makes little sense. Evaluation of clinical trials reveals that most studies demonstrate a benefit to the administration of antibiotic therapy in patients with acute exacerbation of chronic bronchitis¹. However, this benefit is largely clinical. Microbiologic outcomes are murky; patients often carry the same microorganisms before and after therapy.

This issue was addressed by the Advisory Committee Meeting which convened in March, 1997:

Dr. Thompson: ... In discussing the acute exacerbation of chronic bronchitis, it is important to realize that Haemophilus influenzae and Strep. pneumoniae are present in the sputum in 30 to 50 percent of patients with chronic bronchitis, and this is true whether or not patients are undergoing an acute episode at the time.

In addition, it has been clearly shown in the literature that there is no specific correlation with the development of AECB in terms of development of purulence of the sputum.

Again, briefly, referred to already this morning is isolation of other organisms from the sputum of these patients -- viridans streptococci, Staph aureus, gram-negative enteric bacilli. All of these can be isolated occasionally from the sputum of patients who are undergoing an acute exacerbation of chronic bronchitis, and the question of course is whether these represent simply oropharyngeal contamination or whether they may occasionally be playing a pathogenic role.

Lastly, and probably most importantly, the failure to eradicate putative pathogens including, of course, the major three organisms that I have already mentioned in the face [error omitted] of clinical improvement is very common.

...
...The first is that we would suggest that clinical outcome is the primary determinant of efficacy for the indication of bronchitis.

Exacerbations of Chronic Bronchitis" by John G. Bartlett in Infectious Diseases, 2d., eds. Merwood L. Gorbach, John G. Bartlett, and Neil R. Blackow (W.B. Saunders Co.: Philadelphia) 1985:584-586

Medical officer's note: Understood in the above description is that in order to have AECB one must have have underlying chronic bronchitis. The above inclusion criteria are acceptable although minimally restrictive. This is unfortunate because it becomes a lax test of efficacy as equivalence is easy to demonstrate.

Exclusion Criteria: Patients were to be excluded from participating in the study for any of the following reasons:

- Evidence of pneumonia on a prescreen x-ray;
- Diseases that would preclude evaluation of the therapeutic response, including cystic fibrosis, bronchiectasis, carcinoma of the bronchus, or significant pulmonary structural defects;
- History or clinical evidence of significant cardiovascular, renal, hepatic, hematological, gastrointestinal, neurological, psychiatric, or other chronic disease;
- Hepatic disease, obstruction of the biliary tract, or baseline bilirubin or hepatic enzyme levels (AST, ALT) >2 times the upper limit of normal;
- Baseline serum creatinine >2 times the upper limit of normal or creatinine clearance <30 mL/min;
- Hypersensitivity to β -lactams (including penicillins and cephalosporins);
- A baseline pathogen known to be resistant to either study drug prior to randomization;
- Concomitant infections requiring systemic antibacterial therapy;
- Prior participation in this or any other cefdinir study;
- Receipt of any other investigational compound within 4 weeks of study entry; or
- Receipt of another systemic antibacterial agent in the 48 hours prior to the first dose of study medication, or if the time interval between the last dose of the prior antibacterial and the first dose of cefdinir would be less than 5 half-lives of the prior antibacterial agent.

Medical officer's note: The above exclusion criteria are acceptable. Many are general to other studies in the application.

Evaluability Criteria: The Applicant analyzed several populations: intent-to-treat (ITT), modified intent-to-treat (MITT), evaluable (those patients both microbiologically and clinically evaluable), and clinically evaluable (those patients who were clinically but not necessarily microbiologically evaluable). Each is described below.²

Medical officer's note: *Violations which eliminated patients from various populations are described below. As this reviewer has stated earlier, clinical outcome is of the most interest. This reviewer only analyzed those subjects with bacterial cultures deemed likely to be etiologic in AECB. This is the population included in this review. See Medical officer's note on page 164.*

The criteria for evaluability are reasonable, and uncertainties and failures are carried forward as appropriate. The populations analyzed are the same as those evaluated in the community acquired pneumonia study. The reviewer agrees that these populations are acceptable for analysis; however, microbiologically evaluable patients probably have little meaning in AECB.

² Evaluable patients had no known protocol violations that might have affected the efficacy assessments at TOC using specific, predefined criteria. Patients became unevaluable if they had no baseline pathogen, had a resistant baseline pathogen, failed to take study drug as prescribed, had off-schedule cultures or clinical assessments, had missing microbiologic or clinical signs/symptoms data at baseline or follow-up, took a concurrent systemic antibacterial therapy not for disease under study, had a concurrent infection, or lacked the required baseline diagnosis. Patients whose TOC assessments were done early (ie, before the follow-up visit window) or who took a concurrent antibacterial due to early failure did not become unevaluable for these reasons.

A subset of evaluable patients identified as "qualified patients" was examined at LTFU. Qualified patients were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits. Patients whose LTFU assessments were done early or who took a concurrent antibacterial between the TOC and LTFU visits due to recurrence were not disqualified for these reasons.

Patients in the clinically evaluable population had the correct indication, a productive cough with mucopurulent or purulent sputum, and no resistant pathogens at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy for other concurrent infections; and had their clinical evaluations performed within the range of days specified in the protocol. Patients were not excluded from this data set due to having no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

A subset of clinically evaluable patients identified as "clinically qualified patients" was examined at LTFU. Clinically qualified patients were clinically evaluable patients who did not have any additional protocol variations between the TOC and LTFU visits. Patients whose LTFU assessments were done early or who took a concurrent antibacterial between the TOC and LTFU visits due to recurrence were not disqualified for these reasons.

Patients in the ITT population were those randomized to treatment. Patients who had no baseline pathogen or no follow-up culture were considered to have microbiologic persistence in the ITT summaries and analyses. Similarly, patients who had no follow-up clinical assessment were categorized as failures in the ITT summaries and analyses. The ITT population was the same at TOC and LTFU.

NDA 50-739(Cefdinir 300 mg capsules) & NDA 50-749(Cefdinir oral suspension, 125 mg/5ml)
Acute Exacerbation of Chronic Bronchitis (Study 983-5)

Endpoints defined: The sponsor had three primary endpoints -- microbiologic eradication rate summarized by pathogen, microbiologic eradication rate summarized by patient, and clinical cure rate summarized by patient. A secondary endpoint was the appearance of new pathogens.

Clinical endpoints: The investigator assessed the following clinical signs and symptoms at the baseline, TOC, and LTFU visits: cough, sputum production, sputum appearance, dyspnea, fever, and chest sounds. The recorded signs and symptoms provided the basis for all assessments of patient clinical response.

The investigator's impression of patient clinical response used the following protocol-specified definitions.

Investigator's Assessment of Clinical Response at TOC:

- **Cure:** Absence or satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- **Failure:** No significant remission of baseline signs and symptoms; further antibacterial therapy required; or
- **Not Assessable:** Unable to assess patient; no data.

Investigator's Assessment of Clinical Response at LTFU:

- **Cure:** Absence of satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- **Failure/Recurrence:** Worsening or no significant remission of baseline signs and symptoms since the previous visit; further antibacterial therapy required; or
- **Not Assessable:** Unable to assess patient; no data.

Sponsor's Assessment of Clinical Response at TOC:

- **Cure:** $\geq 50\%$ decrease in clinical score at TOC relative to baseline;
- **Failure:** $< 50\%$ decrease in clinical score at TOC relative to baseline; or
- **Not Assessable:** No baseline signs/symptoms or no follow-up data.

Sponsor's Assessment of Clinical Response at LTFU:

- **Cure:** Cure at TOC and < 2 -point increase in clinical score at LTFU relative to TOC and $\geq 50\%$ decrease in clinical score at LTFU relative to baseline;
- **Recurrence:** Cure at TOC and either ≥ 2 -point increase in clinical score at LTFU relative to TOC or $< 50\%$ decrease in clinical score at LTFU relative to baseline;
- **Failure:** Failure at TOC; or
- **Not Assessable:** No baseline signs/symptoms or no follow-up data.

Table 98. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU^{a,b}

Sponsor Assessment at TOC	Investigator Assessment at TOC		
	Cure	Failure	Not Assessable
Cure	Cure	Failure	Cure
Failure	Cure	Failure	Failure
Not Assessable	Cure	Failure	Not Assessable
Sponsor Assessment at LTFU	Investigator Assessment at LTFU		
	Cure	Recurrence	Not Assessable
Cure	Cure	Recurrence	Cure
Failure	Cure	Recurrence	Failure
Recurrence	Cure	Recurrence	Recurrence
Not Assessable	Cure	Recurrence	Not Assessable

^a The combined assessments are shown in bold typeface.

^b NOTE: If a patient had a combined clinical assessment of failure at the TOC visit, the patient was automatically a failure on the combined assessment scale at the LTFU visit.

The clinical cure rate was the percentage of patients rated as Cure on the combined assessment scale. Each patient provided 1 observation. Clinical cure rates were calculated separately for the TOC and LTFU visits.

Microbiologic Response by Pathogen: Specimens were collected for culture at baseline, 3 to 5 days after initiation of therapy, and at the TOC and LTFU visits. Sputum samples were taken most commonly, but samples of bronchial fluid, lung tissue, or transtracheal aspirate were also allowed.

At the TOC and LTFU visits, the microbiologic response of each baseline pathogen was classified as:

- **Eradication** — Baseline pathogen not present in follow-up culture or no material available to culture at follow-up (presumed eradication);
- **Persistence** — Baseline pathogen present in follow-up culture; or
- **Not Assessable** — No follow-up data.

Microbiologic eradication rate by pathogen was defined as the percentage of baseline pathogens that were absent from specimens obtained at the TOC or LTFU visits. Patients with multiple baseline pathogens provided multiple observations in the analyses of microbiologic efficacy on a per pathogen basis. The eradication rate by pathogen was calculated separately for each of the follow-up visits.

Qualified patients who had persistent pathogens at TOC were automatically considered to have persistent pathogens at the LTFU visit. Patients without baseline pathogens could become superinfected.

Microbiologic Response by Patient: At the TOC visit, patients were classified by their overall microbiologic response based on the baseline and 7- to 14-day posttherapy culture results as:

- **Patients With Eradication** — All baseline pathogens eradicated at TOC *or* no material available to culture at TOC (presumed eradication);
- **Patients With Persistence** — Presence of at least 1 baseline pathogen in the TOC culture; *or*
- **Not Assessable** — No proven baseline pathogen *or* no follow-up data.

At the LTFU visit, patients were classified by their microbiologic response based on the baseline, 7- to 14-day posttherapy, and 21- to 35-day posttherapy culture results as:

- **No Relapse** — Patients with Eradication at TOC *and* either continued eradication of all baseline pathogens at LTFU or no material available to culture at LTFU;
- **Relapse** — Patients with Eradication at TOC *and* reappearance of at least 1 baseline pathogen at LTFU;
- **Patient With Persistence** — Patients with Persistence at TOC; *or*
- **Not Assessable** — No proven baseline pathogen *or* no follow-up data.

The microbiologic eradication rate by patient was the percentage of patients who had all baseline pathogens eradicated. Each patient provided only one observation. The microbiologic eradication rate by patient was calculated separately for each follow-up visit.

Medical officer's note: *The above outcomes are reasonable assignments. As discussed earlier in this review, greater weight is given to clinical outcome; this reviewer questions the utility of microbiologic outcome in AECB. A category of "Patient with Relapse" is reasonable at LTFU. This reviewer is pleased that no "improved" categories are included in the final outcome measures. Relapse and persistence are appropriate assignments at LTFU. Although a sort of failure, it is a very common outcome in AECB. In fact, microbiologic eradication is probably not a reasonable expectation.*

Appearance of New Pathogens: The appearance of a new pathogen during or after treatment was classified as:

- **Superinfection** — The appearance of a nonbaseline pathogen (in the respiratory tract) at any time during treatment through the TOC visit *and* <50% decrease in clinical score at the corresponding clinical evaluation of signs and symptoms relative to baseline;
- **Reinfection** — The appearance of a new pathogen (ie, not present at any prior visit) at the LTFU visit, *and* the clinical assessment of Recurrence at LTFU; or
- **Not Assessable** — No follow-up data.

The appearance of a new pathogen together with a clinical worsening or failure at the corresponding clinical assessment also constituted a superinfection or a reinfection.

If a patient had a new organism(s) isolated in any postbaseline culture, but had no corresponding clinical assessment of signs and symptoms, the determination of pathogenicity was made by the sponsor.

***Medical officer's note:** These assignments are reasonable and important to monitor.*

Statistical Considerations: This double-blind, randomized, comparative study of cefdinir versus cefuroxime was designed with a sample size of 190 evaluable patients per randomized group (570 total evaluable patients).

A microbiologic eradication rate of 90% across all randomized groups was assumed in the sample size calculations. Equivalence was to be assessed by comparing a two-tailed 95% confidence interval (CI) for the difference (cefdinir minus cefuroxime) in microbiologic eradication rates to a set of predetermined, fixed criteria. The sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and cefuroxime microbiologic eradication rates at the TOC visit, using this CI method.

The following are the fixed criteria for establishing equivalence utilizing a two-tailed, 95% confidence interval for each treatment difference, using a standard normal approximation.

Table 99. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Response Rate	Treatments Are Equivalent If 95% Confidence Interval for Treatment Difference Is Within Bounds
≥90%	-10%, +10%
80%-89%	-15%, +15%
70%-79%	-20%, +20%

Medical officer's note: *The above is the Applicant's strategy for analysis. The reviewer believes that 90% microbiologic eradication rate is probably not realistic; clinical outcome is more important. Thus, the clinical outcome will be tantamount.*

Safety: Safety data were summarized for all patients who received study medication. A CMH analysis, adjusting for center, was performed to compare the cefdinir treatment groups to cefuroxime with respect to the rates (i.e., incidence) of all adverse events, drug-associated adverse events, diarrhea, and treatment discontinuations due to adverse events. Pairwise treatment comparisons were made. The Breslow-Day test was reviewed in evaluating the consistency of the relationship between adverse events and treatment among centers.

Medical officer's note: *The above represents the Applicant's analysis plan for safety data; this reviewer finds it acceptable.*

Medical officer's note: *Review of a subset of case report forms convinced this reviewer that outcome assignments were appropriately made. Therefore the Applicant's outcome assignments will be used in the analysis. Populations differ only with respect to those patients microbiologically evaluable. See Medical officer's note on page 164.*

Demographics

Demographics, Evaluability

The following demonstrates the numbers of the populations analyzed:

Table 100. Patients With Data Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
Intent-to-Treat (ITT) ^a	349	(100.0)	347	(100.0)	349	(100.0)
Clinically Evaluable ^b	278	(79.7)	286	(82.4)	286	(81.9)
Evaluable ^c	119	(34.1)	120	(34.6)	110	(31.5)
Qualified ^d	78	(22.3)	68	(19.6)	66	(18.9)

^a All patients who were randomized to treatment

^b Total number of patients who were clinically evaluable at TOC

^c Total number of patients who were microbiologically and clinically evaluable at TOC

^d Total number of evaluable patients who were microbiologically and clinically qualified at LTFU

Table 101. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir				Cefuroxime N = 349		Total N = 1045	
	600 mg QD N = 349		300 mg BID N = 347					
Sex								
Men	223	(63.9)	202	(58.2)	210	(60.2)	635	(60.8)
Women	126	(36.1)	145	(41.8)	139	(39.8)	410	(39.2)
Race								
White	321	(92.0)	326	(93.9)	327	(93.7)	974	(93.2)
Black	17	(4.9)	17	(4.9)	21	(6.0)	55	(5.3)
Asian	7	(2.0)	2	(0.6)	1	(0.3)	10	(1.0)
Other ^a	4	(1.1)	2	(0.6)	0	(0.0)	6	(0.6)
Age, yr								
Median	59		59		61		59	
Range	18-91		15-88		20-92		15-92	
Distribution								
13 to <18	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
18 to <65	221	(63.3)	233	(67.1)	209	(59.9)	663	(63.4)
≥65	128	(36.7)	113	(32.6)	140	(40.1)	381	(36.5)

^a Arabian, Gypsy, Mixed

Of all patients randomized to treatment, about 60% were men and over 90% were white. Although there was a wide age range (15 to 92 years), only one patient was under 18 years old, and most patients were in the 18 to <65 years-old age bracket. Just over one-third of patients were 65 years of age or older.

Medical officer's note: The demographic provide adequate representation by sex, but racial variation is extremely limited. DAIDP's Guidelines recommends that adults aged 18 and over be evaluated for this indication. Although the protocol had allowed for adolescence to be enrolled, so very few were that the reviewer need not eliminate this patient from analysis.

Smoking History:

Table 104: Smoking Status for All Enrolled Patients

Smoking Status	cefdinir bid N (%)	cefdinir qd N (%)	cefuroxime N (%)
Never	124(35.7)	133(38.1)	117(33.5)
Past Avg yrs	117(33.7) 27.7	118(33.8) 33.8	120(34.4) 28.2
Current Avg yrs	106(30.5) 33.2	98(28.1) 28.1	112(32.1) 33.0
Total Avg yrs	347 (100.0) 30.3	349(100.0) 31.6	349(100.0) 30.5

Table 105: Number of Cigarettes Smoked for All Enrolled Patients
Reporting Past or Present Smoking History

Smoking Status	Average number of cigarettes smoked/day	cefdinir bid N (%)	cefdinir qd N (%)	cefuroxime N(%)
Past	light (1-10 per day)	19(16.2)	15(12.7)	16(13.3)
	moderate (11-20 per day)	64(54.7)	60(50.8)	63(52.5)
	heavy (≥ 21 per day)	34(29.1)	43(36.4)	41(34.2)
Current	light (1-10 per day)	18(17.0)	17(17.3)	28(25.0)
	moderate (11-20 per day)	45(42.5)	51(52.0)	45(40.2)
	heavy (≥ 21 per day)	42(39.6)	30(30.6)	39(34.8)
	unknown	1(0.9)	0	0
Total	light (1-10 per day)	37(16.6)	32(14.8)	44(19.0)
	moderate (11-20 per day)	109(48.9)	111(51.4)	108(46.6)
	heavy (≥ 21 per day)	76(34.1)	73(33.8)	80(34.5)
	unknown	1(0.4)	0	0

Medical officer's note: It is surprising that such a great number of subjects have no prior smoking history. Roughly a third are past smokers, a third are current smokers and a third have never smoked. Although environmental factors can cause AECB, the failure of this submission to collect such critical information which would provide more compelling evidence for the diagnosis is extremely unfortunate. Among those who smoke

or smoked, the vast majority are moderate to heavy smokers. Because smokers are very apt to underestimate their habit, these subjects probably have a very significant exposure. The amount of exposure reported by the subjects is reassuring to this reviewer.

Concomittant Medical Conditions: In addition to chronic bronchitis, nearly half of the patients had other respiratory tract conditions. Common conditions were chronic obstructive pulmonary disease (COPD), asthma, and emphysema. Similar numbers of patients in each treatment group had experienced one or more lower respiratory tract infections during the year prior to the study: 63% in the cefdinir QD group, 70% in the cefdinir BID group, and 72% in the cefuroxime group. Thirty-four percent of patients in each treatment group were past smokers and 28% to 32% of patients in each treatment group were current smokers.

Table 106: Prior Pulmonary Diagnoses & Conditions Predisposing to Acute Exacerbation of Chronic Bronchitis for All Clinically Evaluable Patients

Diagnosis	cef qd	cef bid	cefurox
Aspergillosis	1		
Asthma	43	45	42
Tuberculosis	8	14	10
Emphysema/COPD	96	108	104
Pulmonary cancer	2	1	2
Allergic bronchitis	1	1	
Cold	2		
Pulmonary embolus	1		2
Bronchiectasis	1	4	1
Pulmonary abscess	1		
Pneumonia	2		2
Collapsed lung	1		
Chronic inhalant allergies	1		
Chronic airflow obstruction		1	
Silicosis			1
Sarcoidosis		1	2
Pleurisy		1	
Interstitial pulmonary fibrosis		2	2
Pigeon Fancier's Lung			1
History of pneumothorax		2	1

Medical officer's note: *Because the information of prior and current pulmonary diagnoses was generated by an open ended question regarding medical history, the information obtained is extremely limited. Although the diagnoses of emphysema/COPD and asthma are the most common, many of the other diagnoses do not provide an insight into the etiology of the subjects' AECB. It would have been preferable to have obtained this important data in a more structured fashion that would provide more information into the subjects' chronic bronchitis. In addition, information regarding recent prior therapy for exacerbations would have been useful. The Applicant provides in his report*

the following: "Similar numbers of patients in each treatment group had experienced 1 or more lower respiratory tract infections during the year prior to the study: 63% in the cefdinir QD group, 70% in the cefdinir BID group, and 72% in the cefuroxime group." More details on the range, severity and exact diagnosis would have been helpful.

Pathogens Isolated

The most common pathogens were *Haemophilus influenzae* (218 patients), *Streptococcus pneumoniae* (82 patients), *Haemophilus parainfluenzae* (72 patients), and *Moraxella catarrhalis* (53 patients). Multiple pathogens were cultured from 115 patients, of which 31 (27%) had *S. pneumoniae* and *H. influenzae*.

Table 108. Distribution of Patients by Baseline Pathogen
(Number of Patients)

	Cefdinir		Cefuroxime
	600 mg QD	300 mg BID	
Gram-Positive			
<i>Streptococcus pneumoniae</i>	37	22	23
Gram-Negative			
<i>Haemophilus influenzae</i>	74	74	70
<i>Haemophilus parainfluenzae</i>	21	28	23
<i>Moraxella catarrhalis</i>	20	15	18

Medical officer's note: The Applicant submitted a long list of pathogens that included many Enterobacteriaceae species and commensal Neisseria species. This Reviewer believes that the above pathogens are of interest and that it would be very difficult, if not impossible to prove that any of the other pathogens listed by the Applicant were truly responsible for the subject's symptoms.

Of *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis* isolates with documented β -lactamase results, 29/272 (11%), 10/73 (14%), and 37/74 (50%), respectively, were β -lactamase positive. Of the β -lactamase-positive isolates, only one *H. parainfluenzae* isolate was resistant to cefdinir and none were resistant to cefuroxime.

Medical officer's note: It greatly supprises this Reivewer that such a small percent of isolates were obtained. Nationwide, beta lactamase resistant occurs in about 95% of *Moraxella catarrhalis* isolates and 40% of *Haemophilus influenzae* isolates.

Clinical Signs and Symptoms

At baseline, productive cough and purulent or mucopurulent sputum were required for eligible patients. Over 95% of patients enrolled in the study had a moderate or severe

cough at baseline, and over 90% of patients had moderate or severe sputum production at baseline. The majority of patients also presented with rhonchi, wheezing, and some degree of dyspnea. Approximately one third of the patients presented with rales, 20% with fever, and less than 10% with fremitus or pleural rub at baseline. There were no apparent differences between treatment groups or between the ITT and evaluable patient populations.

*Table 109. Patient Disposition - All Patients
(Number of Patients)*

Patient Disposition	Cefdinir		Cefuroxime	Total
	600 mg QD	300 mg BID		
Randomized to Treatment	349	347	349	1045
Discontinued Treatment				
Adverse Event	17 ^a	15	13	44 ^b
No Baseline Pathogen	5	3	8	16
Lack of Compliance	5	3	7	15
Resistant Baseline Pathogen	3 ^c	3	7	13
Failure at End of Therapy ^f	4	4	3	11
Other/Administrative ^d	2	2	2	6
Completed Treatment^e	314	317	309	940

^a Patient 40, Center 20, discontinued treatment with cefdinir QD because her baseline pathogen was resistant to both study drugs (CRF 10) and also because she experienced severe diarrhea beginning on the first day of treatment (CRF 8).

^b Another 9 patients were withdrawn from the study due to an adverse event that occurred after treatment ended but before LTFU.

^c These patients did not complete treatment. They discontinued due to lack of efficacy.

^d Patient choice (2 patients), lost to follow-up (1 patient), lost sputum sample (1 patient), history of epilepsy (1 patient), patient died during the study and the day of death was unknown (1 patient).

^e Based on the investigator assessment of patient status at the end of treatment (Case Report Form 10)

Medical officer's note: The above table provides reasonable explanation of patient outcome. It is unfortunate, but many studies have this much loss to follow up. There does not appear to be bias by treatment arm. The "No baseline pathogen" category is derived by Applicant and includes many microorganisms that the reviewer does not consider undisputed pathogens in AECB.

Table 110. Reasons Patients Were Not Evaluable at TOC or Were Disqualified at LTFU

(Number of Patients)

	Cefdinir		Cefuroxime
	QD	BID	
Test-of-Cure Visit			
Exclusions From Evaluable Analyses^a			
No Proven Baseline Pathogen	158	144	163
Culture Out of Time Range ^b	45	23	39
Clinical Assessment Out of Range ^b	35	21	29
Culture Missed	15	20	23
Baseline Pathogen(s) Resistant to Either Study Drug	12	20	15
Medication Not Taken as Prescribed ^b	13	11	16
Baseline X-Ray Missed	9	10	12
No Baseline Susceptibility Tests	4	9	5
Disallowed Prior Antibacterial	7	8	5
Clinical Assessment Missed	5	4	5
Concurrent Antibacterial ^b	7	3	5
Randomization Violation	4	1	2
No Baseline Signs or Symptoms	0	2	0
Condition Prevented Assessment	0	1	0
Wrong Indication	0	1	1
Long-Term Follow-Up Visit			
Disqualifications From Qualified Analyses^a			
Culture Missed	33	39	34
Clinical Assessment Missed	33	36	31
Concurrent Antibacterial ^b	9	17	16
Clinical Assessment Out of Range ^b	11	9	7
Culture Out of Range ^b	11	9	6
Total Disqualified	54	65	54

^a Patients who had multiple reasons for exclusion or disqualification are displayed for each reason that applied.

^b Patients who had cultures or assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early failures/recurrences were not removed from the analyses for these reasons.

Medical officer's note: It is unfortunate that such emphasis was placed on microbiologic outcomes for evaluability; the clinical outcomes are of greater interest. However, this Reviewer spot finds the above reasons acceptable and discerns no bias by

treatment arm. "No baseline pathogens" eliminates all pathogens but Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Haemophilus parainfluenzae.

Table 111. Patients With Data Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
Intent-to-Treat (ITT) ^a	349	(100.0)	347	(100.0)	349	(100.0)
Clinically Evaluable ^b	278	(79.7)	286	(82.4)	286	(81.9)
Evaluable ^c	119	(34.1)	120	(34.6)	110	(31.5)
Qualified ^d	78	(22.3)	68	(19.6)	66	(18.9)

^a All patients who were randomized to treatment

^b Total number of patients who were clinically evaluable at TOC

^c Total number of patients who were microbiologically and clinically evaluable at TOC

^d Total number of evaluable patients who were microbiologically and clinically qualified at LTFU

Medical officer's note: The FDA and Applicant populations are identical in the ITT and clinically evaluable populations. However, the reviewer only evaluated those patients with bacterial pathogens reasonably likely to be etiologic in AECB. This includes Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. Although the role of Haemophilus parainfluenzae is a subject of debate, the Applicant has demonstrated efficacy against this pathogen in CAP and was therefore considered here. Staphylococcus aureus was eliminated because it is impossible to determine whether this agent is a contaminant, colonizer or pathogen. Series that have evaluated Staphylococcus aureus in AECB have concluded it to be an uncommon cause. The Applicant's submission identified it as a fairly common cause. Thus, the reviewer feels justified in her conclusion that the data provided does not support. It is extremely difficult to imagine assigning causality to many of the other bacteria, such as Enterobacteriaceae, other streptococci, and commensal Neisseria species, which were incorporated into the Applicant's analysis.

Safety Evaluations

Patient 17, Center 6, and Patient 17, Center 7, both randomized to cefdinir BID, did not receive study medication and are not included in the safety evaluations.

Medical officer's note: This is acceptable.

Efficacy

Table 112. Microbiologic Eradication Rate by Baseline Pathogen at the Test-of-Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID		n/N	%
	n/N	%	n/N	%		
<i>Streptococcus pneumoniae</i>	34/38	89.5	35/40	87.5	30/30	100.0
<i>Haemophilus influenzae</i>	56/70	80.0	58/74	78.4	52/71	73.2
β-Lactamase positive	4/4	100.0	4/7	57.1	8/10	80.0
β-Lactamase negative	51/65	78.4	53/66	80.3	43/60	71.7
β-Lactamase unknown	1/1	100.0	1/1	100.0	1/1	100.0
<i>Haemophilus parainfluenzae</i>	19/19	100.0	27/30	90.0	20/21	95.2
β-Lactamase positive	2/2	100.0	3/3	100.0	3/3	100.0
β-Lactamase negative	13/13	100.0	21/24	87.5	15/16	93.8
β-Lactamase unknown	4/4	100.0	3/3	100.0	2/2	100.0
<i>Moraxella catarrhalis</i>	19/19	100.0	17/20	85.0	20/21	95.2
β-lactamase positive	14/14	100.0	4/6	66.7	8/9	88.9
β-lactamase negative	5/5	100.0	13/14	92.9	12/12	100.0
Total	222/254	87.4	239/288	82.9	214/256	83.6

n/N = Number of pathogens eradicated/total number of pathogens.

Table 113 displays the 95% confidence intervals with continuity correction.

Table 113. Comparisons of Microbiologic Eradication Rates by Pathogen for Evaluable Patients at TOC

Comparison	95% CI	Criterion	Result
Cefdinir QD-Cefuroxime	(-2.69, 10.30)	15%	Equiv.
Cefdinir BID-Cefuroxime	(-7.25, 6.04)	15%	Equiv.
Cefdinir QD-Cefdinir BID	(-1.91, 10.74)	15%	Equiv.

Medical officer's note: Equivalence is demonstrated by these comparisons.

Microbiologic Eradication by Patient

Table 114. Microbiologic Eradication Rate by Patient According to Baseline Pathogen at the Test-of Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID		n/N	%
	n/N	%	n/N	%		
Gram-Positive						
<i>Streptococcus pneumoniae</i>	25/27	92.6	19/21	90.5	19/19	100.0
Gram-Negative						
<i>Haemophilus influenzae</i>	49/59	83.1	45/58	77.6	40/56	71.4
<i>Haemophilus parainfluenzae</i>	17/17	100.0	24/27	88.9	18/19	94.7
<i>Moraxella catarrhalis</i>	16/16	100.0	11/14	78.6	15/16	93.8
Total	107/119	89.9	99/120	82.5	92/110	83.6

n/N = Number of patients with baseline pathogens eradicated/total number of patients.

Table 115 displays the 95% confidence intervals with continuity correction.

Table 115. Comparisons of Microbiologic Eradication Rates by Patient for Evaluable Patients at TOC

Comparison	Pooled Rates		
	95% CI	Criterion	Result
<i>Cefdinir QD-Cefuroxime</i>	(-3.37, 15.93)	15%	Equiv.
<i>Cefdinir BID-Cefuroxime</i>	(-11.70, 9.43)	15%	Equiv.
<i>Cefdinir QD-Cefdinir BID</i>	(-2.11, 16.94)	15%	Equiv.

Medical officer's note: Cefdinir qd and bid compare favorably to cefuroxime; cefdinir qd appears superior to cefdinir bid by this analysis. Good numbers of the pathogens of interest have been isolated in this study.

Clinical Cure by Patient

Table 116. Clinical Cure Rate^a by Patient According to Baseline Pathogen at the Test-of Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID		n/N	%
	n/N	%	n/N	%		
Gram-Positive						
<i>Streptococcus pneumoniae</i>	25/27	92.6	15/21	71.4	15/19	78.9
Gram-Negative						
<i>Haemophilus influenzae</i>	44/59	74.6	40/58	69.0	41/56	73.2
<i>Haemophilus parainfluenzae</i>	15/17	88.2	22/27	81.5	15/19	78.9
<i>Moraxella catarrhalis</i>	13/16	81.3	9/14	64.3	13/16	81.3
Total	97/119	81.5	86/120	71.7	84/110	76.4

n/N = Number of patients with a clinical cure at TOC/total number of patients.

^a Combined investigator/sponsor determination

Table 117. Comparisons of Clinical Cure Rates by Patient for Microbiologically-Clinically Evaluable Patients at TOC

Comparison	Pooled Rates		
	95% CI	Criterion	Result
Cefdinir QD-Cefuroxime	(-6.29, 16.59)	20%	Equiv
Cefdinir BID-Cefuroxime	(-16.88, 7.49)	20%	Equiv
Cefdinir QD-Cefdinir BID	(-1.65, 21.34)	20%	Equiv

Medical officer's note: Equivalence is demonstrated by in both cefdinir regimens against cefuroxime. Inexplicably, the cefdinir bid regimen is inferior to the cefinir qd regimen by this analysis.

Long-Term Follow-Up Visit (21-35 Days Posttherapy): Microbiologic Eradication by Pathogen and Patient

Evaluable patients who continued to satisfy necessary protocol requirements between the TOC and LTFU visits were considered qualified at LTFU. Qualified patients who had persistent pathogens at the TOC visit were automatically considered to have persistent pathogens at the LTFU visit.

Table 119. Microbiologic Eradication Rate by Baseline Pathogen at the Long-Term Follow-Up Visit - Evaluable Patients Who Qualified for Long-Term Analysis

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
<i>Streptococcus pneumoniae</i>	23/27	85.2	27/27	100.0	21/21	100.0
Gram-Negative						
<i>Haemophilus influenzae</i>	38/42	90.5	40/40	100.0	38/39	97.4
<i>Haemophilus parainfluenzae</i>	13/13	100.0	19/19	100.0	13/13	100.0
<i>Moraxella catarrhalis</i>	15/15	100.0	11/11	100.0	14/14	100.0
Total	89/97	91.8	77/77	100.0	86/87	98.8

n/N = Number of pathogens eradicated/total number of pathogens.

Table 120. Microbiologic Eradication Rate by Patient According to Baseline Pathogen at the Long-Term Follow-Up Visit - Evaluable Patients Who Qualified for Long-Term Analysis

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
<i>Streptococcus pneumoniae</i>	18/20	90.0	15/15	100.0	14/14	100.0
<i>Streptococcus pyogenes</i>	3/3	100.0	3/3	100.0	1/1	100.0
Gram-Negative						
<i>Haemophilus influenzae</i>	32/35	91.4	30/30	100.0	28/28	100.0
<i>Haemophilus parainfluenzae</i>	11/11	100.0	17/17	100.0	13/13	100.0
<i>Moraxella catarrhalis</i>	12/12	100.0	6/6	100.0	11/11	100.0
Total	73/78	93.6	68/68	100.0	66/66	100.0

n/N = Number of patients with baseline pathogens eradicated/total number of patients.

Medical officer's note: Acceptable rates of microbiologic eradication rates by patient and pathogens are seen in every treatment arm. By these analyses, cefdinir qd performs worse than either cefdinir bid or cefuroxime. However, these are not primary outcome measures and all the rates are acceptable.

Clinically Evaluable and Clinically Qualified Analyses

TOC Visit (7-14 Days Posttherapy)

Clinical Cure Rate

In the clinically evaluable patient population at the TOC visit, the clinical cure rates were 229/278 (82%) in the cefdinir qd group, 225/286 (79%) in the cefdinir bid group, and

NDA 50-739(Cefdinir 300 mg capsules) & NDA 50-749(Cefdinir oral suspension, 125 mg/5ml)
Acute Exacerbation of Chronic Bronchitis (Study 983-5)

232/286 (81%) in the cefuroxime group. Table 121 displays the 95% confidence intervals with continuity correction

Table 121. Comparisons of Clinical Cure Rates by Patient (Clinically Evaluable Population) at TOC

Comparison	95% CI	Criterion	Result
Cefdinir QD-Cefuroxime	(-5.47, 7.98)	15%	Equiv
Cefdinir BID-Cefuroxime	(-9.36, 4.47)	20%	Equiv
Cefdinir QD-Cefdinir BID	(-3.18, 10.58)	20%	Equiv

Medical officer's note: This reviewer considers this outcome measure the most important. No differences in cure rates by treatment arm are detected among clinically evaluable patients.

LTFU Visit (21-35 Days Posttherapy)

Clinical Cure

Among clinically qualified patients who were classified as cures at the TOC visit, the overall clinical cure rates at the LTFU visit (ie, no clinical recurrence) were similar in all three groups: 181/192 (94%) in the cefdinir QD group, 185/194 (95%) in the cefdinir BID group, and 186/195 (95%) in the cefuroxime group.

Medical officer's note: No differences are detected in clinical cure rate among the clinically evaluable population qualified at long term follow up. All cure rates at LTFU are very acceptable.

Table 122. Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at LTFU - Clinically Qualified Patients

Investigator Determination	Combined Investigator/Sponsor Determination								
	Cefdinir						Cefuroxime		
	QD N = 200			BID N = 202			N = 203		
	Cure	Failure	Recurrence	Cure	Failure	Recurrence	Cure	Failure	Recurrence
Cure	181	5	0	184	2	0	186	4	0
Failure/Recurrence	0	3	11	0	6	9	0	4	9
Not Assessable	0	0	0	1	0	0	0	0	0

NDA 50-739(Cefdinir 300 mg capsules) & NDA 50-749(Cefdinir oral suspension, 125 mg/5ml)
Acute Exacerbation of Chronic Bronchitis (Study 983-5)

Medical officer's note: *It is reassuring that application of the combined investigator/sponsor determination shows little discrepancy from the investigatory determination alone.*

Intent-to-Treat Analyses

Test-of-Cure Visit (7-14 Days Posttherapy)

Table 123. Clinical Efficacy Results
at TOC - ITT Patients

	Clinical Cure Rate	
	n/N	%
Cefdinir QD	229/349	65.6
Cefdinir BID	225/347	64.8
Cefuroxime	232/349	66.5

n/N = Number of patients with combined determination
of cure/total number of patients.

Medical officer's note: *As would be expected in the intent to treat analysis, clinical cure rate is lower than in evaluable population. However, all three treatment arms demonstrate similar efficacy.*

Long-Term Follow-Up Visit (21-35 Days Posttherapy)

Table 124. Clinical Cure Rate by
Patient Results at LTFU -
ITT Population

	Clinical Cure Rate by Patient	
	n/N	%
Cefdinir QD	181/349	51.9
Cefdinir BID	185/347	53.3
Cefuroxime	186/349	53.3

n/N = Number of patients with combined
investigator/sponsor determination of cure
(ie, no recurrence) at LTFU/total number of
patients.

Medical officer's note: *As would be expected, the further out the follow up, the smaller the population. Once again, all three treatment arms demonstrate similar efficacy.*

Patients With Cefdinir-Resistant *Streptococcus pneumoniae*

Three patients who were treated with cefdinir had cefdinir-resistant *S. pneumoniae* at baseline. All three patients completed treatment and were assessed as clinically cured at TOC. One patient (Patient 5, Center 28; cefdinir 600 mg QD) had microbiologic persistence. The other two patients (Patient 34, Center 35, cefdinir 600 mg QD; Patient 46, Center 35, cefdinir 300 mg BID) had microbiologic eradication at TOC. All three patients had a second, cefdinir-sensitive pathogen at baseline, each of which had the same microbiologic response as the resistant *S. pneumoniae*. There were no known penicillin-resistant *S. pneumoniae* isolates at baseline.

Medical officer's note: The numbers are too small to draw any conclusions. In addition, because microbiologic outcomes are problematic in AECB, it would be dangerous to conclude efficacy based on this indication.

Appearance of New Pathogens During the Study

Reinfections

Seven patients were reinfected after the TOC visit with pathogens not present at baseline.

Table 125. Patients With Reinfections - ITT Patients
(Number of Patients)

Pathogen(s)	Cefdinir		Cefuroxime
	QD	BID	
Gram-Positive			
<i>Streptococcus pneumoniae</i>	0	1	0
Gram-Negative			
<i>Haemophilus influenzae</i>	0	1	0
<i>Moraxella catarrhalis</i>	2	3	0
Total	2	5	0

Medical officer's note: The Applicant appears to have included the appearance of any new bacterial species in its analysis of this topic. This reviewer limited this analysis only to the pathogens of interest. The numbers are too small to draw conclusions.

NDA 50-739(Cefdinir 300 mg capsules) & NDA 50-749(Cefdinir oral suspension, 125 mg/5ml)
Acute Exacerbation of Chronic Bronchitis (Study 983-5)

Safety

All and Drug-Associated Adverse Events

More patients in all three treatment groups experienced adverse events in the gastrointestinal system than in any other body system. Diarrhea was the most frequently occurring adverse event, occurring in 10% of cefdinir QD-treated patients, 8% of cefdinir BID-treated patients, and 6% of cefuroxime-treated patients. There was no significant difference between the treatment groups in the rates of patients who experienced diarrhea ($p = 0.281$). Diarrhea was generally considered drug-associated. Other adverse events that occurred in at least 2% of patients in any treatment group were headache, nausea, rash, and accidental injury.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 126. All and Associated Adverse Events by Body System - All Patients Who Received Study Medication
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir						Cefuroxime	
	600 mg QD N = 349			300 mg BID N = 345			N = 349	
	All	Assoc		All	Assoc		All	Assoc
DIGESTIVE SYSTEM	44* (12.6)	37* (10.6)		43 (12.5)	36* (10.4)		40 (11.5)	31* (8.9)
Diarrhea	33 (9.5)	29 (8.3)		28 (8.1)	27 (7.8)		22 (6.3)	19 (5.4)
Nausea	9 (2.6)	7 (2.0)		5 (1.4)	3 (0.9)		9 (2.6)	8 (2.3)
Constipation	1 (0.3)	0 (0.0)		3 (0.9)	2 (0.6)		1 (0.3)	0 (0.0)
Dyspepsia	2 (0.6)	2 (0.6)		3 (0.9)	2 (0.6)		2 (0.6)	1 (0.3)
Gastritis	0 (0.0)	0 (0.0)		3 (0.9)	2 (0.6)		1 (0.3)	0 (0.0)
Abnormal Stools	2 (0.6)	2 (0.6)		2 (0.6)	2 (0.6)		0 (0.0)	0 (0.0)
Vomiting	1 (0.3)	0 (0.0)		2 (0.6)	1 (0.3)		3 (0.9)	2 (0.3)
Dry Mouth	0 (0.0)	0 (0.0)		1 (0.3)	1 (0.3)		0 (0.0)	0 (0.0)
Flatulence	1 (0.3)	1 (0.3)		1 (0.3)	1 (0.3)		0 (0.0)	0 (0.0)
Increased Appetite	0 (0.0)	0 (0.0)		1 (0.3)	1 (0.3)		0 (0.0)	0 (0.0)
Melena	1 (0.3)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Anorexia	2 (0.6)	1 (0.3)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Gastrointestinal Hemorrhage	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	1 (0.3)
Hepatitis	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.6)	1 (0.3)
Intestinal Obstruction	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Periodontal Abscess	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Rectal Hemorrhage	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
BODY AS A WHOLE	18* (5.2)	7* (2.0)		17 (4.9)	4 (1.2)		25 (7.2)	7 (2.0)
Headache	2 (0.6)	1 (0.3)		7 (2.0)	1 (0.3)		8 (2.3)	4 (1.1)
Abdominal Pain	6 (1.7)	6 (1.7)		3 (0.9)	1 (0.3)		4 (1.1)	3 (0.9)
Back Pain	1 (0.3)	0 (0.0)		2 (0.6)	0 (0.0)		0 (0.0)	0 (0.0)
Moniliasis	1 (0.3)	1 (0.3)		2 (0.6)	2 (0.6)		0 (0.0)	0 (0.0)
Pain	1 (0.3)	0 (0.0)		2 (0.6)	0 (0.0)		1 (0.3)	0 (0.0)
Accidental Injury	3 (0.9)	0 (0.0)		1 (0.3)	0 (0.0)		7 (2.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		1 (0.3)	0 (0.0)
Flu Syndrome	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		1 (0.3)	0 (0.0)
Generalized Edema	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Abscess	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Chest Pain	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.6)	0 (0.0)
Infection	4 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.6)	0 (0.0)
Intentional Injury	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Neck Pain	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
RESPIRATORY SYSTEM	11 (3.2)	0 (0.0)		15 (4.3)	0 (0.0)		10 (2.9)	0 (0.0)
Bronchitis	1 (0.3)	0 (0.0)		4 (1.2)	0 (0.0)		2 (0.6)	0 (0.0)
Pneumonia	1 (0.3)	0 (0.0)		3 (0.9)	0 (0.0)		2 (0.6)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)		2 (0.6)	0 (0.0)		1 (0.3)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

* The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

Table 126. All and Associated Adverse Events by Body System - All Patients Who Received Study Medication
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir								Cefuroxime N = 349			
	600 mg QD N = 349				300 mg BID N = 345				All	Assoc		
	All	Assoc			All	Assoc						
RESPIRATORY SYSTEM (continued)												
Rhinitis	5	(1.4)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Asthma	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Epistaxis	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Sinusitis	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)
Lung Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Lung Edema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Respiratory Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Voice Alteration	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SKIN AND APPENDAGES	11	(3.2)	9	(2.6)	9	(2.6)	6	(1.7)	4	(1.1)	1	(0.3)
Rash	7	(2.0)	5	(1.4)	5	(1.4)	4	(1.2)	1	(0.3)	0	(0.0)
Herpes Zoster	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.6)	1	(0.3)	1	(0.3)
Cutaneous Moniliasis	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fungal Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Herpes Simplex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Sweating	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(0.6)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR SYSTEM	5	(1.4)	0	(0.0)	5	(1.4)	0	(0.0)	3*	(0.9)	0	(0.0)
Pulmonary Embolus	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Palpitation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Vasodilation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Angina Pectoris	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Atrial Fibrillation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Congestive Heart Failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Cor Pulmonale	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Heart Failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial Infarction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Syncope	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tachycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
METABOLIC AND NUTRITIONAL	1*	(0.3)	0	(0.0)	4	(1.2)	1	(0.3)	1	(0.3)	0	(0.0)
Alkaline Phosphatase Increased	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dehydration	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Edema	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Hyperuricemia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Hypokalemia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral Edema	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

* The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 126. All and Associated Adverse Events by Body System - All Patients Who Received Study Medication
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir						Cefuroxime N = 349	
	600 mg QD N = 349			300 mg BID N = 345			All	Assoc
	All	Assoc		All	Assoc			
HEMIC AND LYMPHATIC SYSTEM	0 (0.0)	0 (0.0)		3 (0.9)	0 (0.0)		1 (0.3)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)		2 (0.6)	0 (0.0)		0 (0.0)	0 (0.0)
Eosinophilia	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Ecchymosis	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
NERVOUS SYSTEM	3 (0.9)	1 (0.3)		3 (0.9)	0 (0.0)		5* (1.4)	1 (0.3)
Delirium	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Dizziness	1 (0.3)	1 (0.3)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Neuralgia	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Agitation	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Anxiety	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Hallucinations	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	1 (0.3)
Insomnia	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Nervousness	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Paresthesia	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Somnolence	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.6)	0 (0.0)
UROGENITAL SYSTEM	8 (2.3)	3 (0.9)		3 (0.9)	1 (0.3)		6 (1.7)	1 (0.3)
Urinary Tract Disorder	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Urinary Tract Infection	2 (0.6)	0 (0.0)		1 (0.3)	0 (0.0)		1 (0.3)	0 (0.0)
Vaginal Moniliasis ^b	2 (1.6)	2 (1.6)		1 (0.7)	1 (0.7)		1 (0.7)	1 (0.7)
Albuminuria	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Cystitis	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Dysuria	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.6)	0 (0.0)
Glycosuria	1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Urine Abnormality	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Vaginitis ^b	1 (0.8)	1 (0.8)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
MUSCULOSKELETAL SYSTEM	2 (0.6)	0 (0.0)		2 (0.6)	0 (0.0)		1 (0.3)	0 (0.0)
Arthralgia	1 (0.3)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Myalgia	1 (0.3)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Arthritis	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
SPECIAL SENSES	1 (0.3)	1 (0.3)		2 (0.6)	1 (0.3)		6 (1.7)	2 (0.6)
Ear Pain	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)		1 (0.3)	1 (0.3)		0 (0.0)	0 (0.0)
Conjunctivitis	1 (0.3)	1 (0.3)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Ear Disorder	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.6)	0 (0.0)
Otitis Media	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)
Taste Loss	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	1 (0.3)
Taste Perversion	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.3)	1 (0.3)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

* The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

^b The percentages are based on the number of women in each treatment group: 126 in the cefdinir QD group, 144 in the cefdinir BID group, and 139 in the cefuroxime group.

Adverse Events by Age, Sex and Race

Overall, there was very little difference in adverse event or associated adverse event rates between patients 18 to <65 years of age and patients ≥65 years of age. The incidence of diarrhea was somewhat lower in older patients treated with either cefdinir BID or cefuroxime (4% and 5%, respectively, versus 10% and 7% in younger patients). The incidence of diarrhea in patients receiving cefdinir QD was approximately the same in patients 18 to <65 or ≥65 years of age (10% vs 9%). Other adverse events occurred with such low frequency that there were no obvious differences between the two age groups. Women had a slightly higher overall incidence of adverse events than men in all treatment groups. This was partly due to a higher incidence of adverse events in the urogenital system, including urinary tract infection, vaginal moniliasis, and vaginitis. Other than this, no particular body system or event appeared to be responsible for the difference. The rates of associated adverse events were more similar between the sexes: 14% of both men and women treated with cefdinir QD experienced an associated adverse event, and 11% of men and women treated with cefuroxime experienced an associated adverse event. In the cefdinir BID group, 10% of men versus 17% of women experienced an associated adverse event. This difference was primarily due to small differences in adverse event rates in the body as a whole (moniliasis, headache abdominal pain), digestive system (diarrhea), and urogenital system (vaginal moniliasis, vaginitis). Over 90% of patients in the study were white. No clinically important differences in adverse event profiles were apparent based on race.

***Medical officer's note:** This safety data is consistent with that submitted in other sections of this application and resembles other extended spectrum cephalosporins. There are no surprises.*

Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events

Deaths

Seven patients died during this study. None of the deaths was considered to be associated with study medication.

Table 127. Patients Who Died During the Study

Center	Patient Number	Age (yr), Sex	Cause of Death	Day of Last Dose of Study Drug	Day of Death
Cefdinir 600 mg QD					
6	7	53, M	Murder ^a	Unknown	Unknown (≤ 16)
26	10	80, M	Cardiopulmonary Decompensation	8	12
Cefdinir 300 mg BID					
3	10	78, M	Pulmonary Embolism	1	2
17	118	80, M	Respiratory Failure ^b	7	11
Cefuroxime Axetil 250 mg BID					
24	11	74, M	Respiratory Failure ^b	10	21
28	6	83, M	Cardiopulmonary Arrest	4	4
34	4	68, F	Cerebral Embolism	10	48

^a This patient was presumed to have been a murder victim. His body was found some time after death occurred, so the time of death and number of doses of cefdinir taken are not known.

^b Due to AECD

Medical officer's note: Review of the narratives submitted by the Applicant show no suggestion of treatment effect in the deaths. All but one of the deaths (i.e., the murder) occurred in seriously debilitated patients and were not unexpected.

Serious Adverse Events

Twenty patients experienced a serious, nonfatal adverse event. Only one was considered by the investigator to be treatment-associated: Patient 91, Center 17, experienced a severe gastrointestinal hemorrhage after four days of treatment with cefuroxime that the investigator considered possibly related to study drug.

Patient 4, Center 34, was hospitalized for a myocardial infarction on Day 16 after completing treatment with cefuroxime. While still hospitalized, she experienced a probable cerebral embolism and died. Thus, although her myocardial infarction was a serious adverse event and not directly fatal, this patient is listed in the deaths section of this report.

Medical officer's note: Review of the narratives submitted by the Applicant do not convincingly suggest that the treatment was etiologic.

Table 128. Nonfatal Serious Adverse Events
(Page 1 of 2)

Center	Patient Number	Age (yr), Sex	Adverse Event ^a	Intensity	Relationship to Study Medication ^b	Study Day of Onset	Management of Study Drug	Outcome ^c
Cefdinir 600 mg QD								
20	4	66, M	Asthma	Severe	Definitely Not	31	None	Not Yet Recovered
24	8	60, M	Pneumonia	Moderate	Unlikely	11	None	Recovered
34	31	70, F	Angina (Angina Pectoris)	Moderate	Definitely Not	32	None	Recovered
35	11	53, F	Exacerbation of Chronic Bronchitis (Bronchitis)	Severe	Definitely Not	4	Discontinued	Recovered
	48	42, F	Syncope	Moderate	Definitely Not	3	None	Recovered
36	3	19, M	Asthma	Severe	Definitely Not	11	None	Recovered
	12	41, F	Congestive Heart Failure	Severe	Definitely Not	20	None	Recovered
Cefdinir 300 mg BID								
1	21	75, M	Bronchitis	Severe	Definitely Not	5	Discontinued	Recovered
17	67	67, M	Epistaxis	Severe	Unlikely	21	None	Recovered
26	2	73, M	Tonsillitis (Pharyngitis)	Moderate	Unlikely	15	None	Recovered
	14	64, M	Pneumonia	Moderate	Definitely Not	16	None	Recovered
34	22	79, M	Exacerbation of Bronchitis (Bronchitis)	Moderate	Definitely Not	35	None	Recovered
			Chronic Obstructive Pulmonary Disease (Lung Disorder)	Moderate	Definitely Not	35	None	Recovered
35	40	75, M	Worsening of AECB (Bronchitis)	Severe	Definitely Not	15	None	Recovered
			Ear Ache (Ear Pain)	Severe	Definitely Not	15	None	Recovered

^a When the investigator and COSTART terms differ, the COSTART term appears in parentheses.

^b According to the investigator

^c As of the last study visit

TABLE 128. Nonfatal Serious Adverse Events
(Page 2 of 2)

Center	Patient Number	Age (yr), Sex	Adverse Event ^a	Intensity	Relationship to Study Medication ^b	Study Day of Onset	Management of Study Drug	Outcome ^c
Cefuroxime 250 mg BID								
1	13	77, M	Chronic Bronchitis (Bronchitis)	Moderate	Definitely Not	4	Discontinued	Recovered
17	91	34, M	Gastrointestinal Bleed (Gastrointestinal Hemorrhage)	Severe	Possibly	4	Discontinued	Recovered
	134	78, M	Laceration of Eyebrow Area (Accidental Injury)	Moderate	Definitely Not	39	None	Recovered
			Laceration of Chin (Accidental Injury)	Moderate	Definitely Not	39	None	Recovered
			Bruising of Hand (Ecchymosis)	Moderate	Definitely Not	39	None	Recovered
24	4	72, M	Atypical Chest Pain (Chest Pain)	Moderate	Unlikely	4	None	Recovered
	5	90, M	Hip Fracture (Accidental Injury)	Severe	Unlikely	12	None	Recovered/ Sequelae
31	6	83, F	Lung Oedema (Lung Edema)	Moderate	Definitely Not	24	None	Recovered
			Pneumonia	Mild	Definitely Not	24	None	Recovered
35	1	81, F	Atrial Fibrillation	Moderate	Definitely Not	5	None	Recovered

^a When the investigator and COSTART terms differ, the COSTART term appears in parentheses.

^b According to the investigator

^c As of the last study visit

Withdrawals Due to Adverse Events

Forty-five patients discontinued treatment because of an adverse event; 17 (5%) from the cefdinir QD group, 15 (4%) from the cefdinir BID group, and 13 (4%) from the cefuroxime group. Nine patients withdrew from the study after completing treatment but before the LTFU because of an adverse event; 3 (1%) from the cefdinir QD group, 2 (1%) from the cefdinir BID group, and 4 (1%) from the cefuroxime group.

Diarrhea, which occurred in all three treatment groups, was the most common reason patients discontinued medication. Two percent of cefdinir QD-treated patients, 2% of cefdinir BID-treated patients, and 1% of cefuroxime-treated patients discontinued treatment because of diarrhea.

Rash caused discontinuation in 1% of both cefdinir treatment groups, and in none of cefuroxime-treated patients. Other events that caused discontinuation or withdrawal in two or more patients included abdominal pain, headache, pulmonary embolus, dyspepsia, nausea, bronchitis, sinusitis, and urticaria.

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ON ORIGINAL**

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 1 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event ^a	Relationship to Study Medication ^b	Study Day of Onset	Study Day Drug Discontinued	Outcome ^c
Cefdinir 600 mg QD							
11	12	47, F	Melaena (Melena)	Unlikely	7	7	Recovered
17	42	49, M	Diarrhoea (Diarrhea)	Probably	2	7	Recovered
	107	74, M	Abdominal Pain	Possibly	3	3	Recovered
	115	67, F	Diarrhoea (Diarrhea)	Probably	2	6	Recovered
	129	70, M	Diarrhoea (Diarrhea)	Probably	2	5	Recovered
	136	46, M	Dyspepsia	Probably	3	5	Recovered
	142	43, F	Diarrhoea (Diarrhea)	Probably	3	4	Recovered
18	2	40, M	Diarrhoea (Diarrhea)	Probably	7	7	Recovered
	5	63, M	Urticarial Rash (Urticaria)	Probably	6	6	Recovered
20	18	57, M	Conjunctivitis	Probably	4	6	Recovered
			Exanthema (Rash)	Probably	5		Recovered
	40	22, F	Diarrhoea (Diarrhea)	Definitely	1	2	Recovered
	60	38, M	Gastralgia (Abdominal Pain)	Probably	1	2	Recovered
			Diarrhoea (Diarrhea)	Probably	1		Recovered
			Cephalgia (Headache)	Probably	1		Recovered

^a If the investigator and COSTART terms differ, the COSTART term appears in parentheses.

^b According to the investigator

^c As of the last study visit

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 2 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event ^a	Relationship to Study Medication ^b	Study Day of Onset	Study Day Drug Discontinued	Outcome ^c
Cefdinir 600 mg QD (cont)							
20	66	44, F	Diarrhoea (Diarrhea)	Possibly	4	6	Recovered
			Exanthema (Rash)	Possibly	5		Recovered
	67	55, M	Allergic Exanthema (Rash)	Probably	5	7	Recovered
	83	50, M	Gastralgia (Abdominal Pain)	Possibly	2	3	Recovered
			Nausea	Possibly	2		Recovered
32	35	43, M	Sinusitis	Definitely Not	12	Completed Medication	Recovered
34	28	71, F	Urinary Tract Infection	Definitely Not	18	Completed Medication	Recovered
	31	70, F	Angina (Angina Pectoris)	Definitely Not	32	Completed Medication	Recovered
35	11	53, F	Exacerbation of Chronic Bronchitis (Bronchitis)	Definitely Not	4	4	Recovered
	59	50, F	Urticaria	Definitely	1	1	Recovered
Cefdinir 300 mg BID							
1	21	75, M	Bronchitis	Definitely Not	5	5	Recovered
3	10	78, M	Pulmonary Embolism (Pulmonary Embolus)	Definitely Not	2	1	Died
6	32	31, F	Diarrhoea (Diarrhea)	Probably	3	8	Recovered
			Allergic Exanthema (Rash)	Probably	5		Recovered
	39	56, F	Neuralgia	Unlikely	2	3	Recovered

^a If the investigator and COSTART terms differ, the COSTART term appears in parentheses.

^b According to the investigator

^c As of the last study visit

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 3 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event ^a	Relationship to Study Medication ^b	Study Day of Onset	Study Day Drug Discontinued	Outcome ^c
<i>Cefdinir 300 mg BID (cont)</i>							
11	16	68, M	Herpes Zoster	Unlikely	6	6	Recovered/Sequelae
	24	56, F	Diarrhoea (Diarrhea)	Probably	4	4	Recovered
	29	72, M	Pyrosis (Dyspepsia)	Possibly	2	2	Recovered
17	87	33, F	Erythematous Rash (Rash)	Probably	5	5	Recovered
	90	52, F	Flatulence	Possibly	6	8	Recovered
	113	42, M	Diarrhoea (Diarrhea)	Possibly	4	3	Recovered
20	9	75, M	Diarrhoea (Diarrhea)	Probably	2	5	Not Yet Recovered
	51	55, F	Allergic Exanthema (Rash)	Definitely	1	2	Recovered
	62	64, F	Gastralgia (Abdominal Pain)	Unlikely	5	6	Recovered
			Diarrhoea (Diarrhea)	Possibly	5		Recovered
			Cephalgia (Headache)	Unlikely	5		Recovered
			Palpitation	Unlikely	5		Recovered
			Exanthema (Rash)	Unlikely	5		Recovered
22	7	34, M	Dysphagia	Definitely Not	2 ^d	2	Not Yet Recovered
25	7	58, F	Pulmonary Embolism (Pulmonary Embolus)	Definitely Not	8	Completed Medication	Recovered

^a If the investigator and COSTART terms differ, the COSTART term appears in parentheses.

^b According to the investigator

^c As of the last study visit

^d Present at baseline, not treatment-emergent

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 4 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event ^a	Relationship to Study Medication ^b	Study Day of Onset	Study Day Drug Discontinued	Outcome ^c
Cefdinir 300 mg BID (cont)							
30	11	26, F	Diarrhoea (Diarrhea)	Definitely	3	4	Recovered
			Nausea	Definitely	3		Recovered
35	40	75, M	Worsening of AECSB (Bronchitis)	Definitely Not	15	Completed Medication	Recovered
Cefuroxime 250 mg BID							
1	13	77, M	Chronic Bronchitis (Bronchitis)	Definitely Not	4	5	Recovered
11	33	74, M	Nausea	Probably	2	5	Recovered
17	91	34, M	Gastrointestinal Bleed (Gastrointestinal Hemorrhage)	Possibly	4	4	Recovered
	94	57, M	Nausea	Possibly	1	3	Recovered
	102	57, F	Diarrhoea (Diarrhea)	Probably	2	4	Recovered
18	1	75, F	Diarrhoea (Diarrhea)	Probably	10	10	Recovered
20	32	67, M	Diarrhoea (Diarrhea)	Probably	3	5	Recovered
24	11	74, M	COPD Exacerbation (Lung Disorder)	Unlikely	13	Completed Medication	Died
25	6	72, M	Diarrhea	Possibly	2	5	Recovered
28	6	83, M	Bronchoaspiration (Respiratory Disorder)	Definitely Not	4	4	Died
29	6	75, M	Epigastralgia (Abdominal Pain)	Probably	2	6	Recovered
32	34	50, M	Sinusitis	Definitely Not	19	Completed Medication	Recovered

^a If the investigator and COSTART terms differ, the COSTART term appears in parentheses.

^b According to the investigator

^c As of the last study visit

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 5 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event ^a	Relationship to Study Medication ^b	Study Day of Onset	Study Day Drug Discontinued	Outcome ^c
<i>Cefuroxime 250 mg BID (cont)</i>							
34	4	68, F	Myocardial Infarction (Myocardial Infarct)	Definitely Not	16	Completed Medication	Died*
35	12	55, F	Chest Discomfort (Chest Pain)	Definitely Not	7	7	Recovered
			Otitis Media	Definitely Not	7		Recovered
	62	67, F	Hallucinations	Definitely	3	3	Recovered
			Itching (Pruritus)	Definitely	3		Recovered
37	8	83, M	Tachycardia	Unlikely	9	9	Recovered
	32	52, M	Sinusitis	Definitely Not	20	Completed Medication	Recovered

* If the investigator and COSTART terms differ, the COSTART term appears in parentheses.

^b According to the investigator

^c As of the last study visit

* Died of a pulmonary embolism following coronary bypass surgery

TABLE 130. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir		Cefuroxime N = 349
	600 mg QD N = 349	300 mg BID N = 345	
BODY AS A WHOLE	3* (0.9)	1* (0.3)	2 (0.6)
Abdominal Pain	3 (0.9)	1 (0.3)	1 (0.3)
Headache	1 (0.3)	1 (0.3)	0 (0.0)
Chest Pain	0 (0.0)	0 (0.0)	1 (0.3)
CARDIOVASCULAR SYSTEM	1 (0.3)	3 (0.9)	2 (0.6)
Pulmonary Embolus	0 (0.0)	2 (0.6)	0 (0.0)
Palpitation	0 (0.0)	1 (0.3)	0 (0.0)
Angina Pectoris	1 (0.3)	0 (0.0)	0 (0.0)
Myocardial Infarction	0 (0.0)	0 (0.0)	1 (0.3)
Tachycardia	0 (0.0)	0 (0.0)	1 (0.3)
DIGESTIVE SYSTEM	11 (3.2)	9* (2.6)	7 (2.0)
Diarrhea	8 (2.3)	6 (1.7)	4 (1.1)
Dyspepsia	1 (0.3)	1 (0.3)	0 (0.0)
Dysphagia	0 (0.0)	1 (0.3)	0 (0.0)
Flatulence	0 (0.0)	1 (0.3)	0 (0.0)
Nausea	1 (0.3)	1 (0.3)	2 (0.6)
Gastrointestinal Hemorrhage	0 (0.0)	0 (0.0)	1 (0.3)
Melena	1 (0.3)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM	0 (0.0)	1 (0.3)	1 (0.3)
Neuralgia	0 (0.0)	1 (0.3)	0 (0.0)
Hallucinations	0 (0.0)	0 (0.0)	1 (0.3)
RESPIRATORY SYSTEM	2 (0.6)	2 (0.6)	5 (1.4)
Bronchitis	1 (0.3)	2 (0.6)	1 (0.3)
Lung Disorder	0 (0.0)	0 (0.0)	1 (0.3)
Respiratory Disorder	0 (0.0)	0 (0.0)	1 (0.3)
Sinusitis	1 (0.3)	0 (0.0)	2 (0.6)
SKIN AND APPENDAGES	5 (1.4)	5 (1.4)	1 (0.3)
Rash	3 (0.9)	4 (1.2)	0 (0.0)
Herpes Zoster	0 (0.0)	1 (0.3)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	1 (0.3)
Urticaria	2 (0.6)	0 (0.0)	0 (0.0)
SPECIAL SENSES	1 (0.3)	0 (0.0)	1 (0.3)
Conjunctivitis	1 (0.3)	0 (0.0)	0 (0.0)
Otitis Media	0 (0.0)	0 (0.0)	1 (0.3)
UROGENITAL SYSTEM	1 (0.3)	0 (0.0)	0 (0.0)
Urinary Tract Infection	1 (0.3)	0 (0.0)	0 (0.0)

* The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have ≥1 adverse event per system.

Medical officer's note: Review of this information shows no unexpected findings: all are consistent with administration of extended spectrum cephalosporins.

Clostridium difficile-Associated Diarrhea

Only one patient who discontinued treatment because of diarrhea was tested for *C. difficile*. Patient 6, Center 25, discontinued treatment with cefuroxime on Day 5 and later had a positive test for *C. difficile* toxin. An endoscopy was not performed.

Medical officer's note: *This is not unexpected with the administration of extended spectrum cephalosporins.*

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CONCLUSIONS

- ▶ Cefdinir 600 mg qd and cefdinir 300 mg bid are as effective in the treatment of AECB as cefuroxime.
- ▶ Cefdinir 600 mg qd and cefdinir 300 mg bid demonstrated adequate efficacy against the pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Moraxella catarrhalis* in the treatment of AECB. In addition, the Applicant has submitted two adequately and well controlled pivotal clinical trials in support of the CAP indication. These add significant strength to this single trial in support of the AECB indication.
- ▶ Cefdinir and cefuroxime are equally well-tolerated by most patients. Most adverse events experienced by cefdinir-treated patients are mild and do not require treatment discontinuation.

/S/

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Concurrences:

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cc: Orig NDAs 50-674 & 50-675

HFD-520/Division File
HFD-520/CSO Bduvall-Miller
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague
HFD-520/Pharm/FPelsor
HFD-520/MO/HHamilton
HFD-520/TL/JSoreth
HFD-725/Stat/AChakravarty
HFD-725/Stat/TL/DLin
HFD-40/DO MAC/S. Spearman

Introduction to the Skin and Skin Structure Infection Indications

The applicant is requesting approval of an NDA for Omnicef Capsules and Omnicef Suspension for the treatment of uncomplicated skin and skin structure infections caused by *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *K. pneumoniae*. In support of this request, data from two clinical trials, an adult study with 34 investigators and 975 patients, and a pediatric study with 18 investigators and 394 patients, were submitted.

Both studies were randomized, comparative, multicenter studies with two parallel treatment groups. The adult study involved therapy with the capsule formulation and was double-blinded. The pediatric study involved therapy with the oral suspension and was investigator-blinded. In both studies, cephalexin was the comparator agent.

In the adult study, according to the applicant, there were 178 evaluable patients with 215 pathogens in the cefdinir treatment group and 204 evaluable patients with 247 pathogens in the cephalexin treatment group. The eradication rate for all pathogens in the cefdinir group was 200/215 (93.0%) compared to 221/247 (89.5%) for all pathogens in the cephalexin treatment group. The clinical cure rates for cefdinir and cephalexin were 148/178 (83.1%) and 163/204 (79.9%), respectively. Based on the 95% confidence interval, the two treatment arms were shown to be therapeutically equivalent.

In the FDA clinical reviewer's analysis of the data, the results were evaluated according to the specific organisms requested and the baseline diagnoses. There was a total of 181 evaluable cefdinir patients and 203 evaluable cephalexin patients with skin and skin structure infections caused by the four organisms requested. The overall clinical cure rates for cefdinir and cephalexin were 153/181 (84.5%) and 156/203 (76.8%), respectively.

The clinical cure rate for cefdinir patients with infections caused by *S. aureus* was 122/143 (85.3%) compared to 133/165

(80.6%) for cephalexin patients with similar infections due to *S. aureus*. The clinical cure rates for cefdinir patients and cephalexin patients with infections due to *S. pyogenes* were 14/17 (82.4%) and 10/11 (90.9%), respectively. For the evaluable patients with infections due to *S. agalactiae*, the clinical cure rates were 10/13 (76.9%) for the cefdinir group and 10/18 (55.6%) for the comparator group. Likewise, the clinical cure rates for cefdinir patients and cephalexin patients with infections caused by *K. pneumoniae* were 7/8 (87.5%) and 3/9 (33.3%), respectively.

In the pediatric study, according to the applicant, there were 118 evaluable patients with 166 pathogens in the cefdinir treatment group and 113 evaluable patients with 156 pathogens in the cephalexin treatment group. The eradication rate for all pathogens in the cefdinir group was 165/166 (99.4%) compared to 152/156 (97.4%) for all pathogens in the cephalexin group. The clinical cure rates for cefdinir and cephalexin were 116/118 (98.3%) and 106/113 (93.8%), respectively. Based on the 95% confidence interval, the two treatment arms were shown to be therapeutically equivalent.

In the FDA clinical reviewer's analysis, there was a total of 116 evaluable cefdinir patients and 116 evaluable cephalexin patients with skin and skin structure infections caused by the four organisms requested. The overall clinical cure rates for cefdinir and cephalexin were 114/116 (98.3%) and 110/116 (94.8%), respectively.

The clinical cure rate for pediatric cefdinir patients with infections caused by *S. aureus* was 73/75 (97.3%) compared to 73/77 (94.8%) for cephalexin patients with similar infections. The clinical cure rates for pediatric cefdinir patients and cephalexin patients with infections due to *S. pyogenes* were 34/34 (100%) and 31/33 (93.9%), respectively. For the evaluable pediatric patients with infections due to *S. agalactiae*, the clinical cure rates were 4/4 (100%) for the cefdinir group and 6/6 (100%) for the cephalexin group. The clinical cure rate for cefdinir pediatric patients with infections due to *K. pneumoniae* was 3/3 (100%); while in the comparator group, there were no evaluable patients with an infection caused by *K. pneumoniae*.

In both studies, diarrhea was the most frequently reported adverse event among the cefdinir patients. There were 78 reports (16.5%) of diarrhea in the adult study and 15 cases (10.6%)

2. Introduction/Skin Infections

reported in the pediatric study. Other frequently reported adverse events included nausea with 17 reports (3.6%) and moniliasis with 14 reports (7.3%) in the adult study. Infection with 13 cases (9.2%) was the second most frequently reported adverse event, following diarrhea, in the pediatric study.

The applicant has submitted sufficient data to show that cefdinir is safe and effective in the treatment of uncomplicated skin and skin structure infections in both an adult and pediatric population. Data from both clinical trials show the drug to be effective in the eradication of various types of skin and skin structure infections caused by *S. aureus* and *S. pyogenes*, when used as directed. The data regarding *S. agalactiae* and *K. pneumoniae* are insufficient because of the much smaller number of cases involving these organisms, their occurrence primarily in polymicrobial infections, and their questionable role at this time as pathogens or contaminants in these infections.

Therefore, it is recommended that cefdinir capsules and cefdinir suspension be approved for the treatment of uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β -lactamase producing strains) and *Streptococcus pyogenes*.

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NDA 50-739 (Cefdinir 300 mg capsules)
NDA 50-749 (Cefdinir oral suspension, 125 mg/mL)

Clinical Review of Studies for Skin and Skin Structure Infections (SSSI)

Indication: Uncomplicated Skin and Skin Structure Infections.

Title and Study Number: A phase 3, 10-day, double-blind, randomized, comparative, multi center study of cefdinir (CI-983) versus cephalixin in the treatment of patients with skin and skin structure infections (SSSI) (protocol 983-8).

Objective: To evaluate the efficacy and safety of cefdinir (300 mg bid or 600 mg qd) and cephalixin (500 mg qid) in the treatment of adults and adolescents with SSSI.

Clinical reviewer's note: Originally, patients were randomly assigned to 1 of 3 treatment groups to receive cefdinir 600 mg QD or 300 mg BID, or cephalixin 500 mg QID for 10 days. The 600 mg cefdinir QD treatment group in the original study was discontinued due to a theoretical concern about maintaining therapeutic blood and tissue concentrations of cefdinir for extended periods, i.e., QD dosing might not be adequate for treating serious, potentially life-threatening SSSIs. After the protocol was amended to stop cefdinir QD enrollment, patients continued to be randomized to cefdinir BID and cephalixin. Subsequent patient numbers associated with cefdinir QD were skipped and the next sequential patient number was used. A second deviation from the original protocol involved changing the test-of-cure determination from the short-term follow-up visit (3 to 7 days posttherapy) to a longer term follow-up visit (7 to 16 days posttherapy).

Study Design: This was a double-blind, randomized, comparative, multi center study with 2 parallel treatment groups. Patients were assigned by a blinded randomization code to receive one of two dosage regimens of cefdinir or cephalixin for 10 days. Screening, dosing, follow-up visits, and the test-of-cure (TOC) visit window used in data analyses are illustrated in Figure 1. The short-term follow-up (STFU) and long-term follow-up (LTFU) visits are defined in the figure. The TOC visit window shown in the figure was determined after the study was completed; it provided a more stringent test of the study medication.

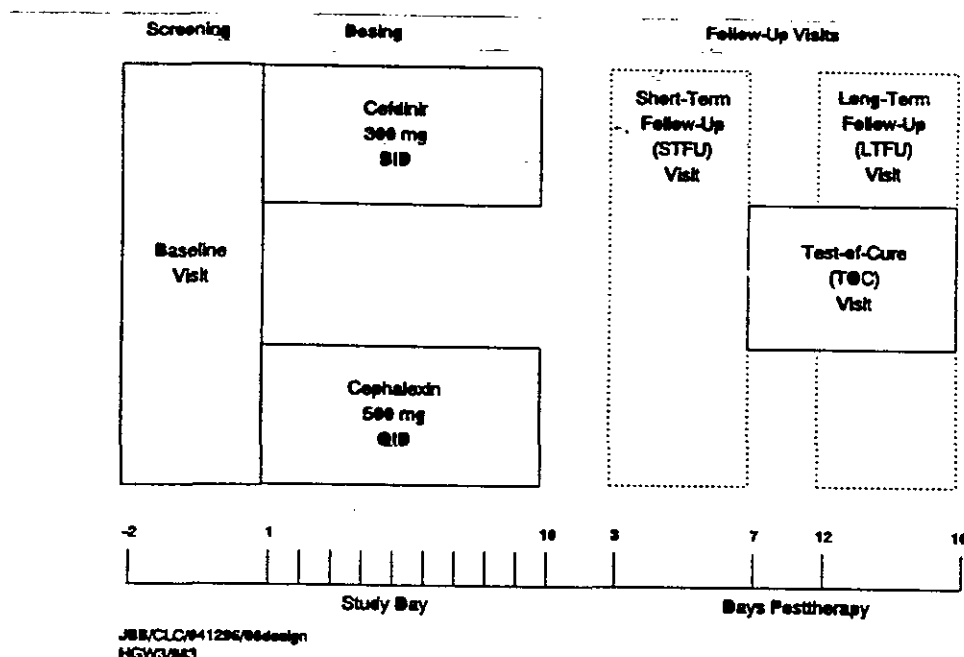


FIGURE 1. Protocol 983-8 Study Design

Protocol Overview

Population and Inclusion/Exclusion Criteria (as duplicated from the Applicant's submission)

Population: Participants included males and nonpregnant, nonlactating females aged 13 years or older. Females were also to be either adolescent and not sexually active, using an effective means of contraception and have a negative pregnancy test at baseline, postmenopausal, or surgically sterilized.

Inclusion Criteria: Eligible patients had acute bacterial SSSIs serious enough to warrant oral antimicrobial therapy. SSSIs could include: abscess, infected burn, carbuncle, cellulitis, infected dermatitis, erysipelas, folliculitis, furuncle, impetigo, paronychia, acutely infected ulcer, or an infected traumatic/surgical wound. Bacterial etiology of the infection from a skin or wound aspirate, biopsy, or swab was to be confirmed by a positive culture.

Eligible patients were also required to have at least 2 clinical signs and symptoms for study entry including pain/tenderness, erythema/warmth, swelling, induration, fluctuation, or drainage.

Exclusion Criteria: Patients were to be excluded from participating in the study for any of the following reasons:

- A disease or condition that precluded evaluation of the therapeutic response, including a terminal illness;
- Pregnancy or lactation;
- Hepatic disease, obstruction of the biliary tract, bilirubin or hepatic enzyme levels (AST, ALT) >2 times the upper limit of normal;
- Baseline serum creatinine >1.5 times the upper limit of normal or creatinine clearance <30 mL/min;
- Previous antibacterial therapy within 7 days of the start of study medication, except for patients who had no more than a 24-hour course of therapy within that 7-day period provided that at least 5 half-lives of the previous antibacterial had passed;
- Hypersensitivity to β -lactams;
- Baseline pathogen(s) known to be resistant to either study medication prior to randomization;
- Concomitant infection(s) requiring systemic or topical antibacterial therapy, except metronidazole administered when a mixed aerobic/anaerobic infection was suspected;
- An infection thought to be purely anaerobic;
- Prior participation in this or any other cefdinir study;
- Radiographic evidence of the presence of osteomyelitis;
- Taking iron-containing medications concomitantly, including multivitamins with iron;
- Seeking treatment for the primary diagnosis of acne;
- Taking any other investigational compound within 4 weeks of study entry; or
- Taking probenecid concomitantly.

Clinical reviewer's note: Both the patient inclusion and exclusion criteria are consistent with the guidelines recently developed by the DAIDP.

Evaluability Criteria: Patients could be withdrawn from study medication because of insufficient efficacy, an adverse event, a clinical laboratory abnormality, lack of patient cooperation, patient request, failure to isolate a baseline pathogen, or isolation of a baseline pathogen resistant to either cefdinir or cephalexin. Reasons for withdrawal were reported on the appropriate case report form.

Confirmation of bacteriological etiology and lack of *in vitro* resistance to study medication was required for a patient to be

evaluatable for efficacy analyses. If these conditions were not met, a patient could be discontinued from study medication and given appropriate therapy. The investigator could continue to treat patients who had a baseline pathogen resistant to cefdinir or cephalexin (but not both) provided, in his or her judgement, they were exhibiting satisfactory clinical improvement.

When treatment was discontinued early, the following were to be completed: skin culture (from the baseline site of infection) and susceptibility testing, a clinical evaluation, a physical examination, clinical laboratory tests, as well as records of adverse events and concurrent medications. If additional antibiotics were not required at the time study medication was discontinued and the patient had received at least 3 days of study medication, both follow-up visits were scheduled to be completed. If additional antibiotics were required or if the patient had no baseline pathogen, follow-up visits were not requested.

Assessments of specific microbiologic and clinical parameters at the TOC visit, 7 to 16 days posttherapy, were used to evaluate the efficacy of cefdinir. Efficacy measures used included microbiologic eradication rate by pathogen, microbiologic eradication rate by patient, and clinical cure rate by patient.

Clinical reviewer's note: The reviewer agrees with the above evaluability criteria. The applicant strictly adhered to these criteria when determining patient outcome.

Endpoints Defined (Clinical and Microbiological)

The schedule of visits, examinations and evaluations for the patients in this study is shown in Table 1.

Each patient had a baseline evaluation within 48 hours prior to the initiation of therapy. This included a medical history, a physical examination, a clinical assessment of signs and symptoms (classified as absent, mild, moderate, or severe at each visit), specimen collection from the SSSI site, and clinical laboratory tests.

TABLE 1. Schedule of Clinical Observations and Laboratory Measurements

Procedure/Observation	Baseline	Day 1	Days 3-5	Day 10	Posttherapy Visits	
					3 to 7 Days	12 to 16 Days
Medical History	X					
Physical Examination ^a	X				X	X
Clinical Assessment of Signs and Symptoms ^a	X		X		X	X
Skin Culture from Baseline Site of Infection and Susceptibility Testing ^a	X				X	X
Adverse Events		X			X	X
Clinical Laboratory Testing ^{a,d}	X				X	X ^e
Investigator Assessment of Clinical Efficacy ^a					X	X
Radiographic Evaluation ^f	X					
Pharmacokinetic Specimen Collection ^g			X			
Dosing		X		X		

^a Prior to treatment (within 48 hours) or Day 1

^b Test-of-cure visit occurred 7 to 16 days posttherapy and was not defined in terms of the posttherapy visits.

^c Performed whenever a patient was withdrawn

^d Tests performed are listed in the protocol (Appendix A.2).

^e Performed only if abnormalities were detected at the previous visit

^f Only to rule out osteomyelitis

^g Optional; at selected centers, blood was collected 4 hours after the morning dose of study medication for analysis of plasma-drug concentration (Addendum A, Appendix A.2).

Microbiological endpoints: Specimens were collected for culture and susceptibility testing at baseline, STFU and TOC, if material was available. If multiple sites of infection existed at baseline, the most severely affected (ie, the largest, most purulent, or most erythematous) site was to be chosen and followed throughout the entire length of the study. All isolated bacteria suspected of being pathogens were identified to genus and species, and testing for β -lactamase production was performed when appropriate. Organisms cultured from SSSI sites and classified as contaminants or not otherwise speciated were not considered pathogens in this study.

All isolates were tested for susceptibility to cefdinir and cephalixin using both broth microdilution and Kirby-Bauer disk diffusion methods. Test procedures as well as minimum inhibitory concentration (MIC) and zone diameter standards conformed with National Committee for Clinical Laboratory Standards (NCCLS) guidelines.

Microbiologic Response by Pathogen: At the TOC visit, the microbiologic response of each baseline pathogen was classified as:

- **Eradication** - Baseline pathogen not present in follow-up culture or no material available to culture at follow-up;
- **Persistence** - Baseline pathogen present in follow-up culture; or
- **Not Assessable** - No follow-up data.

Patients with multiple pathogens provided multiple observations in the analysis of microbiological efficacy on a per pathogen basis. A patient's microbiologic response was evaluated based on baseline and posttherapy culture results. The microbiologic eradication rate by pathogen was defined as the percentage of pathogens present in baseline specimens that were eliminated (or presumed to be eliminated) from specimens obtained at the TOC visit.

Microbiologic Response by Patient: At the TOC visit, patients were classified by their overall microbiologic response based on the baseline and 7- to 16-day posttherapy culture results as:

- **Patients With Eradication** - All baseline pathogens eradicated or no material available to culture at follow-up (ie, presumed eradication);
- **Patients With Persistence** - Presence of at least 1 baseline pathogen in the TOC culture; or
- **Not Assessable** - No proven baseline pathogen or no follow-up data.

The microbiologic eradication rate by patient was the percentage of patients in whom all baseline pathogens were eradicated. Each patient provided 1 observation.

Superinfection - The appearance of a nonbaseline pathogen at any time during treatment through the TOC visit and a clinical worsening or failure at the corresponding clinical assessment.

If a patient had a nonbaseline pathogen at follow-up, the sponsor reviewed the progress of the patient's clinical signs and symptoms and determined whether or not the patient had experienced a superinfection.

Clinical reviewer's note: The reviewer agrees with these definitions which are consistent with guidelines requiring the complete eradication of an organism to establish efficacy.

Clinical endpoints: An evaluation of each patient's signs and symptoms was made at baseline, after 3-5 days of therapy, at the short term follow up, and the long term follow up (TOC). The following criteria were used by each investigator at both the STFU and the TOC visits:

- **Cure** - Disappearance of all baseline site signs and symptoms
- **Improvement** - Satisfactory remission but not complete disappearance of baseline site signs and symptoms
- **Failure** - Worsening or no significant remission of baseline site signs and symptoms
- **Not assessable** - Cannot assess the patient

Clinical reviewer's note: The reviewer accepts the applicant's definitions for these endpoints which are very similar to those recently proposed by the DAIDP in its draft document. It is important to note that most of the clinical failures were patients who showed no improvement; their conditions did not necessarily worsen.

The protocol specified that investigator and sponsor assessments of patient clinical response would be made. Based on the investigator's assessment of signs and symptoms at the TOC and before unblinding, the sponsor used a scoring algorithm to calculate an assessment of clinical efficacy.

A combination of investigator and sponsor assessments, referred to as the combined investigator/sponsor clinical assessment in this report, was used as the primary measure of patient clinical response in the efficacy analyses (Table 2). The purpose of the combined investigator/sponsor clinical assessment was to address patients who were classified as improvement or not assessable by the investigator and reclassify them as cure, failure, or not assessable using the sponsor assessment.

TABLE 2. Determination of Combined Investigator/Sponsor Clinical Assessment

Sponsor Assessment	Investigator Assessment			
	Cure Disappearance of all baseline site clinical signs and symptoms	Improvement Satisfactory remission but not complete disappearance of baseline site clinical signs and symptoms	Failure Worsening or no significant remission of baseline site clinical signs and symptoms	Not Assessable Cannot assess the patient
Cure ≥50% decrease in clinical score at TOC relative to baseline	Cure	Cure ^a	Failure	Cure ^a
Failure <50% decrease in clinical score at TOC relative to baseline	Cure	Failure ^a	Failure	Failure ^a
Not Assessable No baseline clinical signs and symptoms or no follow-up clinical assessment	Cure	Not Assessable ^a	Failure	Not Assessable ^a

TOC = Test-of-cure.

^a The sponsor assessment was substituted for the investigator assessment.

The clinical cure rate was the percentage of patients identified as cured using the combined investigator/sponsor clinical assessment. All patients who had postbaseline surgical intervention were considered treatment failures by the sponsor. Since only TOC data were used in these analyses, follow-up clinical scores were only calculated for the TOC visit, not for the STFU and LTFU visits.

Clinical reviewer's note: The reviewer finds the definitions and clinical assessment method to be acceptable.

Statistical Considerations:

Sample Size: This study was designed to use two-tailed 95% confidence intervals (CI) to assess the equivalence of response rates from evaluable patients without surgical intervention at admission who were treated with cefdinir BID or cephalixin. An overall response rate of 85% regardless of treatment was assumed.

This provided an 80% probability (power) that the limits of the 95% CI for the difference between the response rates (cefdinir BID minus cephalixin) would fall within the accepted equivalence range (± 15 percentage points) if the treatments were truly equivalent.

Originally this was a multi center study with three treatment arms: cefdinir 600 mg QD; cefdinir 300 mg BID; and cephalixin 500 mg QID. Each treatment arm was supposed to have 160 microbiologically evaluable patients for a total enrollment of 480 patients. When the cefdinir QD dosing arm was stopped, patients continued to be enrolled in the other two arms using a 1:1 randomization. A total of 476 patients were enrolled in the cefdinir BID arm and 479 in the cephalixin arm.

At TOC, the microbiologic eradication rates by pathogen and by patient were calculated for each treatment group in the evaluable (with and without surgical intervention), MITT, and ITT patient populations. Clinical cure rates were calculated for each treatment group in the evaluable (with and without surgical intervention), clinically evaluable, and the ITT patient populations.

Methods: Statistical analyses were performed across all diagnoses for the cefdinir BID and cephalixin treatment groups. Efficacy data summaries by baseline diagnosis were generated for each treatment group. No statistical analyses were performed on the efficacy or safety data collected from patients in the cefdinir QD treatment group; descriptive statistics, however, were calculated. All analyses and data summaries were prepared using SAS Version 6.

Two methods of investigating treatment equivalence at TOC were used. One method was based on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient (or each pathogen, for the by-pathogen case) in the analysis, and were calculated as the total number of cures or eradications in the study population, divided by the total number

of cases.

The second method used estimates of the response rates in which each center was given equal weight. These center-adjusted estimates and their standard errors were obtained from a model which contained terms for treatment group, study center, and treatment by center interaction.

The treatment difference was defined as cefdinir BID minus cephalixin. The estimated response rate differences and their standard errors were used to construct a two-tailed 95% confidence interval for the treatment difference, using a standard normal approximation. Each 95% confidence interval was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the 2 rates (pooled or center-adjusted) under comparison (Table 3). To demonstrate equivalence, each 95% confidence interval must contain 0 and its limits must fall within the indicated bounds.

TABLE 3. Fixed Criteria for Evaluating Treatment
Equivalence

Maximum Estimated Response Rate	Treatments are Equivalent if 95% Confidence Interval for Treatment Difference is Within Bounds
90% or greater	-10%, +10%
80%-89%	-15%, +15%
70%-79%	-20%, +20%

Statistical reviewer's note: The criteria for equivalence (Table 3) are to be clarified to be the following:

The maximum estimated response rates to be restated as greater than 90%, between 80% and 90%, and less than 80%, respectively. It is also to be noted that the upper boundary of the confidence interval is not held to a fixed percentage; the lower boundary is of critical importance. As stated by the sponsor, the confidence

interval must contain zero to demonstrate therapeutic equivalence.

The confidence intervals will be expressed as: $_{nt,nc}$ (lower limit, upper limit) $_{pt,pc}$, where nt = number of subjects in the treatment arm; nc = number of subjects in the control arm; pt = number of successes in the treatment arm; pc = number of successes in the control arm. Yates' continuity correction will be applied to the calculation of the confidence intervals.

Results of the two methods were compared for consistency. In this study, both methods agreed in all cases and the pooled analysis was presented as the final analysis.

Study Results

Demographics, Evaluability

The cefdinir group consisted of 20 patients who received a dosage of 600 mg QD and 476 patients who received a dosage of 300 mg BID. The QD dosing arm of the study was discontinued shortly after initiation due to a concern regarding appropriate therapeutic concentrations of cefdinir for extended periods. The following table shows the patient disposition, including the number of patients who were considered evaluable by each investigator.

TABLE 4. List of Investigators

* Center	Investigator	Number of Patients		
		Entered ^a	Completed ^b	Evaluable ^c
1	J. Applegate	22	12	5
2	R. Chiulli	25	9	9
3	H. Collins	4	1	1
4	K. Dowd	6	3	3
5	B. Lipsky	24	11	6
6	T. Littlejohn	71	40	22
7	Y. Lynfield	2	1	0
8	L. Parish	47	21	20 ^d
9	R. Paster	48	30	27
10	A. Puopolo	62	41	30
11	C. Rich	60	37	28
12	M. Sperling	59	28	13
13	S. Weakley	41	32	23
15	P. DiLorenzo	86	60	34
16	R. Smith	4	4	3
17	R. Snow	24	10	5
18	R. Schwartz	15	13	7
19	A. Herbert	43	29	22
20	Z. Munk	52	34	19
21	V. Elinoff	37	23	14 ^d
22	A. Balin	47	36	21
23	D. Stewart	32	23	12
24	S. Davis	30	24	14
25	C. Mathias	5	4	1
28	A. Rosenthal	2	1	0
29	R. McCabe	2	2	1
30	C. Khurana	3	2	1
31	D. Stryker	5	4	4
32	R. Margolis	31	26	21
33	C. DeAbate	7	3	0
36	D. Williams	27	12	7
49	R. Herdener	4	2	2
50	M. Goldman	23	14	7
52	W. Gooch	25	16	15
Total		975	608	391

^a Randomized to treatment

^b Completed treatment and long-term follow-up visit (12-16 days posttherapy)

^c Included in evaluable patient analyses

^d Some patients in this total completed the test-of-cure visit (7-16 days posttherapy) and met all evaluability criteria, but withdrew prior to the long-term follow-up visit window. These patients do not appear in the completed column.

Patient Demographics: The patient demographics for all patients (ITT) and evaluable patients according to the sponsor are summarized in the following tables.

TABLE 5. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir				Cephalexin		Total	
	QD N = 20		BID N = 476		N = 479		N = 975	
Sex								
Male	13	(65.0)	282	(59.2)	283	(59.1)	578	(59.3)
Female	7	(35.0)	194	(40.8)	196	(40.9)	397	(40.7)
Race								
White	12	(60.0)	383	(80.5)	400	(83.5)	795	(81.5)
Black	4	(20.0)	49	(10.3)	40	(8.4)	93	(9.5)
Asian	0	(0.0)	4	(0.8)	1	(0.2)	5	(0.5)
Other	4	(20.0)	40	(8.4)	38	(7.9)	82	(8.4)
Age, yr								
Median	36.0		36.0		37.0		36.0	
Range	15 - 81		13 - 88		13 - 86		13 - 88	
Distribution								
13 to <18	1	(5.0)	23	(4.8)	34	(7.1)	58	(5.9)
18 to <65	18	(90.0)	381	(80.0)	375	(78.3)	774	(79.4)
≥65	1	(5.0)	72	(15.1)	70	(14.6)	143	(14.7)
Baseline Diagnosis*								
Abscess	4	(20.0)	146	(30.7)	129	(26.9)	279	(28.6)
Infected Traumatic/Surgical Wound	4	(20.0)	80	(16.8)	96	(20.0)	180	(18.5)
Folliculitis	7	(35.0)	42	(8.8)	37	(7.7)	86	(8.8)
Cellulitis	3	(15.0)	35	(7.4)	43	(9.0)	81	(8.3)
Paronychia	0	(0.0)	41	(8.6)	39	(8.1)	80	(8.2)
Infected Dermatitis	1	(5.0)	39	(8.2)	33	(6.9)	73	(7.5)
Furuncle	0	(0.0)	31	(6.5)	38	(7.9)	69	(7.1)
Impetigo	0	(0.0)	32	(6.7)	30	(6.3)	62	(6.4)
Carbuncle	0	(0.0)	17	(3.6)	19	(4.0)	36	(3.7)
Acutely Infected Ulcer	1	(5.0)	10	(2.1)	11	(2.3)	22	(2.3)
Infected Burn	0	(0.0)	3	(0.6)	4	(0.8)	7	(0.7)

Other = Cuban, Hawaiian, Hispanic/Latin, Indian, Native American, Pacific Islander, Persian, Spanish, Syrian, Tongan.

* A total of 113 patients had conditions predisposing them to SSSIs: 3 treated with cefdinir QD, 47 treated with cefdinir BID, and 63 treated with cephalexin. Section 5.1.4 contains information about patients with predisposing conditions.

TABLE 6. Patient Characteristics - Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir				Cephalexin		Total	
	QD N = 9		BID N = 178		N = 204		N = 391	
Sex								
Male	6	(66.7)	111	(62.4)	118	(57.8)	235	(60.1)
Female	3	(33.3)	67	(37.6)	86	(42.2)	156	(39.9)
Race								
White	5	(55.6)	139	(78.1)	165	(80.9)	309	(79.0)
Black	2	(22.2)	15	(8.4)	18	(8.8)	35	(9.0)
Asian	0	(0.0)	4	(2.2)	1	(0.5)	5	(1.3)
Other	2	(22.2)	20	(11.2)	20	(9.8)	42	(10.7)
Age, yr								
Median	32.0		35.0		35.0		35.0	
Range	15 - 43		13 - 88		14 - 82		13 - 88	
Distribution								
13 to <18	1	(11.1)	13	(7.3)	14	(6.9)	28	(7.2)
18 to <65	8	(88.9)	142	(79.8)	171	(83.8)	321	(82.1)
≥65	0	(0.0)	23	(12.9)	19	(9.3)	42	(10.7)
Baseline Diagnosis								
Abscess	1	(11.1)	44	(24.7)	44	(21.6)	89	(22.8)
Infected Traumatic/Surgical Wound	3	(33.3)	32	(18.0)	44	(21.6)	79	(20.2)
Paronychia	0	(0.0)	23	(12.9)	22	(10.8)	45	(11.5)
Impetigo	0	(0.0)	18	(10.1)	17	(8.3)	35	(9.0)
Cellulitis	1	(11.1)	17	(9.6)	17	(8.3)	35	(9.0)
Infected Dermatitis	1	(11.1)	19	(10.7)	15	(7.4)	35	(9.0)
Folliculitis	3	(33.3)	9	(5.1)	20	(9.8)	32	(8.2)
Furuncle	0	(0.0)	10	(5.6)	12	(5.9)	22	(5.6)
Carbuncle	0	(0.0)	3	(1.7)	6	(2.9)	9	(2.3)
Acutely Infected Ulcer	0	(0.0)	3	(1.7)	5	(2.5)	8	(2.0)
Infected Burn	0	(0.0)	0	(0.0)	2	(1.0)	2	(0.5)

Other = Hawaiian, Hispanic/Latin, Indian, Pacific Islander, Spanish, Syrian, Tongan.

Clinical reviewer's note: The study arms (cefdinir bid and cephalexin qid) appear balanced with regard to gender, race, age

and baseline diagnoses.

Statistical reviewer's note: Cefdinir BID and cephalixin are balanced with regard to demographic characteristics - sex (p-value = 0.369), race (p-value = 0.446), and age (p-value = 0.466).

Drug Administration: The distribution for the duration of therapy for all patients according to the applicant is provided in the table below.

**TABLE 7. Patient Exposure to Study
Medication - All Patients
(Number of Patients)**

Days on Study Medication	Cefdinir		Cephalexin N = 479
	QD N = 20	BID N = 476	
1	1	2	2
2	1	8	6
3	1	14	8
4	3	12	17
5	1	30	27
6	1	25	19
7	0	14	19
8	0	16	12
9	0	4	4
10	3	116	133
11	9	218	215
12	0	1	4
13	0	1	1
14	0	0	1
Median	10	10	10
Unknown	0	15	11

Clinical reviewer's note: The median patient exposure to cefdinir was 10 days, the treatment duration proposed in the label. Among the cefdinir BID group, 334 (70%) patients received 10-11 days of therapy. Patients who started cefdinir or

cephalexin at or after noon on Day 1 finished medication on the morning of or later on Day 11, which accounts for the number of patients with 11 days of treatment.

Unevaluable Patients: The following patients were excluded from all efficacy analysis by the applicant, and the reasons for exclusion were as follows:

TABLE 8. Reasons Patients Were Not Evaluable at TOC
(Number of Patients)

	Cefdinir		Cephalexin
	QD	BID	
Randomized to Treatment	20	476	479
Reasons Patients Were Excluded From			
Evaluable Analyses^a			
Clinical Evaluation Out of Date	5	123	104
Range ^b			
Culture ^c Out of Date Range ^b	6	112	104
Medication Not As Prescribed	7	100	91
No Proven Baseline Pathogen	7	195	177
Resistant Baseline Pathogen(s)	1	64	65
Culture ^c Missed	0	28	20
Clinical Evaluation Missed	1	18	14
Prior Antibacterial	0	7	6
Concurrent Antibacterial ^b	1	5	8
No Baseline Susceptibility Tests	0	1	0
Wrong Indication	0	0	1
Not Evaluable	11	298	275

^a Patients who had multiple reasons for being excluded from efficacy analyses are included under each reason that applied.

^b Patients who had microbiologic and/or clinical assessments done early or who took a concurrent antibacterial because they were early failures were not removed from the evaluable analyses for this reason.

^c Baseline or TOC culture

Of the 476 patients in the cefdinir BID group, 298 were not

evaluable for both microbiological and clinical analysis, leaving a total of 178 evaluable cefdinir patients. In the cephalixin group, 275 patients out of 479 enrolled patients were unevaluable, leaving a total of 204 evaluable cephalixin patients. In both drug treatment groups, the absence of a baseline pathogen was the most common reason for exclusion.

Efficacy

Table 9 compares the number of patients randomized to treatment (i.e., the ITT population) to the number of patients in the other populations. Four different patient groups were analyzed for efficacy as follows:

TABLE 9. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	Cefdinir				Cephalexin	
	QD		BID			
Intent-to-Treat (ITT) ^a	20	(100.0)	476	(100.0)	479	(100.0)
Modified Intent-to-Treat (MITT) ^b	13	(65.0)	273	(57.4)	292	(61.0)
Clinically Evaluable ^c	11	(55.0)	287	(60.3)	303	(63.3)
Evaluable ^d	9	(45.0)	178	(37.4)	204	(42.6)
With Uncomplicated SSSIs	5	(25.0)	124	(26.1)	138	(28.8)
Without Surgical Intervention at Admission	9	(45.0)	138	(29.0)	159	(33.2)
With Surgical Intervention at Admission	0	(0.0)	40	(8.4)	45	(9.4)

^a All patients who were randomized to treatment

^b Total number of patients who had the correct indication and received study medication, at least 1 baseline pathogen, and a follow-up skin culture attempted

^c Total number of patients who were evaluable without regard to microbiologic evaluability criteria

^d Total number of patients who were microbiologically and clinically evaluable at TOC

Clinical reviewer's note: The reviewer examined all case report forms and summaries for patients considered to be nonevaluable and clinical failures. The summaries for all patients with pathogens requested for inclusion in the SSSI indication were reviewed along with case report forms when necessary. All of the data was found to be consistent with that presented in the sponsor's report.

Clinical Efficacy

A summary of the clinical response rates by patient according to the investigators is shown in Table 10. The investigators rated patients on the basis of improvements in sign/symptoms as cures, improvements, failures, and not assessable. The results show the cefdinir 300 mg BID regimen to be comparable to the control drug in the response rates for all categories.

Table 10. Summary of clinical response rates by patient as determined by investigators at the test of cure visit - All patients.

Clinical Response	Number (%) of Patients			
	Cefdinir 300 mg BID		Cephalexin	
	N	%	N	%
Cure	269	56.5	285	59.5
Improvement	117	24.6	118	24.6
Failure	59	12.4	55	11.5
Not Assessable	31	6.5	21	4.4
Total	476	100.0	479	100.0

The primary measure of patient clinical response in the following tables for efficacy analysis was a combination of investigator and sponsor assessments referred to as the combined investigator/sponsor clinical assessment. The purpose for this combined assessment was to account for patients considered as improvements or not assessable by the investigators. The sponsor reclassified them as cures, failures, or not assessable using the sponsor's criteria. Table 11 shows the results of this reclassification for the patients who are both microbiologically and clinically evaluable.

TABLE 11. Investigator vs Combined Investigator/Sponsor Clinical Assessments at the Test-of-Cure Visit - Evaluable Patients

Investigator Assessment	Combined Investigator/Sponsor Clinical Assessment			
	Cefdinir BID N = 178		Cephalexin N = 204	
	Cure	Failure	Cure	Failure
Cure	132	0	145	0
Improvement	16	9	18	14
Failure	0	21	0	27

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TABLE 12. Clinical Cure Rate^a by Patient (According to Their Baseline Pathogens) Across Baseline Diagnoses at the Test-of-Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
<i>Staphylococcus aureus</i>	103/118	87.3	110/133	82.7
<i>Streptococcus agalactiae</i>	2/3	66.7	5/6	83.3
<i>Streptococcus pyogenes</i>	8/10	80.0	4/5	80.0
<i>Streptococcus</i> Group G	1/1	100.0	0/1	0.0
Gram-Negative				
<i>Acinetobacter calcoaceticus</i> var <i>lwoffi</i>	2/2	100.0	1/1	100.0
<i>Citrobacter amalonaticus</i>	1/1	100.0	0/0	—
<i>Citrobacter diversus</i>	0/1	0.0	0/0	—
<i>Enterobacter agglomerans</i>	0/0	—	1/1	100.0
<i>Escherichia coli</i>	1/2	50.0	5/6	83.3
<i>Escherichia hermanii</i>	0/1	0.0	0/0	—
<i>Haemophilus parahaemolyticus</i>	0/0	—	1/1	100.0
<i>Haemophilus parainfluenzae</i>	1/2	50.0	1/1	100.0
<i>Klebsiella oxytoca</i>	0/0	—	1/1	100.0
<i>Klebsiella pneumoniae</i>	1/1	100.0	1/3	33.3
<i>Pasteurella multocida</i>	1/1	100.0	0/0	—
<i>Proteus mirabilis</i>	3/4	75.0	6/6	100.0
<i>Providencia rettgeri</i>	0/0	—	1/1	100.0
<i>Xanthomonas maltophilia</i>	0/0	—	1/1	100.0
Multiple	24/31	77.4	25/37	67.6
Total	148/178	83.1	163/204	79.9

n/N = Number of patients who were cured/total number of patients.

^a Based on combined investigator/sponsor clinical assessments

In Table 12 the clinical cure rates for all microbiologically evaluable patients according to the baseline pathogen isolated is shown. For the 178 cefdinir patients, 148 (83.1%) were cures, while 163 of the 204 (79.9%) cephalexin patients were cured.

Clinical reviewer's note: The data presented in Table 12 are based on the assignment of one organism as the primary pathogen for each evaluable patient. In reality, the majority of the patients in the study had mixed or polymicrobial infections consisting of two or more organisms, both pathogenic and non-pathogenic species. For example, Table 12 shows three cefdinir patients who had infections with positive cultures for *Streptococcus agalactiae* only. There were 25 cefdinir patients with infections involving *Streptococcus agalactiae*, 13 of them evaluable patients. All of those patients had mixed infections with other microorganisms.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rate by patients at the TOC visit, the 95% confidence intervals being 178,204 (-0.0506, 0.1155) 83.18, 79.98.

TABLE 13. Clinical Cure Rate* by Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	38/44	86.4	39/44	88.6
Infected Traumatic/Surgical Wound	27/32	84.4	32/44	72.7
Paronychia	19/23	82.6	18/22	81.8
Impetigo	15/18	83.3	12/17	70.6
Cellulitis	15/17	88.2	15/17	88.2
Infected Dermatitis	14/19	73.7	12/15	80.0
Furuncle	9/10	90.0	9/12	75.0
Folliculitis	6/9	66.7	14/20	70.0
Carbuncle	3/3	100.0	6/6	100.0
Acutely Infected Ulcer	2/3	66.7	4/5	80.0
Infected Burn	0/0	—	2/2	100.0
Across Diagnosis	148/178	83.1	163/204	79.9

n/N = Number of patients who were cured/total number of patients.

* Based on combined investigator/sponsor clinical assessments

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalixin with respect to the clinical cure rate by baseline diagnosis at the TOC visit, the 95% confidence intervals being 178,204 (-0.0506, 0.1155) 83.1%, 79.9%.

TABLE 14. Microbiologic vs Clinical Response Rates at the Test-of-Cure Visit - Evaluable Patients
[Number (%) of Patients]

Microbiologic Response	Clinical Response ^a	
	Cure	Failure
Cefdinir BID, N = 178		
Patients With Eradication	144 (80.9)	20 (11.2)
Patients With Persistence	4 (2.2)	10 (5.6)
Cephalexin, N = 204		
Patients With Eradication	158 (77.5)	23 (11.3)
Patients With Persistence	5 (2.5)	18 (8.8)

^a Based on combined investigator/sponsor clinical assessments

Clinical reviewer's note: There were four cefdinir patients who had persistent *S. aureus*, obtained from swabs, present at the TOC visit. All were clinical cures and devoid of all signs/symptoms associated with their infections. Two of the patients had impetigo, one had an abscess, and the fourth had paronychia. There were five cephalixin patients who were clinical cures with persistent pathogens at the TOC visit. Three patients had *S. aureus*, one patient had *S. aureus* and *P. mirabilis*, and the fifth patient had *P. mirabilis* and *S. haemolyticus* isolated from their baseline cultures. All clinical signs/symptoms were absent at the TOC visit.

Clinically evaluable patients: The following table shows the clinical cure rate for all clinically evaluable patients, without regard to the presence or absence of a baseline pathogen, according to their diagnosis.

TABLE 15. Clinical Cure Rate* by Baseline Diagnosis at the Test-of-Cure Visit
-Clinically Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	66/83	79.5	73/82	89.0
Infected Traumatic/Surgical Wound	36/44	81.8	39/54	72.2
Paronychia	24/28	85.7	21/25	84.0
Impetigo	21/24	87.5	17/23	73.9
Cellulitis	20/23	87.0	16/21	76.2
Folliculitis	19/25	76.0	23/34	67.6
Infected Dermatitis	18/25	72.0	15/20	75.0
Furuncle	16/18	88.9	18/23	78.3
Carbuncle	9/11	81.8	13/13	100.0
Acutely Infected Ulcer	3/5	60.0	4/5	80.0
Infected Burn	1/1	100.0	3/3	100.0
Across Diagnosis	233/287	81.2	242/303	79.9

n/N = Number of patients cured/total number of patients.

* Based on combined investigator/sponsor clinical assessments

Clinical reviewer's note: There were 287 clinically evaluable cefdinir patients with 233 of them clinically cured (81.2%). Of the 303 cephalexin patients, 242 were cured for a 79.9% cure rate.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rate by baseline diagnosis for clinically evaluable patients at the TOC visit, the 95% confidence intervals being $_{287,303}(-0.0541, 0.0805)$ 81.2%, 79.9%.

Superinfections: Thirty-three patients in the cefdinir BID group and 23 patients in the cephalexin group had superinfections. The following table shows the 54 superinfecting pathogens isolated

from the cefdinir patients and the 31 organisms isolated from the cephalixin patients. Nineteen of the cefdinir pathogens were resistant to it, while 14 of the cephalixin pathogens were resistant to cephalixin.

TABLE 16. Patients With Superinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir BID N = 476	Cephalixin N = 479
Gram-Positive*		
<i>Enterococcus faecalis</i>	2	1
<i>Staphylococcus epidermidis</i>	8	6
<i>Staphylococcus hominis</i>	1	0
<i>Staphylococcus simulans</i>	2	1
<i>Streptococcus agalactiae</i>	0	1
<i>Streptococcus anginosus</i>	1	0
Gram-Negative*		
<i>Acinetobacter calcoaceticus</i> var <i>anitratus</i>	1	1
<i>Enterobacter cloacae</i>	2	2
<i>Proteus mirabilis</i>	0	1
<i>Pseudomonas aeruginosa</i>	0	1
<i>Pseudomonas fluorescens</i>	0	1
<i>Pseudomonas stutzeri</i>	0	1
<i>Sphingomonas paucimobilis</i>	1	0
Multiple	15	7
Total	33	23

* Pathogens appearing as sole superinfecting pathogens

Clinical reviewer's analysis of data: The applicant has requested the approval of an indication for the treatment of uncomplicated skin and skin structure infections caused by

susceptible strains of *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *K. pneumoniae*. Therefore, a closer examination of the data concerning these four organisms is necessary. In the analysis of the clinical data presented by the applicant, these four organisms are grouped together with regard to the various baseline diagnoses. In the following tables, the clinical cure rates for each pathogen from the microbiologically evaluable patients is listed, according to the specific SSSI diagnosis.

Table 17. Clinical cure rates - Evaluable patients with *S. aureus* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 143		Cephalexin n = 165	
	Cure	Failure	Cure	Failure
Impetigo	14	2	10	4
Abscess	33	4	29	4
Paronychia	14	3	14	3
Infected Dermatitis	14	3	12	3
Infected Wound	21	4	27	9
Cellulitis	9	1	13	1
Folliculitis	4	2	11	6
Infected Ulcer	2	1	4	0
Furuncle	8	1	8	2
Carbuncle	3	0	3	0
Infected Burn	0	0	2	0
Total	122	21	133	32

Table 17 shows the clinical cure rates, according to baseline diagnosis, for the 143 cefdinir patients and 165 cephalexin

patients with *S. aureus* as a baseline pathogen. There were 122 cefdinir patients (85.3%) and 133 cephalixin patients (80.6%) who were cured. The numbers of patients in both treatment groups for each of the diagnostic categories were very similar with the exception of patients with folliculitis and infected burns.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalixin with respect to clinical cure rate with *S. aureus*, the 95% confidence interval (with continuity correction) being $143.165 (-0.0432, 0.1373)$ 85.3%, 80.6%.

Table 18. Clinical cure rates - Evaluable patients with *S. pyogenes* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 17		Cephalixin n = 11	
	Cure	Failure	Cure	Failure
Impetigo	1	2	0	0
Abscess	0	0	1	0
Paronychia	0	0	3	0
Infected Dermatitis	1	0	1	0
Infected Wound	5	0	2	0
Cellulitis	4	1	2	1
Folliculitis	2	0	1	0
Furuncle	1	0	0	0
Total	14	3	10	1

Table 18 shows the results for the 17 evaluable cefdinir patients and the 11 evaluable cephalixin patients with *S. pyogenes* as a baseline pathogen. There were 14 cures (82.4%) and three failures (17.6%) in the cefdinir group, while the cephalixin

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-8/Adults

group had 10 cures (90.9%) and one failure (9.1%).

Statistical reviewer's note: Cefdinir fails to establish therapeutic equivalence to cephalexin with respect to the clinical cure rates in evaluable patients with *S. pyogenes*. The exact 95% confidence interval is $_{17,11} (-0.4953, 0.2844)$ $_{82.4\%, 90.9\%}$, the asymptotic 95% confidence interval is $_{17,11} (-0.3340, 0.1628)$ $_{82.4\%, 90.9\%}$.

Table 19. Clinical cure rates - Evaluable patients with *S. agalactiae* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 13		Cephalexin n = 18	
	Cure	Failure	Cure	Failure
Impetigo	0	1	2	2
Abscess	3	1	2	1
Paronychia	2	1	0	1
Infected Dermatitis	0	0	1	1
Infected Wound	3	0	3	1
Cellulitis	2	0	0	0
Folliculitis	0	0	0	2
Infected Ulcer	0	0	1	0
Carbuncle	0	0	1	0
Total	10	3	10	8

Among the 13 evaluable cefdinir patients with *S. agalactiae* as a baseline pathogen, there were 10 cures and 3 failures for a 76.9% cure rate. For the 18 evaluable cephalexin patients, there were 10 cures and eight failures for a 55.6% cure rate.

Clinical reviewer's note: It should be noted that all 13 evaluable cefdinir patients had mixed infections with other microorganisms present. Along with the *S. agalactiae*, six of these patients had *S. aureus*, seven patients had a gram negative rod, two had *S. epidermidis*, one had *Enterococcus*, and one had *C. albicans*.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalixin with respect to clinical cure rates due to *S. agalactiae*. The 95% exact confidence interval is $_{13,18} (-0.1504, 0.5987)$ $_{76.9\%,55.6\%}$ and the 95% asymptotic confidence interval is $_{13,18} (-0.1106, 0.5379)$ $_{76.9\%,55.6\%}$. It is to be noted that the sample sizes are not adequate to ensure acceptable level of power to the statistical inferences obtained.

Table 20. Clinical cure rates - Evaluable patients
with *K. pneumoniae* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 8		Cephalexin n = 9	
	Cure	Failure	Cure	Failure
Impetigo	0	1	1	1
Abscess	1	0	1	0
Paronychia	2	0	1	2
Infected Wound	2	0	0	2
Cellulitis	1	0	0	0
Folliculitis	1	0	0	0
Infected Ulcer	0	0	0	1
Total	7	1	3	6

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-8/Adults

Among the eight evaluable cefdinir patients with *K. pneumoniae* as a baseline pathogen, there were seven cures (87.5%) and one failure (12.5%). For the nine evaluable cephalixin patients with *K. pneumoniae*, there were three cures (33.3%) and six failures (66.7%).

Clinical reviewer's note: All of the cefdinir patients, except for one patient with paronychia, had mixed infections with other organisms. The cefdinir patient who failed therapy had impetigo with four organisms (*E. faecium*, *S. aureus*, *S. agalactiae*, and *K. pneumoniae*).

Statistical reviewer's note: It is to be noted that the sample size is not adequate to ensure acceptable power to the statistical inferences.

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Table 21. Clinical cure rates - Summary of Evaluable patients with requested organisms according to diagnosis.

Baseline Diagnosis	Cefdinir n = 181		Cephalexin n = 203	
	Cure	Failure	Cure	Failure
Impetigo	15	6	13	7
Abscess	37	5	33	5
Paronychia	18	4	18	6
Infected Dermatitis	15	3	14	4
Infected Wound	31	4	32	12
Cellulitis	16	2	15	2
Folliculitis	7	2	12	8
Carbuncle	9	1	8	2
Infected Burn	0	0	2	0
Infected Ulcer	2	1	5	1
Carbuncle	3	0	4	0
Total	153	28	156	47

Table 21 shows a summary of the evaluable patients with all of the requested organisms according to diagnosis and their outcomes. Among the patients treated with cefdinir, there were 153 cures (84.5%) and 28 failures (15.5%). For the cephalexin patients, there were 156 cures (76.8) and 47 failures (23.2%).

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rates with the requested organisms, the 95% confidence interval being 181,203 (-0.0067, 0.1604) 84.5%, 76.8%.

Microbiology

Table 22 shows the eradication rates for the applicant's proposed baseline pathogens at the Test of Cure visit for the 178 evaluable patients in the cefdinir group and the 204 evaluable patients in the cephalexin group.

TABLE 22 Microbiologic Eradication Rate by Baseline Isolate at the Test-of-Cure Visit
Evaluable Patients

Baseline Pathogen	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
<i>Enterococcus faecalis</i>	0/0	—	1/1	100.0
<i>Enterococcus faecium</i>	1/1	100.0	0/0	—
<i>Staphylococcus aureus</i>	131/143	91.6	145/165	87.9
<i>Streptococcus agalactiae</i>	13/13	100.0	16/18	88.9
<i>Streptococcus pyogenes</i>	17/17	100.0	11/11	100.0
<i>Streptococcus</i> Group G	2/2	100.0	5/6	83.3
Gram-Negative				
<i>Acinetobacter calcoaceticus</i> var <i>lwoffi</i>	4/4	100.0	4/4	100.0
<i>Alcaligenes faecalis</i>	0/0	—	1/1	100.0
<i>Citrobacter amalonaticus</i>	1/1	100.0	0/0	—
<i>Citrobacter diversus</i>	½	50.0	0/0	—
<i>Citrobacter freundii</i>	1/1	100.0	1/1	100.0
<i>Enterobacter agglomerans</i>	4/4	100.0	4/4	100.0
<i>Escherichia coli</i>	4/4	100.0	12/13	92.3
<i>Escherichia hermannii</i>	1/1	100.0	0/0	—
<i>Haemophilus parahaemolyticus</i>	0/0	—	1/1	100.0
<i>Haemophilus parainfluenzae</i>	2/2	100.0	1/1	100.0
<i>Klebsiella oxytoca</i>	2/2	100.0	2/2	100.0
<i>Klebsiella pneumoniae</i>	8/8	100.0	8/9	88.9
<i>Pasteurella multocida</i>	1/1	100.0	0/0	—
<i>Proteus mirabilis</i>	6/8	75.0	7/8	87.5
<i>Proteus vulgaris</i>	1/1	100.0	0/0	—
<i>Providencia rettgeri</i>	0/0	—	1/1	100.0
<i>Xanthomonas maltophilia</i>	0/0	—	1/1	100.0
Total	200/215	93.0	221/247	89.4

n/N = Number of pathogens eradicated/total number of pathogens.

In the cefdinir group, 200 of 215 (93.0%) isolates were eradicated at the test of cure visit, while in the comparator

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-8/Adults

drug group, 221 of 247 (89.5%) isolates were eradicated.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalexin with regard to overall microbiologic eradication by baseline isolate at the test of cure visit. When overall eradication is considered [95% confidence interval being 215,247 (-0.0201, 0.0911) 93%,89.4%] as well as when only patients with *S. aureus* as a baseline pathogen are considered [95% confidence interval is 143,165 (-0.0366, 0.1112) 91.6%,87.9%]

TABLE 23. Microbiologic Eradication Rate by Isolate and Baseline Diagnosis at the Test-of-Cure Visit - Isolates From Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	44/48	91.7	48/50	96.0
Infected Traumatic/Surgical Wound	36/40	90.0	43/53	81.1
Paronychia	28/30	93.3	31/33	93.9
Cellulitis	22/22	100.0	21/21	100.0
Infected Dermatitis	22/23	95.7	18/19	94.7
Impetigo	20/23	87.0	15/21	71.4
Folliculitis	12/12	100.0	19/23	82.6
Furuncle	11/11	100.0	12/12	100.0
Carbuncle	3/3	100.0	6/6	100.0
Acutely Infected Ulcer	2/3	66.7	6/7	85.7
Infected Burn	0/0	—	2/2	100.0
Across Diagnosis	200/215	93.0	221/247	89.4

n/N = Number of isolates eradicated/total number of isolates.

In Table 23 the microbial eradication rate according to baseline diagnosis for both treatment groups is shown. The eradication rates for both drugs are similar for the 11 diagnoses listed.

Clinical reviewer's note: The Evaluability Criteria for SSSI

presented to the Division's Anti-Infective Advisory Committee in March 1997 specified that the following organisms would be considered in uncomplicated SSSI: *Staphylococcus aureus* and *Streptococcus pyogenes*. Therefore, the eradication rates for *S. aureus* and *S. pyogenes* according to baseline diagnosis for both treatment groups is very important. That information was extracted from the above table and is shown in Tables 24 and 25.

Statistical reviewer's note: Cefdinir BID is therapeutically equivalent to cephalexin with regard to microbiologic eradication by pathogen and baseline diagnosis at the TOC visit, the 95% confidence interval being $_{215,247} (-0.0201; 0.0911)$ $_{93\%,89.4\%}$.

TABLE 24. Microbiologic Eradication Rate for *S. aureus* and Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	33/37	89.2	32/33	97.0
Infected Traumatic/Surgical Wound	23/25	92.0	28/36	77.8
Paronychia	16/17	94.1	15/17	88.2
Cellulitis	10/10	100.0	14/14	100.0
Infected Dermatitis	16/17	94.1	14/15	93.3
Impetigo	13/16	81.3	9/14	64.3
Folliculitis	6/6	100.0	14/17	82.4
Furuncle	9/9	100.0	10/10	100.0
Carbuncle	3/3	100.0	3/3	100.0
Acutely Infected Ulcer	2/3	66.7	4/4	100.0
Infected Burn	0/0	0.0	2/2	100.0
Across Diagnosis	131/143	91.6	145/165	87.9

n/N = Number of isolates eradicated/total number of isolates.

Clinical reviewer's note: Of the 143 isolates of *S. aureus* from

the cefdinir group, 118 were found as single pathogens and 25 were isolated from polymicrobial infections. Among the cephalixin patients with this organism, 133 of the isolates were found as single pathogens, while 32 occurred as part of a mixed infection. The overall eradication rate for the cefdinir group was 131/143 (91.6%) compared to 145/165 (87.9%) for the cephalixin patients.

Statistical reviewer's note: Cefdinir BID is therapeutically equivalent to cephalixin with respect to microbiologic eradication at TOC of *S. aureus* as a baseline pathogen, the 95% Confidence Interval being $_{143,165} (-0.0367, 0.1112)$ $_{91.6\%,87.9\%}$.

TABLE 25. Microbiologic Eradication Rate for *S. pyogenes* and Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID	Cephalixin
Abscess	0	1
Infected Traumatic/Surgical Wound	5	2
Paronychia	0	3
Cellulitis	5	3
Infected Dermatitis	1	1
Impetigo	3	0
Folliculitis	2	1
Furuncle	1	0
Across Diagnosis	17	11

There were 17 isolates of *S. pyogenes* among the evaluable cefdinir patients and 11 isolates among the cephalixin patients. All of them were eradicated from both treatment groups for a 100% eradication rate.

Clinical reviewer's note: Of the 17 isolates of *S. pyogenes* from the cefdinir treatment group, 10 were found as single pathogens and 7 were isolated from polymicrobial infections. In the cephalixin treatment group, five of the 11 isolates were found as single pathogens, while 7 isolates were from mixed infections.

TABLE 26. Microbiologic Eradication Rate by Patient (According to Their Baseline Cultures) at the Test-of-Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
<i>Staphylococcus aureus</i>	109/118	92.4	119/133	89.5
<i>Streptococcus agalactiae</i>	3/3	100.0	6/6	100.0
<i>Streptococcus pyogenes</i>	10/10	100.0	5/5	100.0
<i>Streptococcus</i> Group G	1/1	100.0	1/1	100.0
Gram-Negative				
<i>Acinetobacter calcoaceticus</i> var <i>lwoffii</i>	2/2	100.0	1/1	100.0
<i>Citrobacter amalonaticus</i>	1/1	100.0	0/0	—
<i>Citrobacter diversus</i>	0/1	0.0	0/0	—
<i>Enterobacter agglomerans</i>	0/0	—	1/1	100.0
<i>Escherichia coli</i>	2/2	100.0	6/6	100.0
<i>Escherichia hermanii</i>	1/1	100.0	0/0	—
<i>Haemophilus parahaemolyticus</i>	0/0	—	1/1	100.0
<i>Haemophilus parainfluenzae</i>	2/2	100.0	1/1	100.0
<i>Klebsiella oxytoca</i>	0/0	—	1/1	100.0
<i>Klebsiella pneumoniae</i>	1/1	100.0	2/3	66.7
<i>Pasteurella multocida</i>	1/1	100.0	0/0	—
<i>Proteus mirabilis</i>	4/4	100.0	5/6	83.3
<i>Providencia rettgeri</i>	0/0	—	1/1	100.0
<i>Xanthomonas maltophilia</i>	0/0	—	1/1	100.0
Multiple	27/31	87.1	30/37	81.1
Total	164/178	92.1	181/204	88.7

n/N = Number of patients with eradication/total number of patients.

In Table 26 the microbial eradication rate by patient according to the microorganisms isolated at baseline is shown for the 178

evaluable cefdinir patients and the 204 evaluable cephalixin patients. In the cefdinir group, 164 of 178 (92.1%) of the patients had their baseline organisms eradicated, while 181 of 204 (88.7%) cephalixin patients had their baseline organisms eradicated.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalixin with regard to microbiologic eradication by patient at the TOC visit, the 95% confidence interval being $_{178,204} (-0.0298, 0.0981)$ 92.1%, 88.7%.

TABLE 27. Microbiologic Eradication Rate by Patient and Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	40/44	90.9	42/44	95.5
Infected Traumatic/Surgical Wound	29/32	90.6	36/44	81.8
Paronychia	21/23	91.3	20/22	90.9
Infected Dermatitis	18/19	94.7	14/15	93.3
Cellulitis	17/17	100.0	17/17	100.0
Impetigo	15/18	83.3	11/17	64.7
Furuncle	10/10	100.0	12/12	100.0
Folliculitis	9/9	100.0	17/20	85.0
Carbuncle	3/3	100.0	6/6	100.0
Acutely Infected Ulcer	2/3	66.7	4/5	80.0
Infected Burn	0/0	—	2/2	100.0
Across Diagnosis	164/178	92.1	181/204	88.7

n/N = Number of patients with eradication/total number of patients.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalixin with regard to microbiologic eradication by patient and baseline diagnosis at the TOC visit, the 95% confidence interval being $_{178,204} (-0.0298, 0.0981)$ 92.1%, 88.7%.

Clinical Reviewer's Analysis of Data

The applicant has requested the approval of an indication for the treatment of uncomplicated skin and skin structure infections caused by susceptible strains of *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *K. pneumoniae*. Therefore, a closer examination of the data concerning these four organisms is necessary. The following table shows the microbiologic eradication rate for the requested pathogens from evaluable patients.

Table 28. Microbiologic eradication rate for requested pathogens from evaluable patients.

Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	131/143	91.6	145/165	87.9
<i>Streptococcus agalactiae</i>	13/13	100.0	16/18	88.9
<i>Streptococcus pyogenes</i>	17/17	100.0	11/11	100.0
<i>Klebsiella pneumoniae</i>	8/8	100.0	8/9	88.9
Total	169/181	93.4	180/203	88.7

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalexin with regard to overall microbiologic eradication in evaluable patients [95% CI being 181,203 (-0.0149, 0.1089) 93.4%, 88.7%], as well as in patients with *S. aureus* as a baseline pathogen, the 95% confidence interval being 143,165 (-0.0366, 0.1112) 91.6%, 87.9%. It is to be noted that except

for *S. aureus* on total eradication rates, the sample sizes are not adequate to ensure acceptable level of power to the statistical inferences obtained.

Safety

The safety of cefdinir was assessed using adverse event data (occurrence, intensity, and relationship to study drug), and the results from physical examinations and clinical laboratory tests (hematology, blood chemistry, and urinalysis). All patients randomized to treatment who received drug were evaluated for safety.

Adverse Events: Adverse events included any concurrent illness or symptom reported by the patient or noted by the investigator during the study. In addition, any new outbreak of an SSSI at a site other than that chosen at baseline was also reported as an adverse event. All adverse events that began during the study or that increased in intensity or frequency from baseline were considered treatment emergent signs and symptoms (TESS). Abnormal clinical laboratory values could also be designated as adverse events at the discretion of the investigator.

Each adverse event reported by a patient or noted by an investigator was recorded on a case report form. Adverse events were evaluated by the investigator for relationship to drug (definitely, probably, possibly, unlikely, definitely not, or insufficient information); intensity (mild, moderate, or severe); duration; management of study medication; and clinical outcome. Drug-associated adverse events were those considered definitely, probably, or possibly related to study medication by the investigator.

Adverse events were considered serious if they were fatal, immediately life-threatening, severely or permanently disabling, required or prolonged hospitalization, or were an intentional or accidental overdose, a congenital anomaly, or cancer. During the

medical review, other events could be identified as serious even if they did not meet the above definition. These other events could include:

- Anaphylaxis,
- Blood dyscrasias,
- Cardiac arrhythmias,
- Collagen disorders (eg, LE syndrome, retroperitoneal fibrosis),
- Deafness,
- Hemorrhage from any site,
- Jaundice of any degree,
- Myopathy,
- Ophthalmic disorders (eg, blindness, cataract, keratitis, glaucoma, optic atrophy, retinal disorder),
- Pseudomembranous colitis,
- Severe CNS/PNS disorders (eg, coma, seizures, dyskinesia, encephalopathy, neuropathy, paralysis),
- Severe dermatologic disorders (eg, exfoliative, desquamative, or vesiculobullous rashes; photosensitivity),
- Severe psychiatric disorders (eg, psychosis, drug dependence), or
- Vasculitis.

There were 494 patients who received cefdinir (20 - QD and 474 - BID) and 478 patients who received cephalixin included in the safety analysis. One hundred ninety-three (39.1%) of the cefdinir patients and 144 (30.1%) of the cephalixin patients reported one or more adverse events. One hundred thirty-five (27.3%) of the adverse events reported by the cefdinir group and 79 (16.5%) of the adverse events reported by the cephalixin patients were considered to be drug associated events. The incidence of adverse events by body system is depicted in table 29.

TABLE 29. Summary of Adverse Events - All Patients Receiving Study Medication
[Number (%) of Patients]

	Cefdinir				Cephalexin	
	QD N = 20		BID N = 474		N = 478	
Adverse Events						
All Adverse Events	10	(50.0)	183	(38.6)	144	(30.1)
Associated ^a Adverse Events	8	(40.0)	127	(26.8)	79	(16.5)
Adverse Events by Age^b						
All Adverse Events						
13 to <18 yr	0	(0.0)	5	(21.7)	11	(32.4)
18 to <65 yr	9	(50.0)	151	(39.7)	114	(30.5)
≥65 yr	1	(100.0)	27	(38.0)	19	(27.1)
Associated Adverse Events						
13 to <18 yr	0	(0.0)	5	(21.7)	5	(14.7)
18 to <65 yr	7	(38.9)	103	(27.1)	60	(16.0)
≥65 yr	1	(100.0)	19	(26.8)	14	(20.0)
Adverse Events by Gender^c						
Male	7	(53.8)	113	(40.2)	79	(27.9)
Female	3	(42.9)	70	(36.3)	65	(33.3)
Adverse Events by Maximum Intensity^d						
All Adverse Events						
Mild	7	(35.0)	128	(27.0)	103	(21.5)
Moderate	4	(20.0)	63	(13.3)	52	(10.9)
Severe	0	(0.0)	14	(3.0)	6	(1.3)
Associated Adverse Events						
Mild	5	(25.0)	87	(18.4)	53	(11.1)
Moderate	4	(20.0)	42	(8.9)	28	(5.9)
Severe	0	(0.0)	8	(1.7)	4	(0.8)
Serious Adverse Events						
	0	(0.0)	7	(1.5)	3	(0.6)
Deaths						
	0	(0.0)	1	(0.2)	0	(0.0)
Discontinuation of Treatment Due to Adverse Events						
All Adverse Events	3	(15.0)	28	(5.9)	17	(3.6)
Associated Adverse Events	2	(10.0)	20	(4.2)	13	(2.7)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	1	(0.2)	2	(0.4)
Associated Adverse Events	0	(0.0)	0	(0.0)	0	(0.0)

^a Considered by the investigator to be possibly, probably, or definitely related to study medication.
^b Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.
^c Percentages based on total numbers of males or females in a treatment group.
^d Patients with multiple adverse events were counted once in each applicable category.

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-8/Adults

TABLE 30. All and Associated* Adverse Events by Body System - Patients Receiving Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir				Cephalexin	
	QD N = 20		BID N = 474		N = 478	
	All	Associated	All ^a	Associated	All	Associated
BODY AS A WHOLE	1^c (5.0)	1 (5.0)	48^c (10.1)	15 (3.2)	67^c (14.0)	14^c (2.9)
Headache	1 (5.0)	1 (5.0)	23 (4.9)	10 (2.1)	26 (5.4)	4 (0.8)
Infection	0 (0.0)	0 (0.0)	5 (1.1)	0 (0.0)	5 (1.0)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	5 (1.1)	0 (0.0)	7 (1.5)	0 (0.0)
Abdominal Pain	0 (0.0)	0 (0.0)	4 (0.8)	3 (0.6)	12 (2.5)	9 (1.9)
Asthenia	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.6)	1 (0.2)
Flu Syndrome	1 (5.0)	0 (0.0)	2 (0.4)	1 (0.2)	3 (0.6)	0 (0.0)
Abscess	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
Accidental Injury	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)
Allergic Reaction	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Back Pain	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	4 (0.8)	1 (0.2)
Chest Pain	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Face Edema	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Neck Pain	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden Death	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hernia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Intentional Injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Neck Rigidity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
CARDIOVASCULAR SYSTEM	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Vasodilatation	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
DIGESTIVE SYSTEM	8^c (40.0)	8^c (40.0)	112 (23.6)	100^c (21.1)	69^c (14.4)	58^c (12.1)
Diarrhea	7 (35.0)	7 (35.0)	82 (17.3)	78 (16.5)	40 (8.4)	36 (7.5)
Nausea	0 (0.0)	0 (0.0)	19 (4.0)	17 (3.6)	20 (4.2)	17 (3.6)
Constipation	0 (0.0)	0 (0.0)	4 (0.8)	3 (0.6)	0 (0.0)	0 (0.0)
Fatulence	1 (5.0)	1 (5.0)	4 (0.8)	3 (0.6)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	5 (1.0)	4 (0.8)
Abnormal Stools	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
Cheilitis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Dry Mouth	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	2 (10.0)	2 (10.0)	1 (0.2)	1 (0.2)	6 (1.3)	4 (0.8)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorder	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Melena	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Pseudomembranous Colitis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Rectal Disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-2/Adults

BODY SYSTEM/ Adverse Event	Cefdinir						Cephalexin N = 478	
	QD N = 20		BID N = 474				All	Associated
	All	Associated	All ^a	Associated				
Increased Appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	0 (0.0)
Peptic Ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	1 (0.2)
Tooth Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)			0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			0 (0.0)	0 (0.0)
Lymphadenopathy	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)
Lymphangitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (5.0)	0 (0.0)	4 ^c (0.8)	3 ^c (0.6)			3 (0.6)	2 (0.4)
ALT Increased	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)			1 (0.2)	1 (0.2)
Alkaline Phosphatase Increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)
AST Increased	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			0 (0.0)	0 (0.0)
Weight Gain	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			0 (0.0)	0 (0.0)
Hyperglycemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	0 (0.0)
Peripheral Edema	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	1 (0.2)
NERVOUS SYSTEM	0 (0.0)	0 (0.0)	12 (2.5)	4 (0.8)			14 ^c (2.9)	7 (1.5)
Dizziness	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)			8 (1.7)	3 (0.6)
Insomnia	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)			0 (0.0)	0 (0.0)
Abnormal Dreams	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			2 (0.4)	0 (0.0)
Hyperkinesia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)
Hypesthesia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			1 (0.2)	0 (0.0)
Nervousness	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			1 (0.2)	1 (0.2)
Somnolence	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			2 (0.4)	2 (0.4)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	1 (0.2)
RESPIRATORY SYSTEM	0 (0.0)	0 (0.0)	6 (1.3)	1 (0.2)			9 (1.9)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)			2 (0.4)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)
Cough Increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			2 (0.4)	0 (0.0)
Hypoxia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)			4 (0.8)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			1 (0.2)	0 (0.0)
SKIN AND APPENDAGES	2 (10.0)	0 (0.0)	17 (3.6)	7 ^c (1.5)			14 ^c (2.9)	3 ^c (0.6)
Rash	1 (5.0)	0 (0.0)	7 (1.5)	6 (1.3)			3 (0.6)	1 (0.2)
Pruritus	1 (5.0)	0 (0.0)	3 (0.6)	1 (0.2)			3 (0.6)	2 (0.4)
Dry Skin	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)			0 (0.0)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)			1 (0.2)	0 (0.0)
Furunculosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			3 (0.6)	0 (0.0)
Pustular Rash	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			1 (0.2)	0 (0.0)
Skin Disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)
Vesiculobullous Rash	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-8/Adults

BODY SYSTEM/ Adverse Event	Cefdinir						Cephalexin N = 478	
	QD N = 20			BID N = 474			All	Associated
	All	Associated		All ^b	Associated			
Contact Dermatitis	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.4)	0 (0.0)
Maculopapular Rash	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.4)	1 (0.2)
Sweating	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)
SPECIAL SENSES	0 (0.0)	0 (0.0)		5 ^c (1.1)	0 (0.0)		2 ^c (0.4)	0 (0.0)
Ear Disorder	0 (0.0)	0 (0.0)		2 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)
Eye Disorder	0 (0.0)	0 (0.0)		2 0	(0.0)		0 (0.0)	0 (0.0)
Deafness	0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)		1 (0.2)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)		1 (0.2)	0 (0.0)
Ear Pain	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		2 (0.4)	0 (0.0)
Otitis Media	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)
UROGENITAL SYSTEM	0 (0.0)	0 (0.0)		18 ^c (3.8)	15 ^c (3.2)		18 (3.8)	11 (2.3)
Vaginal Moniliasis ^{d,e}	0 (0.0)	0 (0.0)		14 (7.3)	14 (7.3)		10 (5.1)	10 (5.1)
Urinary Frequency	0 (0.0)	0 (0.0)		2 (0.4)	1 (0.2)		2 (0.4)	0 (0.0)
Hematuria	0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)		1 (0.2)	0 (0.0)
Menorrhagia ^d	0 (0.0)	0 (0.0)		1 (0.5)	0 (0.0)		0 (0.0)	0 (0.0)
Vaginitis ^{d,e}	0 (0.0)	0 (0.0)		1 (0.5)	1 (0.5)		2 (1.0)	1 (0.5)
Dysmenorrhea ^d	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.5)	0 (0.0)
Dysuria	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)
Urinary Tract Infection	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)

^a Possibly, probably, or definitely related to treatment

^b All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir BI

^c The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse eve

^d Calculated for women who received study medication (cefdinir QD, N = 7; cefdinir BID, N = 193; cephalexin, N = 195).

^e It is likely that vaginitis and vaginal moniliasis represent the same condition in women. Therefore, the total number of patients can be combine totals and percentages (calculated for women who received study medication) for cefdinir BID are 15 (7.8%) for all and associated events, and 12 (6.2%) and 11 (5.6%) for all and associated events, respectively.

All and Drug-Associated Adverse Events: Most adverse events among both cefdinir and cephalexin patients were related to the digestive system, body as a whole, or the urogenital system. Adverse events related to the digestive system were most often considered to be drug-associated by the investigator. Significantly more cefdinir BID-treated patients experienced adverse events ($p = 0.005$) and drug-associated adverse events ($p < 0.001$) than those treated with cephalexin according to the applicant.

The most frequently reported adverse events for patients treated with cefdinir BID included diarrhea (17%), vaginal moniliasis/vaginitis (8% of female patients), headache (5%), and nausea (4%). For patients treated with cephalexin, the most frequently reported adverse events included diarrhea (8%), vaginal moniliasis/vaginitis (6% of female patients), headache (5%), nausea (4%), and abdominal pain (3%). All other adverse events occurred in less than 2% of patients.

An analysis of diarrhea, the most common adverse event during the study, showed that significantly more patients treated with

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-8/Adults

cefdinir BID experienced diarrhea than patients treated with cephalixin ($p < 0.001$ - applicant's analysis).

Deaths: There was one death in the study. It involved a 43 year-old white male who completed 10 days of cefdinir therapy for the treatment of a complicated infected trauma/surgical wound. He expired 14 days after completing therapy. The cause of death was due to alcoholic cardiomyopathy.

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TABLE 31. Serious Adverse Events - Patients Receiving Study Medication

Treatment	Center	Patient Number	Age ^a , Sex	Serious Adverse Event ^b	Intensity	Relationship to Study Medication ^c	Management of Study Drug	Outcome
Cefdinir BID								
	1	12	22, M	Pseudomembranous Colitis Appendicitis (Gastrointestinal Disorder)	Severe Moderate	Probably Possibly	Discontinued Discontinued	Recovered Recovered
	5	6	54, M	Reduced Tissue O ₂ Concentration ^d (Hypoxia)	Severe	Definitely Not	Discontinued	Recovered/ Sequelae
		33	67, M	Chest Pain	Severe	Definitely Not	None	Recovered
	8	32	74, M	Eruption of Bullous Pemphigoid (Vesiculobullous Rash)	Moderate	Definitely Not	Discontinued	Recovered
		66	71, M	Fainting (Syncope)	Moderate	Definitely Not	None	Recovered
				Laceration of Scalp (Accidental Injury)	Moderate	Definitely Not	None	Recovered
	18	19	43, M	Sudden Death	Severe	Definitely Not	None	Died
	49	3	80, M	Severe Asthmatic Attack (Asthma)	Severe	Unlikely	Discontinued	Recovered
Cephalexin								
	5	8	50, M	Exacerbation of Infected Right Toe (Infection)	Moderate	Unlikely	Discontinued	Recovered
	6	62	47, M	Traumatic Blow to Head - Blunt Instrument (Intentional Injury)	Severe	Definitely Not	Discontinued	Recovered/ Sequelae
	19	11	48, M	Hear Loss, Right Ear (Deafness)	Moderate	Unlikely	None	Not Yet Recovered

^a Age at baseline

^b When the investigator term and COSTART term differ, the COSTART adverse event term appears in parentheses.

^c As determined by the investigator

^d At site of infection

Serious Adverse Events: There were seven cefdinir and three cephalalexin patients who experienced serious adverse events, as shown in Table 31. Four of the cefdinir patients and two of the cephalalexin patients withdrew from the study. One patient treated with BID cefdinir had pseudomembranous colitis which was probably related to therapy. A *C. difficile* toxin assay for this patient was negative. There did not appear to be any relationship between an adverse event and the study medication for the other nine patients.

Discontinued Patients: Table 32 is a summary of treatment discontinuations. It shows that three cefdinir QD patients, 33 cefdinir BID patients, and 27 cephalalexin patients withdrew from the study due to adverse events. Diarrhea was the most frequent cause for discontinuation for both study groups.

Clinical Laboratory Values: Baseline values for each patient's clinical laboratory measurements were to be determined prior to the receipt of study medication. At the STFU visit, clinical laboratory tests were repeated and these values were compared to standard normal values and the patient's baseline values. If a significantly abnormal value was noted at STFU, laboratory tests were to be repeated until the abnormality resolved or a reason for the abnormality was determined.

Clinical laboratory values were reviewed by the sponsor to identify any changes that may have occurred during the study. Specifically, these included median changes from baseline, category shift changes, and markedly abnormal values.

Clinical Reviewer's note: For patients treated with cefdinir BID and cephalalexin, there were more decreases than increases in WBCs and PMNs which is consistent with a resolving infection. Also, more decreases than increases were observed for alkaline phosphatase, urine specific gravity, and urine ketones. The comparator drug had more markedly abnormal lab values than the study drug for eosinophils, glucose, ALT, and bicarbonate.

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TABLE 32. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Receiving Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 20		Cefdinir BID N = 474		Cephalexin N = 478	
BODY AS A WHOLE	1	(5.0)	6 ^a	(1.3)	7	(1.5)
Flu Syndrome	1	(5.0)	2	(0.4)	0	(0.0)
Headache	0	(0.0)	2	(0.4)	0	(0.0)
Abdominal Pain	0	(0.0)	1	(0.2)	3	(0.6)
Allergic Reaction	0	(0.0)	1	(0.2)	0	(0.0)
Pain	0	(0.0)	1	(0.2)	0	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	1	(0.2)
Fever	0	(0.0)	0	(0.0)	1	(0.2)
Infection	0	(0.0)	0	(0.0)	1	(0.2)
Intentional Injury	0	(0.0)	0	(0.0)	1	(0.2)
DIGESTIVE SYSTEM	2	(10.0)	16 ^a	(3.4)	13 ^a	(2.7)
Diarrhea	1	(5.0)	11	(2.3)	7	(1.5)
Nausea	0	(0.0)	3	(0.6)	6	(1.3)
Vomiting	0	(0.0)	2	(0.4)	3	(0.6)
Gastrointestinal Disorder	0	(0.0)	1	(0.2)	0	(0.0)
Pseudomembranous Colitis	0	(0.0)	1	(0.2)	0	(0.0)
Dyspepsia	1	(5.0)	0	(0.0)	1	(0.2)
HEMIC AND LYMPHATIC SYSTEM	0	(0.0)	1	(0.2)	0	(0.0)
Lymphangitis	0	(0.0)	1	(0.2)	0	(0.0)
NERVOUS SYSTEM	0	(0.0)	2	(0.4)	3 ^a	(0.6)
Abnormal Dreams	0	(0.0)	1	(0.2)	0	(0.0)
Insomnia	0	(0.0)	1	(0.2)	0	(0.0)
Anxiety	0	(0.0)	0	(0.0)	1	(0.2)
Dizziness	0	(0.0)	0	(0.0)	2	(0.4)
Somnolence	0	(0.0)	0	(0.0)	1	(0.2)
RESPIRATORY SYSTEM	0	(0.0)	2	(0.4)	1	(0.2)
Asthma	0	(0.0)	1	(0.2)	0	(0.0)
Hypoxia	0	(0.0)	1	(0.2)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	1	(0.2)
SKIN AND APPENDAGES	0	(0.0)	4 ^a	(0.8)	1	(0.2)
Rash	0	(0.0)	2	(0.4)	0	(0.0)
Pruritus	0	(0.0)	1	(0.2)	1	(0.2)
Pustular Rash	0	(0.0)	1	(0.2)	0	(0.0)
Vesiculobullous Rash	0	(0.0)	1	(0.2)	0	(0.0)
UROGENITAL SYSTEM	0	(0.0)	1	(0.2)	2	(0.4)
Vaginal Moniliasis ^b	0	(0.0)	1	(0.5)	1	(0.5)
Urinary Tract Infection	0	(0.0)	0	(0.0)	1	(0.2)

^a The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

^b Calculated for women who received study medication (cefdinir QD, N = 7; cefdinir BID, N = 193; cephalexin, N = 195.)

Indication: Uncomplicated skin and skin structure infections

Title and Study Number: A phase 3, 10-day, investigator-blind, randomized, comparative, multicenter study of cefdinir (CI-983) versus cephalexin in the treatment of pediatric patients with uncomplicated skin and skin structure infections (protocol 983-13).

Objective: The objective of this study was to evaluate the efficacy and safety of cefdinir suspension (14 mg/kg/day as 7 mg/kg BID up to a maximum of 600 mg/day) versus cephalexin suspension (40 mg/kg/day as 10 mg/kg QID up to a maximum of 2000 mg/day) in the treatment of acute uncomplicated SSSIs in patients 6 months to 12 years of age.

Study Design: This was an investigator-blind, randomized, comparative, multicenter study with 2 parallel-treatment groups. Screening, dosing, follow-up visits, and the test-of-cure (TOC) visit window are illustrated in Figure 2. An on-therapy visit (Days 3 to 5) was part of the study design but is not illustrated in Figure 2 since it was not used in any efficacy evaluation.

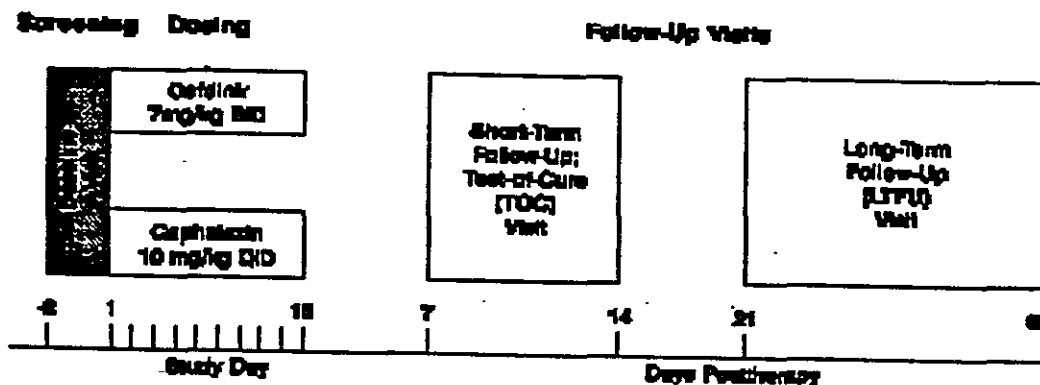


Figure 2. Protocol 983-13 Study Design

Protocol Overview

Population and Inclusion/Exclusion Criteria:

Population: Participants included boys and girls 6 months to 12 years of age. Girls who were postmenarcheal had a negative pregnancy test at baseline.

Inclusion Criteria: Inclusion criteria were similar to that stated in the adult study (protocol 983-8) with the following exception. Pediatric patients were required to have one or more clinical signs and symptoms of SSSI for study entry. They could include pain/tenderness, erythema/warmth, swelling, induration/crusting, fluctuation, or drainage. The investigator performed the evaluation of signs and symptoms and classified them as absent, mild, moderate, or severe at each visit. In the adult study, two clinical signs/symptoms were required.

Exclusion Criteria: The patient exclusion criteria were identical to those found in the adult (capsule) study.

Evaluability Criteria: Patients could be withdrawn from the study because of insufficient efficacy; an adverse event; a clinical laboratory abnormality; lack of patient cooperation; patient, parent, or guardian request; failure to isolate a baseline pathogen; or isolation of a baseline pathogen resistant to either cefdinir or cephalexin. Reasons for withdrawal were reported on the appropriate case report form.

Confirmation of bacteriological etiology and in vitro susceptibility (or intermediate susceptibility) to study medication were required for a patient to be evaluable for efficacy analyses. If these conditions were not met, a patient could be discontinued from study medication and given appropriate therapy. The investigator could continue to treat patients who had a baseline pathogen that was resistant to 1 study medication and susceptible to the other if, in his or her judgement, they were exhibiting satisfactory clinical improvement.

When patients were discontinued early, the following were to be completed: skin culture (from the baseline site of infection) and susceptibility testing, a clinical evaluation (ie, assessment of signs and symptoms as well as an overall assessment of clinical efficacy), a physical examination, clinical laboratory tests, as well as records of adverse events and concurrent medications. If additional antibiotics were not required at the time study medication was discontinued and the patient had received at least 3 days of study medication, both follow-up visits were scheduled to be completed. If additional antibiotics were required or if the patient had no baseline pathogen, follow-up visits were not scheduled.

Assessments of microbiologic and clinical response at the TOC visit, 7 to 14 days posttherapy, were used to evaluate the efficacy of cefdinir. A long-term follow-up (LTFU) visit, 21 to

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-13/Pediatrics

35 days posttherapy, provided information on recurrence of infection.

Three efficacy measures were used in this study: microbiologic eradication rate by pathogen, microbiologic eradication rate by patient, and clinical cure rate by patient.

Endpoints Defined (Clinical and Microbiological)

The schedule of visits, examinations and evaluations for the patients in this study is shown in the following table, which was duplicated from the submission.

The visits, examinations, and collection of specimens were similar to those described in the adult (capsule) study.

TABLE 33. Schedule of Clinical Observations and Laboratory Measurements

Procedure/Observation	Baseline ^a	Day 1	Days 3-5	Day 10	Posttherapy Visits	
					7 to 14 Days	21 to 35 Days
Medical History	X					
Physical Examination ^b	X				X	
Clinical Evaluations (Signs and Symptoms) ^b	X		X		X	X
Skin Culture from Baseline Site of Infection and Susceptibility Testing ^b	X				X	X
Adverse Events		X			X	X
Clinical Laboratory Testing ^{b,c}	X				X	X ^d
Assessment of Clinical Efficacy ^b					X	X
Radiographic Evaluation ^e	X					
Dosing		X		X		

- ^a Prior to treatment (within 48 hours)
- ^b Performed whenever a patient was withdrawn
- ^c Listed in protocol (Appendix A.2)
- ^d Performed only if abnormalities were detected at the previous visit
- ^e Only if indicated to rule out osteomyelitis

Microbiological endpoints: Assessments of microbiologic response at the TOC visit, 7 to 14 days posttherapy, were used to evaluate the efficacy of cefdinir. A long-term follow-up (LTFU) visit, 21 to 35 days posttherapy, provided information on recurrence of infection.

The pediatric protocol differs from the adult study in the test of cure determination. In the adult study, the TOC date occurs at the last visit which is between 12 to 16 days post-therapy. In the pediatric study, the TOC visit occurs at the short term follow-up visit which is between 7 to 14 days post-therapy. The

pediatric study has a long-term follow-up visit between 21 to 35 days post-therapy.

The criteria used for evaluation were identical to those found in the adult study.

Clinical endpoints: The criteria used for evaluation were identical to those found in the adult study.

Statistical Considerations

Sample Size: This double-blind, comparative study of cefdinir versus cephalexin was designed with a sample size of 120 evaluable patients per randomized treatment group for a total of 240 evaluable patients.

A microbiologic eradication rate of 85% across all randomized groups was assumed in the sample size calculations. Equivalence was to be assessed by comparing a two-tailed 95% confidence interval (CI) for the difference (cefdinir minus cephalexin) in microbiologic eradication rates to a set of predetermined, fixed criteria for equivalence. Sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and cephalexin microbiologic eradication rates at TOC, using this CI method.

The statistical analysis was performed as described previously in the adult study.

Study Results

Demographics, Evaluability

A total of 18 investigators enrolled 196 patients in the cefdinir group and 198 patients in the cephalexin group, for a total of 394 patients in the study. The following table shows the patient disposition, including the number of patients who were considered evaluable by each investigator.

TABLE 34. List of Investigators

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed*	Evaluable
2	C. Khurana	3	3	0
3	A. Iravani	30	30	17
4	J. Hedrick	51	50	34
5	W. Gooch	2	2	2
6	S. Wiederhold	28	23	15
7	S. Chartrand	24	24	19
8	J. McCarty	73	63	42
9	E. Rothstein	10	9	7
10	J. Haddad	3	1	0
11	R. Fiddes	75	63	34
12	S. McLinn	6	6	4
15	P. DiLorenzo	19	16	15
16	A. Phillips	6	2	2
17	R. Ford	13	12	8
18	J. Scott	21	19	16
19	S. Weakley	16	12	11
20	S. Davis	1	1	1
21	A. Herbert	13	7	4
Total		394	343	231

* Completed treatment and test-of-cure visit

Patient Demographics: The patient demographics for all patients (ITT) and evaluable patients according to the applicant are summarized in the following tables.

TABLE 35. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir N = 196		Cephalexin N = 198		Total N = 394	
Sex						
Male	110	(56.1)	107	(54.0)	217	(55.1)
Female	86	(43.9)	91	(46.0)	177	(44.9)
Race						
White	107	(54.6)	95	(48.0)	202	(51.3)
Black	24	(12.2)	27	(13.6)	51	(12.9)
Asian	0	(0.0)	2	(1.0)	2	(0.5)
Other ^a	65	(33.2)	74	(37.4)	139	(35.3)
Age, yr						
Median	5.5		5.2		5.3	
Range ^b	0.5-13.0		0.5-13.1		0.5-13.1	
Distribution						
<2 ^c	29	(14.8)	30	(15.2)	59	(15.0)
2 to <6	79	(40.3)	88	(44.4)	167	(42.4)
6 to <13 ^d	88	(44.9)	80	(40.4)	168	(42.6)
Baseline Diagnosis^e						
Impetigo	109	(55.6)	117	(59.1)	226	(57.4)
Infected Dermatitis	20	(10.2)	15	(7.6)	35	(8.9)
Infected Traumatic/Surgical Wound	18	(9.2)	14	(7.1)	32	(8.1)
Cellulitis	16	(8.2)	13	(6.6)	29	(7.4)
Paronychia	9	(4.6)	14	(7.1)	23	(5.8)
Abscess	8	(4.1)	6	(3.0)	14	(3.6)
Folliculitis	7	(3.6)	4	(2.0)	11	(2.8)
Furuncle	4	(2.0)	7	(3.5)	11	(2.8)
Infected Burn	2	(1.0)	2	(1.0)	4	(1.0)
Acutely Infected Ulcer	0	(0.0)	1	(0.5)	1	(0.3)
Carbuncle	1	(0.5)	0	(0.0)	1	(0.3)
Other ^f	2	(1.0)	5	(2.5)	7	(1.8)

^a Other = Hispanic, biracial, Native American, and Tongan.

^b One cefdinir-treated patient's age of 12.97 years was rounded to 13 years for this table. One cephalixin-treated patient was >13 years old and considered a protocol variation.

^c Contains 1 cephalixin-treated patient approximately 5 days <6 months old.

^d Contains 1 cephalixin-treated patient age 13 years, 1 month.

^e Seventeen cefdinir-treated patients and 11 cephalixin-treated patients had conditions predisposing them to SSSIs. Section 5.1.4 contains information about patients with predisposing conditions.

TABLE 36. Patient Characteristics - Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir N = 118		Cephalexin N = 113		Total N = 231	
Sex						
Male	63	(53.4)	53	(46.9)	116	(50.2)
Female	55	(46.6)	60	(53.1)	115	(49.8)
Race						
White	71	(60.2)	58	(51.3)	129	(55.8)
Black	10	(8.5)	15	(13.3)	25	(10.8)
Asian	0	(0.0)	1	(0.9)	1	(0.4)
Other ^a	37	(31.4)	39	(34.5)	76	(32.9)
Age, yr						
Median	5.3		5.3		5.3	
Range	0.5-12.7		0.9-13.1		0.5-13.1	
Distribution						
<2 ^b	17	(14.4)	12	(10.6)	29	(12.6)
2 to <6	51	(43.2)	53	(46.9)	104	(45.0)
6 to <13 ^c	50	(42.4)	48	(42.5)	98	(42.4)
Baseline Diagnosis						
Impetigo	74	(62.7)	76	(67.3)	150	(64.9)
Infected Dermatitis	15	(12.7)	6	(5.3)	21	(9.1)
Infected Traumatic/Surgical Wound	9	(7.6)	8	(7.1)	17	(7.4)
Cellulitis	7	(5.9)	5	(4.4)	12	(5.2)
Paronychia	3	(2.5)	7	(6.2)	10	(4.3)
Abscess	2	(1.7)	4	(3.5)	6	(2.6)
Folliculitis	3	(2.5)	1	(0.9)	4	(1.7)
Furuncle	1	(0.8)	3	(2.7)	4	(1.7)
Infected Burn	2	(1.7)	1	(0.9)	3	(1.3)
Carbuncle	1	(0.8)	0	(0.0)	1	(0.4)
Other ^d	1	(0.8)	2	(1.8)	3	(1.3)

^a Other = Hispanic, Native American, biracial, and Tongan.

^b Contains 1 cephalexin-treated patient approximately 5 days <6 months old.

^c Contains 1 cephalexin-treated patient age 13 years, 1 month.

^d Other = Infected blister, pyoderma, and secondarily infected chickenpox.

Clinical reviewer's note: For all patients and evaluable patients, the study appears balanced with respect to gender, race, age, and baseline diagnoses.

Statistical reviewer's note: The two treatment arms are balanced with respect to baseline demographic variables - sex (p-value = 0.325), race (p-value = 0.374), and age (p-value = 0.664).

Drug Administration: The distribution for the duration of therapy for all patients according to the applicant is provided in the table below.

**TABLE 37. Patient Exposure to Study
Medication - All Patients**

Days on Study Medication	Cefdinir N = 196	Cephalexin N = 198
2	1	0
4	4	2
5	0	2
6	3	0
7	5	1
8	1	4
9	2	2
10	113	29
11	58	138
12	2	4
14	0	2
17	0	1
21	0	1
Median	10	11
Unknown	7	12

Clinical Reviewer's Note: The median patient exposure to cefdinir was 10 days and 11 days for cephalixin. Among the cefdinir group, 171 (87%) patients received 10-11 days of therapy. Patients who started cefdinir or cephalixin at or after noon on Day 1 finished medication on the morning of or later on Day 11, which accounts for the number of patients with 11 days of treatment.

Unevaluable Patients: The following patients were excluded from all efficacy analysis by the applicant, and the reasons for exclusion were as follows:

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TABLE 38. Reasons Patients Were Not Evaluable at TOC or Disqualified at LTFU
(Number of Patients)

	Cefdinir	Cephalexin
Randomized to Treatment	196	198
Reasons Patients Were Not Evaluable for TOC Analyses^a		
Clinical Assessment Missed	8	12
Clinical Evaluation Out of Date Range ^b	25	34
Concurrent Antibacterial ^b	4	3
Culture ^c Out of Date Range ^b	21	32
Culture ^c Missed	13	14
Medication Not As Prescribed	24	17
No Proven Baseline Pathogen	28	22
Prior Antibacterial	4	3
Resistant Baseline Pathogen(s)	23	31
Total Not Evaluable	78	85
Patients Who Were Evaluable at TOC^d	118	113
Reasons Patients Were Disqualified for LTFU Analyses		
Clinical Assessment Missed	7	7
Clinical Evaluation Out of Date Range ^b	4	7
Concurrent Antibacterial ^b	3	1
Culture ^c Out of Date Range ^b	4	7
Culture ^c Missed	6	7
Total Disqualified	14	15
Patients Who Were Qualified at LTFU	104	98

^a Patients who had multiple reasons for being excluded from efficacy analyses were counted for each reason that was applied.

^b Patients who had microbiologic and/or clinical assessments done early or who took a concurrent antibacterial because they were early failures were not removed from the evaluable analyses for these reasons.

^c Baseline or TOC culture

^d These patients were candidates for qualified analyses at LTFU.

Efficacy

Table 39 compares the number of patients randomized to treatment (i.e., the ITT population) to the number of patients in the other populations.

TABLE 39. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	Cefdinir	Cephalexin
ITT ^a	196 (100.0)	198 (100.0)
MITT ^b	161 (82.1)	165 (83.3)
Clinically Evaluable ^c	131 (66.8)	123 (62.1)
Evaluable ^d	118 (60.2)	113 (57.1)
Qualified ^e	104 (88.1)	98 (86.7)

- ^a Patients in the ITT population were those randomized to treatment.
- ^b Patients in the MITT population had the correct indication, received study medication, had at least 1 baseline pathogen, and had a follow-up culture
- ^c Patients in the clinically evaluable population had the correct indication and at least 1 clinical sign or symptom; took study medication as prescribed; did not take nonstudy systemic or topical antibacterial therapy for other concurrent infections; and had their clinical evaluations performed within the range of days specified in the protocol. Patients were not excluded from this data set if they had no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.
- ^d Evaluable patients had no known protocol violations that might have affected efficacy assessments at TOC. Patients who had microbiologic and/or clinical assessments done early (ie, before the follow-up visit window) or who took a concurrent antibacterial because they were early failures were not removed from the evaluable patient population for these reasons.
- ^e Qualified patients were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits (eg, qualified patients did not take concurrent systemic or topical antibacterial agents).

Clinical Results: As in the adult study, the primary measure of patient clinical response for efficacy analysis was a combination of investigator and sponsor assessments referred to as the combined investigator/sponsor clinical assessment. Table 40 shows the results of this reclassification for the patients who are both microbiologically and clinically evaluable.

TABLE 40. Investigator vs Combined Investigator/Sponsor
Clinical Response Determination at the TOC Visit -
Evaluable Patients

Investigator Determination	Combined Investigator/Sponsor Determination			
	Cefdinir N = 118		Cephalexin N = 113	
	Cure	Failure	Cure	Failure
Cure	116	0	106	0
Failure	0	2	0	7

Statistical reviewer's note: The 95% CI for the difference between the cure rates for cefdinir and cephalexin was $_{118,113} (-0.0138, 0.1038)$ $_{98.3\%,93.8\%}$, showing therapeutic equivalence between the two treatment arms with respect to the clinical cure rate by evaluable patients.

TABLE 41. Clinical Cure Rate* by Patient (According to Applicant's
Proposed Baseline Pathogens) Across Baseline Diagnoses at the
TOC Visit - Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
<i>Enterococcus durans</i>	1/1	100.0	0/0	—
<i>Staphylococcus aureus</i>	51/53	96.2	52/56	92.9
<i>Staphylococcus Coagulase-Negative</i>	1/1	100.0	0/0	—
<i>Streptococcus pneumoniae</i>	0/0	—	1/1	100.0
<i>Streptococcus pyogenes</i>	13/13	100.0	13/13	100.0
<i>Streptococcus Group C</i>	1/1	100.0	0/0	—
Gram-Negative				
<i>Acinetobacter calcoaceticus var lwoffii</i>	1/1	100.0	0/0	—
<i>Enterobacter agglomerans</i>	0/0	—	0/1	0.0
<i>Haemophilus influenzae</i>	2/2	100.0	0/0	—
Multiple	46/46	100.0	40/42	95.2
Total	116/118	98.3	106/113	93.8

n/N = Number of patients who were cured/total number of patients.

* Based on combined investigator/sponsor clinical assessments

In Table 41 the clinical cure rates for all microbiologically evaluable patients according to the baseline pathogen isolated is shown. For the 118 cefdinir patients, 116 (98.3%) patients were cured, while 106 of the 113 (93.8%) cephalixin patients were clinically cured.

Clinical reviewer's note: As in the adult study, the data presented in Table 41 are based on the assignment of one organism as the primary pathogen for each evaluable patient. Actually, 72 cefdinir patients and 71 cephalixin patients had a single pathogen present, while 46 cefdinir patients and 42 cephalixin patients had multiple organisms present in their infections.

Statistical reviewer's note: The 95% CI for the difference between the cure rates for cefdinir and cephalixin was $_{116,113} (-0.0138, 0.1038)$ $_{98.3\%,93.8\%}$, showing therapeutic equivalence between the two treatment arms with respect to the clinical cure rate by patients.

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TABLE 42. Clinical Cure Rate* by Baseline Diagnosis at the TOC Visit -
Evaluable Patients

Baseline Diagnosis	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Impetigo	72/74	97.3	73/76	96.1
Infected Dermatitis	15/15	100.0	5/6	83.3
Infected Traumatic/Surgical Wound	9/9	100.0	8/8	100.0
Cellulitis	7/7	100.0	4/5	80.0
Paronychia	3/3	100.0	6/7	85.7
Abscess	2/2	100.0	4/4	100.0
Folliculitis	3/3	100.0	1/1	100.0
Furuncle	1/1	100.0	3/3	100.0
Infected Burn	2/2	100.0	1/1	100.0
Carbuncle	1/1	100.0	0/0	—
Other	1/1	100.0	½	50.0
Across Diagnosis	116/118	98.3	106/113	93.8

n/N = Number of patients who were cured/total number of patients.

Based on combined investigator/sponsor clinical assessments.

Statistical reviewer's note: The 95% CI for the difference between the cure rates for cefdinir and cephalixin was $118, 113$ $(-0.0138, 0.1038)$ $98.38, 93.88$, showing therapeutic equivalence between the two treatment arms with respect to the clinical cure rate by baseline diagnosis.

TABLE 45 Microbiologic vs Clinical Response Rates at the
TOC Visit - Evaluable Patients
[Number (%) of Patients]

Microbiologic Response	Clinical Response ^a	
	Cure	Failure
Cefdinir, N = 118		
Patients With Eradication	116 (98.3)	1 (0.8)
Patients With Persistence	0 (0.0)	1 (0.8)
Cephalexin, N = 113		
Patients With Eradication	105 (92.9)	4 (3.5)
Patients With Persistence	1 (0.9)	3 (2.7)

^a Based on combined investigator/sponsor clinical assessments

Clinical reviewer's note: There were two clinical failures among the 118 evaluable cefdinir patients. One patient was an 8 year-old boy with impetigo due to *S. aureus*. The organism was eradicated; however, his clinical signs/symptoms persisted. He experienced four adverse events, including diarrhea, headache, pharyngitis, and lymphadenopathy.

The second patient was a 22 month-old boy with impetigo due to *S. aureus* which persisted. The patient had clinical signs/symptoms along with *S. aureus* at the TOC visit. He also experienced vomiting and diarrhea but was able to complete therapy.

Among the 113 cephalixin patients, four were clinical failures with eradication of the pathogen and three patients were clinical failures with a persistent pathogen.

Clinically Evaluable Patients: In the clinically evaluable patient population, 126 of 131 (96%) patients in the cefdinir treatment group and 114 of 123 (93%) in the cephalixin treatment group were cured at TOC.

Superinfections: Three cefdinir patients and five cephalixin patients had superinfections due to other pathogens. The following table shows the organisms responsible for these infections.

TABLE 44. Patients With Superinfections - All Patients
 (Number of Patients)

Pathogen	Cefdinir N = 196	Cephalixin N = 198
Gram-Positive*		
<i>Enterococcus faecalis</i>	1	0
<i>Staphylococcus aureus</i>	1	1
Gram-Negative*		
<i>Acinetobacter calcoaceticus</i> var <i>lwoffii</i>	0	1
<i>Enterobacter cloacae</i>	1	1
Multiple	0	2
Total	3	5

* Pathogens appearing as sole superinfecting pathogens

Microbiologic Efficacy

TABLE 45. Microbiologic Eradication Rate by Baseline Pathogen at the TOC Visit - Pathogens From Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
<i>Enterococcus durans</i>	1/1	100.0	0/0	—
<i>Enterococcus faecalis</i>	0/0	—	1/1	100.0
<i>Enterococcus hirae</i>	1/1	100.0	0/0	—
<i>Staphylococcus aureus</i>	96/97	99.0	95/98	96.9
<i>Staphylococcus Coagulase-Negative</i>	1/1	100.0	0/0	—
<i>Streptococcus agalactiae</i>	4/4	100.0	6/6	100.0
<i>Streptococcus pneumoniae</i>	2/2	100.0	1/1	100.0
<i>Streptococcus pyogenes</i>	42/42	100.0	41/42	97.6
<i>Streptococcus Group C</i>	1/1	100.0	0/0	—
Gram-Negative				
<i>Acinetobacter calcoaceticus var lwoffii</i>	2/2	100.0	1/1	100.0
<i>Enterobacter agglomerans</i>	5/5	100.0	5/5	100.0
<i>Enterobacter cloacae</i>	2/2	100.0	0/0	—
<i>Escherichia coli</i>	1/1	100.0	1/1	100.0
<i>Haemophilus influenzae</i>	2/2	100.0	0/0	—
<i>Klebsiella oxytoca</i>	1/1	100.0	0/0	—
<i>Klebsiella pneumoniae</i>	3/3	100.0	0/0	—
<i>Moraxella sp</i>	1/1	100.0	1/1	100.0
Total	165/166	99.4	152/156	97.4

n/N = Number of pathogens eradicated/total number of pathogens.

Table 45 shows the pathogen eradication rates for the 118 evaluable cefdinir patients and the 113 evaluable cephalexin patients. In the cefdinir group, 165 of 166 (99.4%) pathogens were eradicated at the test of cure visit, while in the comparator group, 152 of 156 (97.4%) pathogens were eradicated.

Statistical reviewer's note: The 95% CI for the difference in the eradication rates between cefdinir and cephalexin was

166,156 (-0.0141, 0.0533) 99.4%, 97.4%, noting that cefdinir is

therapeutically equivalent to cephalexin in this respect.

TABLE 46. Microbiologic Eradication Rate by Baseline Diagnosis at the TOC Visit - Isolates From Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Impetigo	103/104	99.0	103/106	97.2
Infected Dermatitis	23/23	100.0	8/8	100.0
Infected Traumatic/Surgical Wound	13/13	100.0	10/10	100.0
Paronychia	6/6	100.0	10/11	90.9
Cellulitis	8/8	100.0	6/6	100.0
Abscess	2/2	100.0	4/4	100.0
Folliculitis	3/3	100.0	2/2	100.0
Furuncle	1/1	100.0	4/4	100.0
Infected Burn	3/3	100.0	1/1	100.0
Carbuncle	1/1	100.0	0/0	—
Other	2/2	100.0	4/4	100.0
Across Diagnosis	165/166	99.4	152/156	97.4

n/N = Number of pathogens eradicated/total number of pathogens.

Table 46 shows the results of microbial eradication according to pathogen isolated and baseline diagnosis for both treatment groups. The eradication rates are similar for both drugs across the 10 diagnoses listed. The numbers of patients in each diagnostic category are similar for the two treatment groups except for patients with infected dermatitis. There were 23 patients in the cefdinir group and only eight in the cephalexin group with this diagnosis.

Statistical reviewer's note: The 95% CI for the difference in the eradication rates between cefdinir and cephalexin was

166,156 (-0.0141, 0.0533) 99.48,97.48, noting that cefdinir is therapeutically equivalent to cephalexin in this respect.

TABLE 47. Microbiologic Eradication Rate by Patient (According to Applicant's Proposed Baseline Pathogens) at the TOC Visit - Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
<i>Enterococcus durans</i>	1/1	100.0	0/0	--
<i>Staphylococcus aureus</i>	52/53	98.1	53/56	94.6
<i>Staphylococcus Coagulase-Negative</i>	1/1	100.0	0/0	--
<i>Streptococcus pneumoniae</i>	0/0	--	1/1	100.0
<i>Streptococcus pyogenes</i>	13/13	100.0	13/13	100.0
<i>Streptococcus Group C</i>	1/1	100.0	0/0	--
Gram-Negative				
<i>Acinetobacter calcoaceticus var lwoffii</i>	1/1	100.0	0/0	--
<i>Enterobacter agglomerans</i>	0/0	--	1/1	100.0
<i>Haemophilus influenzae</i>	2/2	100.0	0/0	--
Multiple	46/46	100.0	41/42	97.6
Total	117/118	99.2	109/113	96.5

n/N = Number of patients with eradication/total number of patients.

In Table 47 the microbial eradication rates by patient according to baseline pathogens isolated are shown for the 118 evaluable cefdinir patients and the 113 cephalixin patients. In the cefdinir group, 117 of 118 (99.2%) patients had their baseline pathogens eradicated, while 109 of 113 (96.5%) of the cephalixin patients had their baseline pathogens eradicated.

Clinical reviewer's note: Note the lack of any cases that list *Streptococcus agalactiae* and *Klebsiella pneumoniae* as primary, baseline pathogens.

Statistical reviewer's note: The 95% CI for the difference in the eradication rates between the two drugs was $_{118,113} (-0.0196, 0.0734)$ 99.2%, 96.5%, noting that cefdinir is therapeutically equivalent to cephalixin with respect to the microbiologic eradication rate by patient.

TABLE 48. Microbiologic Eradication Rate by Baseline Diagnosis at the TOC Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Impetigo	73/74	98.6	73/76	96.1
Infected Dermatitis	15/15	100.0	6/6	100.0
Infected Traumatic/Surgical Wound	9/9	100.0	8/8	100.0
Cellulitis	7/7	100.0	5/5	100.0
Paronychia	3/3	100.0	6/7	85.7
Abscess	2/2	100.0	4/4	100.0
Folliculitis	3/3	100.0	1/1	100.0
Furuncle	1/1	100.0	3/3	100.0
Infected Burn	2/2	100.0	1/1	100.0
Carbuncle	1/1	100.0	0/0	--
Other	1/1	100.0	2/2	100.0
Across Diagnosis	117/118	99.2	109/113	96.5

n/N = Number of patients with eradication/total number of patients.

Table 48 shows the same eradication data according to baseline diagnosis.

Statistical reviewer's note: The 95% CI is identical to that found in the previous table.

Clinical Reviewer's Analysis of Data

Exclusion of Centers under investigation: During the review of the data submitted on December 30, 1996, the Division of Anti-Infective Drug Products was notified that some investigators in the pediatric study were under investigation by FDA's Division of Scientific Investigation. As a result of ongoing investigations, the applicant was contacted and requested to re-analyze the data excluding those centers. On May 6, 1997, the applicant submitted an amendment containing the requested information. The following tables are based on an examination of that data which excludes those centers currently under investigation.

On May 30, 1997, the applicant submitted revised tables based on

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-13/Pediatrics

the exclusion of data from two centers currently under investigation. Those tables are attached as Appendices A through P.

The applicant has requested the approval of an indication for the treatment of uncomplicated skin and skin structure infections in pediatric patients caused by susceptible strains of *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *K. pneumoniae*. As with the adult study, a closer examination of the data concerning these four organisms is necessary. The analysis of the clinical data presented by the applicant grouped these four organisms together with regard to the various baseline diagnoses. In the following tables, the clinical cure rates for each pathogen from the microbiologically evaluable patients according to diagnosis is presented.

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Clinical Efficacy

Table 49. Clinical cure rates - Evaluable pediatric patients with *S. aureus* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 75		Cephalexin n = 77	
	Cure	Failure	Cure	Failure
Impetigo	51	2	53	2
Abscess	1	0	3	0
Paronychia	3	0	5	0
Infected Dermatitis	9	0	3	0
Infected Wound	2	0	5	0
Cellulitis	3	0	1	1
Folliculitis	1	0	0	0
Furuncle	1	0	2	0
Infected Burn	1	0	0	0
Other - Pyoderma	0	0	1	0
Infected Chickenpox	0	0	0	1
Infected Blister	1	0	0	0
Total	73	2	73	4

In Table 49 the clinical cure rates, according to baseline diagnosis, for the 75 pediatric cefdinir patients and the 77 cephalixin patients with *S. aureus* as a baseline pathogen are shown. One cefdinir patient had two different strains of *S.*

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-13/Pediatrics

aureus present, one beta-lactamase positive and one negative.
There were 73 cefdinir patients (97.3%) and 73 cephalixin patients (94.8%) who were cured.

Clinical reviewer's note: The numbers of patients in both treatment groups for each of the diagnostic categories were similar with the exception of patients with infected dermatitis and infected wounds.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalixin with respect to overall clinical cure rates based on the diagnosis excluding centers under investigation, the 95% confidence interval being 75.77 (-0.0494, 0.0999) 97.3%, 94.8%.

Table 50. Clinical cure rates - Evaluable pediatric patients with *S. pyogenes* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 34		Cephalixin n = 33	
	Cure	Failure	Cure	Failure
Impetigo	26	0	18	1
Abscess	0	0	1	0
Paronychia	1	0	3	0
Infected Dermatitis	5	0	3	0
Infected Wound	1	0	2	0
Cellulitis	0	0	2	0
Infected Burn	1	0	1	0
Other - Infected Chickenpox	0	0	0	1
Pyoderma	0	0	1	0
Total	34	0	31	2

Among the 34 cefdinir patients with *S. pyogenes* as a baseline pathogen, all were cured for a 100% cure rate. For the 33 cephalixin patients, there were 31 cures and two failures for a 93.9% cure rate.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalixin with respect to clinical cure rates in patients with *S. pyogenes*, the 95% CI being $_{34,33} (-0.0506, 0.1718)$
100%, 93.9%.

Table 51. Clinical cure rates - Evaluable pediatric patients with *S. agalactiae* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 4		Cephalixin n = 6	
	Cure	Failure	Cure	Failure
Impetigo	3	0	5	0
Paronychia	0	0	1	0
Infected Dermatitis	1	0	0	0
Total	4	0	6	0

All four cefdinir patients and all six cephalixin patients were cures for a 100% cure rate for both treatment groups.

Table 52. Clinical cure rates - Evaluable pediatric patients with *K. pneumoniae* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 3		Cephalexin n = 0	
	Cure	Failure	Cure	Failure
Impetigo	2	0	0	0
Infected Dermatitis	1	0	0	0
Total	3	0	0	0

There were no failures among the three cefdinir patients with *K. pneumoniae* as a baseline pathogen. All of the patients had a polymicrobial infection. Two of the patients had *S. aureus* present and one patient had *E. cloacae* present, along with the *K. pneumoniae*.

Statistical reviewer's note: The sample sizes are too inadequate to perform confidence interval analysis on the data in Tables 51 or 52.

Table 53. Clinical cure rates - Summary of Evaluable pediatric patients with requested organisms according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 116		Cephalexin n = 116	
	Cure	Failure	Cure	Failure
Impetigo	82	2	76	3
Abscess	1	0	4	0
Paronychia	4	0	9	0
Infected Dermatitis	16	0	6	0
Infected Wound	3	0	7	0
Cellulitis	3	0	3	1
Folliculitis	1	0	0	0
Furuncle	1	0	2	0
Infected Burn	2	0	1	0
Other - Pyoderma	0	0	2	0
Infected Chickenpox	0	0	0	2
Infected Blister	1	0	0	0
Total	114	2	110	6

There were 116 evaluable cefdinir patients and 116 evaluable cephalixin patients with the requested organisms as shown in Table 53. There were 114 cefdinir patients (98.3%) and 110 cephalixin patients (94.8%) who were cured. The overall numbers of patients in both treatment groups were similar with the exception of patients with infected dermatitis and infected wounds.

Statistical reviewer's note: Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rates in evaluable patients with the requested organisms (excluding the centers under investigation), the 95% CI being $_{116,116}$ (-0.0208, 0.0898) $_{98.24,94.84}$.

Microbiologic Efficacy

Table 54. Microbiologic eradication rates for requested pathogens from evaluable pediatric patients excluding centers under investigation.

Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
<i>Staphylococcus aureus</i>	75/76	98.7	75/77	97.4
<i>Streptococcus agalactiae</i>	4/4	100.0	6/6	100.0
<i>Streptococcus pyogenes</i>	34/34	100.0	32/33	97.0
<i>Klebsiella pneumoniae</i>	3/3	100.0	0/0	0.0
Total	116/117	99.1	113/116	97.4

Statistical reviewer's note: Cefdinir is therapeutically equivalent in pediatric patients with regards to microbiologic eradication of *S. aureus* [95% CI = $_{76,77}$ (-0.0441, 0.0696) $_{98.74,97.44}$], *S. pyogenes* [95% CI = $_{34,33}$ (-0.0580, 0.1186) $_{100.0,96.94}$], and overall microbiologic eradication rate [95% CI = $_{117,116}$ (-0.0246, 0.0592) $_{99.14,97.44}$]. The sample sizes were inadequate for *S. agalactiae* and *K. pneumoniae* to ensure an acceptable level of power to obtain confidence intervals.

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-13/Pediatrics

Safety

The safety of cefdinir and cephalixin was assessed as described previously in protocol 983-8 using adverse event data, and the results from physical examinations and clinical laboratory tests.

Adverse Events as reported by the applicant: Two hundred eighty-nine patients were included in the safety analysis. Sixty-six of the 142 (46.5%) cefdinir patients and 45 of the 147 (30.6%) cephalixin patients reported one or more adverse events. There were 25 (17.6%) drug-associated adverse events among the cefdinir patients and 16 (10.9%) reported by the patients in the cephalixin group.

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TABLE 55. Summary of Adverse Events -
All Patients Excluding Centers Under Investigation.
[Number (%) of Patients]

(Page 1 of 2)

	Cefdinir N = 142	Cephalexin N = 147
Adverse Events During Study		
All Adverse Events	66 (46.5)	45 (30.6)
Associated* Adverse Events	25 (17.6)	16 (10.9)
Adverse Events During Treatment		
All Adverse Events	30 (21.1)	21 (14.3)
Adverse Events by Sex^b		
All Adverse Events		
Male	35 (46.1)	22 (28.9)
Female	31 (47.0)	23 (32.4)
Associated Adverse Events		
Male	13 (17.1)	7 (9.2)
Female	12 (18.2)	9 (12.7)
Adverse Events by Race^c		
All Adverse Events		
White	44 (50.0)	22 (27.5)
Black	8 (40.0)	5 (20.8)
Asian	0 (0.0)	0 (0.0)
Other	14 (41.2)	18 (42.9)
Associated Adverse Events		
White	13 (14.8)	5 (6.3)
Black	5 (25.0)	3 (12.5)
Asian	0 (0.0)	0 (0.0)
Other	7 (20.6)	8 (19.0)
Adverse Events by Age^d		
All Adverse Events		
<2 yr ^e	17 (85.0)	11 (52.4)
2 to <6 yr	27 (42.2)	24 (32.9)
6 to <13 yr ^f	22 (31.4)	10 (15.6)
Associated Adverse Events		
<2 yr ^e	6 (30.0)	8 (38.1)
2 to <6 yr	10 (15.6)	6 (8.2)
6 to <13 yr ^f	9 (12.9)	2 (3.1)

- * Considered by the investigator to be possibly, probably, or definitely related to study medication.
- ^b Percentages based on total numbers of males or females in a treatment group
- ^c Percentages based on total numbers of patients of each race in a treatment group
- ^d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.
- ^e Includes 1 cephalixin-treated patient approximately 5 days <6 months old
- ^f Includes 1 cephalixin-treated patient age 13 years, 1 month

**TABLE 55. Summary of Adverse Events -
All Patients Excluding Centers Under Investigation.
[Number (%) of Patients]
(Page 2 of 2).**

	Cefdinir N = 142	Cephalexin N = 147
Adverse Events by Maximum Intensity*		
All Adverse Events		
Mild	47 (33.1)	32 (21.8)
Moderate	30 (21.1)	16 (10.9)
Severe	2 (1.4)	1 (0.7)
Associated Adverse Events		
Mild	17 (12.0)	12 (8.2)
Moderate	10 (7.0)	5 (3.4)
Severe	0 (0.0)	0 (0.0)
Serious Adverse Events	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)
Discontinuation of Treatment Due to Adverse Events		
All Adverse Events	2 (1.4)	0 (0.0)
Associated Adverse Events	1 (0.7)	0 (0.0)
Withdrawals After Treatment Due to Adverse Events		
All Adverse Events	9 (6.3)	2 (1.4)
Associated Adverse Events	0 (0.0)	0 (0.0)

* Patients with multiple adverse events were counted once in each applicable category.

Patients who received cefdinir reported a significantly higher number of adverse events (n=66, 46.5%) than those patients who received cephalexin (n=45, 30.6%). The difference between the two treatment groups in drug-associated adverse events was not as great (17.6% versus 10.9%).

TABLE 56. All and Associated^a Adverse Events by Body System - Patients Receiving Study Medication Excluding Centers Under Investigation.
[Number (%) of Patients]
(Page 1 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir ^b N = 142				Cephalexin N = 147			
	All		Associated		All		Associated	
BODY AS A WHOLE	21 ^c	(14.8)	2	(1.4)	18 ^c	(12.2)	0	(0.0)
Infection	13	(9.2)	0	(0.0)	13	(8.8)	0	(0.0)
Headache	4	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Fever	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Accidental Injury	2	(1.4)	0	(0.0)	3	(2.0)	0	(0.0)
Asthenia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
DIGESTIVE SYSTEM	19 ^c	(13.4)	16 ^c	(11.3)	13	(8.8)	10	(6.8)
Diarrhea	15	(10.6)	15	(10.6)	10	(6.8)	9	(6.1)
Gastroenteritis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Vomiting	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Dyspepsia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Constipation	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
HEMIC AND LYMPHATIC SYSTEM	5	(3.5)	4	(2.8)	0	(0.0)	0	(0.0)
Leukopenia	4	(2.8)	4	(2.8)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1	(0.7)	0	(0.0)	1	(0.7)	1	(0.7)
Alkaline Phosphatase Increased	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood Urea Nitrogen Increased	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
NERVOUS SYSTEM	3 ^c	(2.1)	1	(0.7)	2	(1.4)	0	(0.0)
Nervousness	2	(1.4)	1	(0.7)	0	(0.0)	0	(0.0)
Incoordination	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vestibular Disorder	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Insomnia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
RESPIRATORY SYSTEM	16 ^c	(11.3)	0	(0.0)	10 ^c	(6.8)	0	(0.0)
Rhinitis	5	(3.5)	0	(0.0)	3	(2.0)	0	(0.0)
Cough Increased	5	(3.5)	0	(0.0)	2	(1.4)	0	(0.0)
Pharyngitis	5	(3.5)	0	(0.0)	3	(2.0)	0	(0.0)
Bronchitis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Lung Disorder	2	(1.4)	0	(0.0)	2	(1.4)	0	(0.0)
Sinusitis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Asthma	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)

^a Possibly, probably, or definitely related to treatment

^b All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.

^c The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

TABLE 56. All and Associated* Adverse Events by Body System - Patients Receiving Study Medication Excluding Centers Under Investigation.
[Number (%) of Patients]
(Page 2 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir ^b N=142				Cephalexin N=147			
	All		Associated		All		Associated	
SKIN AND APPENDAGES	19 ^c	(13.4)	4 ^c	(2.8)	16	(10.9)	6	(4.1)
Rash	7	(4.9)	2	(1.4)	6	(4.1)	3	(2.0)
Eczema	3	(2.1)	0	(0.0)	2	(1.4)	0	(0.0)
Pustular Rash	3	(2.1)	0	(0.0)	2	(1.4)	1	(0.7)
Contact Dermatitis	2	(1.4)	1	(0.7)	2	(1.4)	0	(0.0)
Cutaneous Moniliasis	2	(1.4)	2	(1.4)	2	(1.4)	2	(1.4)
Nail Disorder	2	(1.4)	0	(0.0)	0	(0.0)	1	(0.7)
Fungal Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Furunculosis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes Simplex	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vesiculobullous Rash	1	(0.7)	0	(0.0)	0	(0.0)	1	(0.7)
Acne	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dry Skin	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
SPECIAL SENSES	9	(6.3)	0	(0.0)	2	(1.4)	0	(0.0)
Otitis Media	4	(2.8)	0	(0.0)	2	(1.4)	0	(0.0)
Conjunctivitis	3	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Disorder	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Pain	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
UROGENITAL SYSTEM	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Hematuria	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Urine Abnormality	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

* Possibly, probably, or definitely related to treatment

^b All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.

^c The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Clinical reviewer's note: As found in the adult study, diarrhea was the most frequently reported adverse event with 15 cases among the cefdinir patients and 10 cases reported by the cephalexin patients. Infection was the second most frequently reported adverse event with 10 cases reported for both treatment groups.

Deaths: There were no deaths during the study.

Serious Adverse Events: There were no serious adverse events reported during the study.

TABLE 57. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Receiving Study Medication Excluding Centers Under Investigation.

	[Number (%) of Patients]	
BODY SYSTEM/ Adverse Event	Cefdinir N=142	Cephalexin N = 147
BODY AS A WHOLE	1 (0.7)	2 (1.4)
Accidental Injury	1 (0.7)	1 (0.7)
Infection	0 (0.0)	0 (0.0)
DIGESTIVE SYSTEM	0* (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)
RESPIRATORY SYSTEM	3 (2.1)	0 (0.0)
Sinusitis	2 (1.4)	0 (0.0)
Bronchitis	1 (0.7)	0 (0.0)
SKIN AND APPENDAGES	2 (1.4)	0 (0.0)
Pustular Rash	1 (0.7)	0 (0.0)
Rash	1 (0.7)	0 (0.0)
SPECIAL SENSES	6 (4.2)	1 (0.7)
Otitis Media	4 (2.8)	1 (0.7)
Conjunctivitis	2 (1.4)	0 (0.0)

* The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

There were two cefdinir patients (1.4%) and no cephalexin patients who discontinued the study medication due to adverse events. One of the cefdinir patients had an adverse event considered drug-associated (rash). Nine cefdinir patients (6.3%) and three cephalexin patients (2.0%) withdrew from the study after completing their respective treatments.

Clinical Laboratory Measurements: No remarkable changes were noted in the median differences between baseline and final laboratory values for both groups of patients receiving study medication. Most laboratory values remained within the same category (i.e., above, within or below normal values) at the final visit when compared with baseline values. For both patient groups, there were more decreases in white cell counts than

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-13/Pediatrics

increases, which is consistent with a resolving infection. The most frequent markedly abnormal laboratory values were increased eosinophil counts (higher frequency with cephalexin), and increased values for lactate dehydrogenase, alkaline phosphatase (higher frequency with cefdinir), phosphorus, and urine pH.

Clinical and Statistical Reviewers' Conclusions Regarding NDA 50-739, Protocol 983-8, and NDA 50-749, Protocol 983-13.

The applicant is requesting approval of an NDA for Omnicef Capsules and Omnicef Suspension for the treatment of uncomplicated skin and skin structure infections caused by *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *K. pneumoniae*. In support of this request, data from two clinical trials, an adult study with 34 investigators and 975 patients, and a pediatric study with 18 investigators and 394 patients, were submitted.

Both studies were randomized, comparative, multicenter studies with two parallel treatment groups. The adult study involved therapy with the capsule formulation and was double-blinded. The pediatric study involved therapy with the oral suspension and was investigator-blinded. In both studies, cephalexin was the comparator agent.

In the adult study, there were 178 evaluable patients with 215 pathogens in the cefdinir treatment group and 204 evaluable patients with 247 pathogens in the cephalexin treatment group. The eradication rate for all pathogens in the cefdinir group was 200/215 (93.0%) compared to 221/247 (89.5%) for all pathogens in the cephalexin treatment group. The clinical cure rates for cefdinir and cephalexin were 148/178 (83.1%) and 163/204 (79.9%), respectively. The 95% CI showed them to be equivalent.

In the FDA clinical reviewer's analysis of the data, the results were evaluated according to the specific organisms requested and the baseline diagnoses. There was a total of 181 evaluable cefdinir patients and 203 evaluable cephalexin patients with skin and skin structure infections caused by the four organisms

requested. The overall clinical cure rates for cefdinir and cephalixin were 153/181 (84.5%) and 156/203 (76.8%), respectively.

The clinical cure rate for cefdinir patients with infections caused by *S. aureus* was 122/143 (85.3%) compared to 133/165 (80.6%) for cephalixin patients with similar infections due to *S. aureus*. The clinical cure rates for cefdinir patients and cephalixin patients with infections due to *S. pyogenes* were 14/17 (82.4%) and 10/11 (90.9%), respectively. For the evaluable patients with infections due to *S. agalactiae*, the clinical cure rates were 10/13 (76.9%) for the cefdinir group and 10/18 (55.6%) for the comparator group. Likewise, the clinical cure rates for cefdinir patients and cephalixin patients with infections caused by *K. pneumoniae* were 7/8 (87.5%) and 3/9 (33.3%), respectively.

In the pediatric study, there were 118 evaluable patients with 166 pathogens in the cefdinir treatment group and 113 evaluable patients with 156 pathogens in the cephalixin treatment group. The eradication rate for all pathogens in the cefdinir group was 165/166 (99.4%) compared to 152/156 (97.4%) for all pathogens in the cephalixin group. The clinical cure rates for cefdinir and cephalixin were 116/118 (98.3%) and 106/113 (93.8%), respectively. Based on the 95% confidence interval, the two treatment arms were shown to be therapeutically equivalent.

In the FDA clinical reviewer's analysis, which excluded centers under investigation, there was a total of 116 evaluable cefdinir patients and 116 evaluable cephalixin patients with skin and skin structure infections caused by the four organisms requested. The overall clinical cure rates for cefdinir and cephalixin were 114/116 (98.3%) and 110/116 (94.8%), respectively.

The clinical cure rate for pediatric cefdinir patients with infections caused by *S. aureus* was 73/75 (97.3%) compared to 73/77 (94.8%) for cephalixin patients with similar infections. The clinical cure rates for pediatric cefdinir patients and

cephalexin patients with infections due to *S. pyogenes* were 34/34 (100%) and 31/33 (93.9%), respectively. For the evaluable pediatric patients with infections due to *S. agalactiae*, the clinical cure rates were 4/4 (100%) for the cefdinir group and 6/6 (100%) for the cephalexin group. The clinical cure rate for cefdinir pediatric patients with infections due to *K. pneumoniae* was 3/3 (100%); while in the comparator group, there were no evaluable patients with an infection caused by *K. pneumoniae*.

In both the adult and pediatric studies, patients who received cefdinir had more adverse events than those patients in the cephalexin treatment group. In the adult study, 193 (39.1%) of the 494 cefdinir patients and 144 (30.1%) of the 478 cephalexin patients reported one or more adverse events. There were 135 (27.3%) drug-associated adverse events among the cefdinir patients and 79 (16.5%) among the patients who received cephalexin.

In the pediatric study with the data excluding centers under investigation, 66 of the 142 (46.5%) cefdinir patients and 45 of the 147 (30.6%) cephalexin patients reported one or more adverse events. There were 25 (17.6%) drug-associated adverse events among the cefdinir patients and 16 (10.9%) reported by the patients in the cephalexin group.

In both studies, diarrhea was the most frequently reported adverse event among the cefdinir patients. There were 78 reports (16.5%) of diarrhea in the adult study and 15 cases (10.6%) reported in the pediatric study. Other frequently reported adverse events included nausea with 17 reports (3.6%) and moniliasis with 14 reports (7.3%) in the adult study. Infection with 13 cases (9.2%) was the second most frequently reported adverse event, following diarrhea, in the pediatric study.

Discussion: The Division of Anti-Infective Drug Products has traditionally divided skin and skin structure infections (SSSI) into two broad categories: uncomplicated SSSI and complicated SSSI (Points to Consider Document, Skin and Skin Structure

Infection Guidelines presented at the Anti-Infective Advisory Committee Meeting, March 5-7, 1997). The uncomplicated category consists of superficial skin infections, e.g., impetigo, simple abscesses, while the complicated category refers to infections involving deeper soft tissue or ones that require surgical intervention.

The pathogens responsible for the various types of SSSI in both categories also differ. For uncomplicated SSSI, the two most commonly seen pathogens are *S. aureus* and *S. pyogenes*.

Traditionally, those two organisms are the only ones included as pathogens for this indication. Other organisms are not universally accepted by academia as pathogens in this indication; most are considered as colonizers or contaminants.

One of the ways to identify a true pathogen from a possible contaminant or colonizer is to examine the frequency in which the organism is isolated in a pure culture. In the case of *S. aureus*, this organism is very often isolated from uncomplicated SSSI as a single pathogen. On the other hand, *K. pneumoniae* is most often part of a mixed or polymicrobial infection. For example, in the applicant's two studies, 11 cases of *K. pneumoniae* were reported, with 10 cases involving other species. There was only one case involving a patient with paronychia where the *K. pneumoniae* appeared as a single pathogen. A similar situation exists with *S. agalactiae* where it was commonly isolated as part of a polymicrobial infection, rather than a primary, baseline pathogen.

Labeling: The applicant has submitted sufficient data to show that cefdinir is safe and effective in the treatment of uncomplicated skin and skin structure infections in both an adult and pediatric population. Data from both clinical trials show the drug to be effective in the eradication of various types of skin and skin structure infections caused by *S. aureus* and *S. pyogenes*, when used as directed. The data regarding *S.*

NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-13/Pediatrics

agalactiae and *K. pneumoniae* are insufficient because of the much smaller number of cases involving these organisms, their occurrence primarily in polymicrobial infections, and their questionable role at this time as pathogens or contaminants in these infections.

Therefore, the proposed indications should be revised to read as follows: "Uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β -lactamase producing strains) and *Streptococcus pyogenes*".

In the Pediatric Use subsection under PRECAUTIONS, the following statement, based on the age of the participants, should be added: "Safety and effectiveness in children below the age of 6 months have not been established."

With regard to the ADVERSE REACTIONS section of the labeling, diarrhea should be listed as an adverse event related to cefdinir therapy in both formulations. Nausea, headache and moniliasis should be listed as adverse events in the labeling for the capsule formulation.

The proposed dosage should be: 300 mg q12h for 10 days for the capsule formulation and 7 mg/kg q12h for 10 days for the oral suspension.

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NDA 50-739 (Cefdinir capsule)
NDA 50-749 (Cefdinir oral suspension)

Skin & Skin Structure Infections
Protocol 983-13/Pediatrics

Recommendation: It is recommended that cefdinir capsules and cefdinir suspension be approved for the treatment of uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β -lactamase producing strains) and *Streptococcus pyogenes*. Additional statements to the labeling should be added as described under Labeling.

/S/

Aloka G. Chakravarty, Ph.D.

/S/

Daphne Lin, Ph.D.

cc: Orig. NDA

HFD-340

HFD-520

HFD-520/MO/Soreth

ClinRev/Blank

Pharm/Osterberg

Chem/Pagay

Micro/Sheldon

PM/Duvall-Miller

HFD-725/Dr. Chakravarty

Dr. Lin

Dr. Huque

Chron.

HFD-344/Dr. Thomas

WP 6.1; 50-739; 5-28-97; 9-26-97; 11-5-97

/S/

James Blank, Ph.D.

/S/

Janice Soreth, M.D.

12/18/98

Concurrence only:

HFD-520/ActDivDir/GChikami

HFD-520/SMO/JSoreth

12/20/98

Appendix A

TABLE 1. List of Investigators without Sites 3 and 11

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed*	Evaluable
2	C. Khurana	3	3	0
4	J. Hedrick	51	50	34
5	W. Gooch	2	2	2
6	S. Wiederhold	28	23	15
7	S. Chartrand	24	24	19
8	J. McCarty	73	63	42
9	E. Rothstein	10	9	7
10	J. Haddad	3	1	0
12	S. McLinn	6	6	4
15	P. DiLorenzo	19	16	15
16	A. Phillips	6	2	2
17	R. Ford	13	12	8
18	J. Scott	21	19	16
19	S. Weakley	16	12	11
20	S. Davis	1	1	1
21	A. Herbert	13	7	4
Total		289	250	180

* Completed treatment and test-of-cure visit

Appendix B

Table 8

Summary of Patient Characteristics
Patients Who Received Study Medication

		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparato- rs	Cephalexin
Total	Patients	142	142	147	147
Sex					
Male	N	76	76	76	76
	Percent	53.5	53.5	51.7	51.7
Female	N	66	66	71	71
	Percent	46.5	46.5	48.3	48.3
Race					
White	N	88	88	80	80
	Percent	62.0	62.0	54.4	54.4
Black	N	20	20	24	24
	Percent	14.1	14.1	16.3	16.3
Asian	N	0	0	1	1
	Percent	0	0	0.7	0.7
Other	N	1	1	6	6
	Percent	0.7	0.7	4.1	4.1
Hispanic	N	33	33	36	36
	Percent	23.2	23.2	24.5	24.5

Appendix B
Table 8

Summary of Patient Characteristics
Patients Who Received Study Medication

		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparato- rs	Cephalexin
Age (Years)					
< 2	N	19	19	21	21
	Percent	13.4	13.4	14.3	14.3
2 to < 6	N	54	54	64	64
	Percent	38.0	38.0	43.5	43.5
6 to < 13	N	69	69	62	62
	Percent	48.6	48.6	42.2	42.2
Age Range	Max	13	13	13	13
	Min	1	1	0	0

Appendix

Table 9

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparato- rs	Cephalexin
Total	Patients	90	90	90	90
Sex					
Male	N	46	46	41	41
	Percent	51.1	51.1	45.6	45.6
Female	N	44	44	49	49
	Percent	48.9	48.9	54.4	54.4
Race					
White	N	61	61	52	52
	Percent	67.8	67.8	57.8	57.8
Black	N	8	8	14	14
	Percent	8.9	8.9	15.6	15.6
Asian	N	0	0	1	1
	Percent	0	0	1.1	1.1
Other	N	1	1	3	3
	Percent	1.1	1.1	3.3	3.3
Hispanic	N	20	20	20	20
	Percent	22.2	22.2	22.2	22.2

Appendix C
Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparato- rs	All Cephalexin
Age (Years)					
< 2	N	11	11	10	10
< 2	Percent	12.2	12.2	11.1	11.1
2 to < 6	N	37	37	38	38
	Percent	41.1	41.1	42.2	42.2
6 to < 13	N	42	42	42	42
	Percent	46.7	46.7	46.7	46.7
Age Range	Max	13	13	13	13
	Min	1	1	1	1

Appendix D
Table 11

Distribution of Baseline Pathogens by Susceptibility to Treatment-
Pathogens from All Patients with Baseline Pathogens

Pathogen		Cefdinir			Cephalexin		
		S	I	R	S	I	R
Total		N	N	N	N	N	N
Gram Positive	Bacil sp	1	0	0	1	0	0
	E faecal	17	3	6	8	1	0
	E faeciu	1	0	0	1	0	0
	E hirae	2	1	0	1	1	0
	S agalac	16	16	0	0	15	1
	S aureus	216	216	0	0	215	0
	S pneumo	3	3	0	0	3	0
	S pyogen	89	89	0	0	89	0
	Strep C	1	1	0	0	1	0
	Strep D	1	0	0	1	0	0
	Strep F	1	1	0	0	1	0
	Total	348	330	6	12	326	1
Gram Negative	A anit	7	0	0	7	1	0
	A lwoffii	2	0	0	2	0	0
	Cdc NOS	1	0	0	1	0	0
	E aeroge	1	1	0	0	0	1
	E agglom	5	5	0	0	4	1
	E cloaca	4	4	0	0	3	0

-S=Susceptible, I=Moderately Susceptible or Intermediate,
R=Resistant, U=Unknown

Appendix D

Distribution of Baseline Pathogens by Susceptibility to Treatment-
Pathogens from All Patients with Baseline Pathogens

Pathogen		Cefdinir			Cephalexin		
		S	I	R	S	I	R
		Total	N	N	N	N	N
Gram	E coli	2	2	0	0	2	0
Negative	K oxytoc	2	2	0	0	2	0
	K pneumo	4	4	0	0	2	0
	Morax sp	2	2	0	0	2	0
	P aerugi	4	0	0	4	0	4
	Pa multo	1	1	0	0	1	0
	S marces	1	0	0	1	0	1
	Total	36	21	0	15	18	2
Total	Pathogens	384	351	6	27	344	3

-S=Susceptible, I=Moderately Susceptible or Intermediate,
R=Resistant, U=Unknown

Appendix E

Summary of Patient Exposure to Study Medication
All Patients

Days on Study Medication	Number (%) of Patients									
	All Cefdinir		Cefdinir 7 mg/kg BID		All Comparators		Cephalexin			
	N	%	N	%	N	%	N	%		
2	1	0.7	1	0.7	0	0	0	0		
4	3	2.1	3	2.1	2	1.4	2	1.4		
5	0	0	0	0	2	1.4	2	1.4		
6	3	2.1	3	2.1	0	0	0	0		
7	5	3.5	5	3.5	0	0	0	0		
8	1	0.7	1	0.7	4	2.7	4	2.7		
9	2	1.4	2	1.4	2	1.4	2	1.4		
10	75	52.8	75	52.8	24	16.3	24	16.3		
11	46	32.4	46	32.4	98	66.7	98	66.7		
12	2	1.4	2	1.4	4	2.7	4	2.7		
14	0	0	0	0	2	1.4	2	1.4		
17	0	0	0	0	1	0.7	1	0.7		
21	0	0	0	0	1	0.7	1	0.7		
Unknown	4	2.8	4	2.8	7	4.8	7	4.8		
Total	142	100.0	142	100.0	147	100.0	147	100.0		

Appendix F

Table 14

Reasons for Exclusion of Patients from Evaluable Analyses
Test-of-Cure Visit

			Number (%) of Patients					
			Cephalexin					
			Cefdinir 7 10 mg/kg					
			mg/kg BID QID Total					
			N	%	N	%	N	%
Exclusions from	*** Total ***		47	33.1	51	34.7	98	33.9
Clinical Analyses								
	Clin asmt missed		5	3.5	7	4.8	12	4.2
	Clin out of range		19	13.4	22	15.0	41	14.2
	Concurrent antibac		4	2.8	3	2.0	7	2.4
	Med not as prescrib		19	13.4	11	7.5	30	10.4
	Prior antibact		4	2.8	3	2.0	7	2.4
	Resistant pathogens		14	9.9	23	15.6	37	12.8
Additional	*** Total ***		5	3.5	6	4.1	11	3.8
Exclusions from								
Microbiological	Cult out of range		16	11.3	20	13.6	36	12.5
Analyses	Culture missed		7	4.9	9	6.1	16	5.5
	No proven pathogen		18	12.7	14	9.5	32	11.1
Total	*** TOTAL ***		52	36.6	57	38.8	109	37.7

Appendix F

Reasons for Disqualification of Microbiologically/Clinically Evaluable Patients from Analysis Long-Term Follow-Up Visit

Disqualification	Number (%) of Patients			
	Cefdinir 7 10 mg/kg		Cephalexin	
	mg/kg BID		QID	
	N	%	N	%
*** Total ***	13	14.4	9	10.0
Clin asmt missed	7	7.8	6	6.7
Clin out of range	3	3.3	2	2.2
Concurrent antibac	3	3.3	1	1.1
Cult out of range	3	3.3	2	2.2
Culture missed	6	6.7	6	6.7

Appendix 5

Table 16

Summary of Microbiologic Response Rates by Pathogen (According to Baseline Pathogen) by Indication
 Test-of-Cure Visit
 Pathogens from Microbiologically-Clinically Evaluable Patients

Pathogen		Number (%) of Pathogens															
		All Cefdinir				Cefdinir 7 mg/kg BID				All Comparators				Cephalexin			
		Eradication		Persistence		Eradication		Persistence		Eradication		Persistence		Eradication		Persistence	
		on	ce	on	ce	on	ce	on	ce	on	ce	on	ce	on	ce	on	ce
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gram Positive	E faecal	0	0	0	0	0	0	0	0	1	100.0	0	0	1	100.0	0	0
	E hirae	1	100.0	0	0	1	100.0	0	0	0	0	0	0	0	0	0	0
	S agalac	4	100.0	0	0	4	100.0	0	0	6	100.0	0	0	6	100.0	0	0
	S aureus	75	98.7	1	1.3	75	98.7	1	1.3	75	97.4	2	2.6	75	97.4	2	2.6
	S pneumo	2	100.0	0	0	2	100.0	0	0	1	100.0	0	0	1	100.0	0	0
	S pyogen	34	100.0	0	0	34	100.0	0	0	32	97.0	1	3.0	32	97.0	1	3.0
	Strep C	1	100.0	0	0	1	100.0	0	0	0	0	0	0	0	0	0	0
Gram Negative	E agglom	3	100.0	0	0	3	100.0	0	0	2	100.0	0	0	2	100.0	0	0
	E cloaca	2	100.0	0	0	2	100.0	0	0	0	0	0	0	0	0	0	0
	E coli	0	0	0	0	0	0	0	0	1	100.0	0	0	1	100.0	0	0
	K oxytoc	1	100.0	0	0	1	100.0	0	0	0	0	0	0	0	0	0	0
	K pneumo	3	100.0	0	0	3	100.0	0	0	0	0	0	0	0	0	0	0
	Morax sp	1	100.0	0	0	1	100.0	0	0	1	100.0	0	0	1	100.0	0	0
Total	Pathogens	127	99.2	1	0.8	127	99.2	1	0.8	119	97.5	3	2.5	119	97.5	3	2.5

Appendix H
Table 18

Summary of Microbiologic Response Rates by Pathogen (By Baseline Diagnosis)

Test-of-Cure Visit
Pathogens from Microbiologically-Clinically Evaluable Patients

Diagnosis at Baseline = Abscess

Pathogen		Number (%) of Pathogens			
		Cephalalexin			
		Cefdinir 7 10 mg/kg			
		mg/kg BID QID			
		Eradicati- Eradicati-			
		on on			
		N % N %			
Gram	S aureus	1 100.0	3 100.0		
Positive	S pyogen	0	0	1 100.0	
Total	Pathogens	1 100.0	4 100.0		

Diagnosis at Baseline = Infected burn

Pathogen		Number (%) of Pathogens			
		Cephalalexin			
		Cefdinir 7 10 mg/kg			
		mg/kg BID QID			
		Eradicati- Eradicati-			
		on on			
		N % N %			
Gram	S aureus	1 100.0	0	0	
Positive	S pyogen	1 100.0	1 100.0		
Total	Pathogens	2 100.0	1 100.0		

Appendix H

Diagnosis at Baseline = Cellulitis

Pathogen		Number (%) of Pathogens			
		Cephalexin			
		Cefdinir 7 10 mg/kg			
		mg/kg BID QID			
		Eradicati- Eradicati-			
		on on			
		N	%	N	%
Gram	S aureus	3	100.0	2	100.0
Positive	S pyogen	0	0	2	100.0
Gram	E cloaca				
Negative		1	100.0	0	0
Total	Pathogens	4	100.0	4	100.0

Diagnosis at Baseline = Infected dermatitis

Pathogen		Number (%) of Pathogens			
		Cephalexin			
		Cefdinir 7 10 mg/kg			
		mg/kg BID QID			
		Eradicati- Eradicati-			
		on on			
		N	%	N	%
Gram	S agalac	1	100.0	0	0
Positive	S aureus	9	100.0	3	100.0
	S pyogen	5	100.0	3	100.0
Gram	E agglom	1	100.0	1	100.0
Negative	E coli	0	0	1	100.0
	K pneumo	1	100.0	0	0
Total	Pathogens	17	100.0	8	100.0

Appendix H

Diagnosis at Baseline = Folliculitis

Pathogen		Number (%) of Pathogens	
		Cefdinir 7 mg/kg BID	
		Eradication	
		N	
		%	
Gram	S aureus		
Positive		1	100.0
Total	Pathogens	1	100.0

Diagnosis at Baseline = Furuncle

Pathogen		Number (%) of Pathogens			
		Cephalexin			
		Cefdinir 7 mg/kg BID			
		10 mg/kg QID			
		Eradication			
		on			
		N			
		%			
Gram	S aureus				
Positive		1	100.0	2	100.0
Total	Pathogens	1	100.0	2	100.0

Appendix H

Diagnosis at Baseline - Impetigo

Pathogen		Number (%) of Pathogens							
		Cephalexin 10 mg/kg				Cefdinir 7 mg/kg BID			
		QID							
		Eradication		Persistence		Eradication		Persistence	
		n	%	n	%	n	%	n	%
Gram Positive	E faecal	0	0	0	0	1	100.0	0	0
	E hirae	1	100.0	0	0	0	0	0	0
	S agalac	3	100.0	0	0	5	100.0	0	0
	S aureus	52	98.1	1	1.9	53	96.4	2	3.6
	S pneumo	2	100.0	0	0	1	100.0	0	0
	S pyogen	26	100.0	0	0	18	94.7	1	5.3
Gram Negative	E agglom	0	0	0	0	1	100.0	0	0
	E cloaca	1	100.0	0	0	0	0	0	0
	K oxytoc	1	100.0	0	0	0	0	0	0
	K pneumo	2	100.0	0	0	0	0	0	0
	Morax sp	1	100.0	0	0	1	100.0	0	0
Total	Pathogens	89	98.9	1	1.1	80	96.4	3	3.6

Appendix H

Diagnosis at Baseline = Paronychia

Pathogen		Number (%) of Pathogens			
		Cephalexin			
		Cefdinir 7 10 mg/kg			
		mg/kg BID QID			
		Eradicati-			
		on on			
		N	%	N	%
Gram	S agalac	0	0	1	100.0
Positive	S aureus	3	100.0	5	100.0
	S pyogen	1	100.0	3	100.0
Gram	E agglom				
Negative		2	100.0	0	0
Total	Pathogens	6	100.0	9	100.0

Diagnosis at Baseline = Infected traum/surg wound

Pathogen		Number (%) of Pathogens			
		Cephalexin			
		Cefdinir 7 10 mg/kg			
		mg/kg BID QID			
		Eradicati-			
		on on			
		N	%	N	%
Gram	S aureus	2	100.0	5	100.0
Positive	S pyogen	1	100.0	2	100.0
	Strep C	1	100.0	0	0
Total	Pathogens	4	100.0	7	100.0

Appendix H

Diagnosis at Baseline = Other

Pathogen		Number (%) of Pathogens			
		Cephalexin			
		Cefdinir 7/10 mg/kg			
		mg/kg BID QID			
		Eradication			
		on			
		N % N			
Gram	S aureus	2	100.0	2	100.0
Positive					
	S pyogen	0	0	2	100.0
Total	Pathogens	2	100.0	4	100.0

Summary of Microbiologic Eradication Rates by Patient (According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		All Cefdinir			Cefdinir 7 mg/kg BID			All Comparators		
		Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%	Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%	Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%
Gram Positive	S aureus	42	41	97.6	42	41	97.6	46	44	95.7
	S pneumo	0	0	0	0	0	0	1	1	100.0
	S pyogen	11	11	100.0	11	11	100.0	11	11	100.0
	Strep C	1	1	100.0	1	1	100.0	0	0	0
Gram Negative	E agglom	0	0	0	0	0	0	1	1	100.0
Multiple	E faecal +									
	S aureus +									
	S pyogen	0	0	0	0	0	0	1	1	100.0
	E hirae +									
	S aureus	1	1	100.0	1	1	100.0	0	0	0
	S agalac +									
	S aureus	3	3	100.0	3	3	100.0	6	6	100.0
	S agalac +									
	S aureus +									
	S pyogen	1	1	100.0	1	1	100.0	0	0	0
	S aureus +									
	S aureus (1)	1	1	100.0	1	1	100.0	0	0	0
	S aureus +									
	S pneumo	2	2	100.0	2	2	100.0	0	0	0
	S aureus +									
	S pyogen	20	20	100.0	20	20	100.0	21	20	95.2

Append. 1

Summary of Microbiologic Eradication Rates by Patient (According to Baseline Pathogen) by Indication

Test-of-Cure Visit

Microbiologically-Clinically Evaluable Patients

Indication: Uncomplicated Skin and Skin Structure Infections

Baseline Pathogen(s)		All Cefdinir			Cefdinir 7 mg/kg BID			All Comparators		
		Number of	Number with		Number of	Number with		Number of	Number with	
		Pts w/	Eradication		Pts w/	Eradication		Pts w/	Eradication	
		Pathogen(s)	at TOC		Pathogen(s)	at TOC		Pathogen(s)	at TOC	
		at Baseline	Visit	%	at Baseline	Visit	%	at Baseline	Visit	%
Multiple	S aureus +									
	E agglom	0	0	0	0	0	0	1	1	100.0
	S aureus +									
	E agglom +									
	E agglom (1)	1	1	100.0	1	1	100.0	0	0	0
	S aureus +									
	E cloaca	1	1	100.0	1	1	100.0	0	0	0
	S aureus +									
	E coli	0	0	0	0	0	0	1	1	100.0
	S aureus +									
	K oxytoc	1	1	100.0	1	1	100.0	0	0	0
	S aureus +									
	K pneumo	2	2	100.0	2	2	100.0	0	0	0
	S aureus +									
	Morax sp	0	0	0	0	0	0	1	1	100.0
	S pyogen +									
	E agglom	1	1	100.0	1	1	100.0	0	0	0
	S pyogen +									
	Morax sp	1	1	100.0	1	1	100.0	0	0	0
	E cloaca +									
	K pneumo	1	1	100.0	1	1	100.0	0	0	0
Total	Patients	90	89	98.9	90	89	98.9	90	87	96.7

Appendix I

Summary of Microbiologic Eradication Rates by Patient (According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		Cephalexin		
		Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%
Gram Positive	S aureus	46	44	95.7
	S pneumo	1	1	100.0
	S pyogen	11	11	100.0
	Strep C	0	0	0
Gram Negative	E agglom	1	1	100.0
Multiple	E faecal +			
	S aureus +			
	S pyogen	1	1	100.0
	E hirae +			
	S aureus	0	0	0
	S agalac +			
	S aureus	6	6	100.0
	S agalac +			
	S aureus +			
	S pyogen	0	0	0
	S aureus +			
	S aureus (1)	0	0	0
	S aureus +			
	S pneumo	0	0	0
	S aureus +			
	S pyogen	21	20	95.2

Appendix I

Summary of Microbiologic Eradication Rates by Patient
(According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		Cephalexin		
		Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%
Multiple	S aureus + E agglom	1	1	100.0
	S aureus + E agglom + E agglom (1)	0	0	0
	S aureus + E cloaca	0	0	0
	S aureus + E coli	1	1	100.0
	S aureus + K oxytoc	0	0	0
	S aureus + K pneumo	0	0	0
	S aureus + Morax sp	1	1	100.0
	S pyogen + E agglom	0	0	0
	S pyogen + Morax sp	0	0	0
	E cloaca + K pneumo	0	0	0
Total	Patients	90	87	96.7

Appendix J

Table 20

Summary of Microbiologic Response Rates by Patient (By Baseline Diagnosis)
Test-of-Cure Visit

Microbiologically-Clinically Evaluable Patients
Diagnosis at Baseline = Abscess

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	1	100.0	4	100.0
Total	1	100.0	4	100.0

Diagnosis at Baseline = Infected burn

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	1	100.0	1	100.0
Total	1	100.0	1	100.0

Diagnosis at Baseline = Cellulitis

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	3	100.0	3	100.0
Total	3	100.0	3	100.0

Appendix J

Diagnosis at Baseline - Infected dermatitis

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	11	100.0	6	100.0
Total	11	100.0	6	100.0

Diagnosis at Baseline - Folliculitis

Microbiologic Response	Number (%) of Patients	
	Cefdinir 7 mg/kg BID	
	N	%
Patients w/ eradication	1	100.0
Total	1	100.0

Diagnosis at Baseline - Furuncle

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	1	100.0	2	100.0
Total	1	100.0	2	100.0

Appendix J

Diagnosis at Baseline = Impetigo

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	63	98.4	58	95.1
Patients w/ persistence	1	1.6	3	4.9
Total	64	100.0	61	100.0

Diagnosis at Baseline = Paronychia

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	3	100.0	5	100.0
Total	3	100.0	5	100.0

Diagnosis at Baseline = Infected traum/surg wound

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	4	100.0	6	100.0
Total	4	100.0	6	100.0

Diagnosis at Baseline = Other

Microbiologic Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7 10 mg/kg	
	mg/kg BID		QID	
	N	%	N	%
Patients w/ eradication	1	100.0	2	100.0
Total	1	100.0	2	100.0

Appendix K

Table 22

Summary of Clinical Response Rate by Pathogen (Across All Diagnoses)
 Combined Investigator/Sponsor Determination
 Test-of-Cure Visit
 Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		Number (%) of Patients							
		Cefdinir 7 mg/kg BID				Cephalexin 10 mg/kg QID			
		Cure		Failure		Cure		Failure	
		N	%	N	%	N	%	N	%
Gram Positive	S aureus	40	95.2	2	4.8	44	95.7	2	4.3
	S pneumo	0	0	0	0	1	100.0	0	0
	S pyogen	11	100.0	0	0	11	100.0	0	0
	Strep C	1	100.0	0	0	0	0	0	0
Gram Negative	E agglom	0	0	0	0	0	0	1	100.0
Multiple	E faecal +								
	S aureus +								
	S pyogen	0	0	0	0	1	100.0	0	0
	E hirae +								
	S aureus	1	100.0	0	0	0	0	0	0
	S agalac +								
	S aureus	3	100.0	0	0	6	100.0	0	0
	S agalac +								
	S aureus +								
	S pyogen	1	100.0	0	0	0	0	0	0
	S aureus +								
	S aureus (1)	1	100.0	0	0	0	0	0	0
	S aureus +								
	S pneumo	2	100.0	0	0	0	0	0	0

Appendix K

Baseline Pathogen(s)		Number (%) of Patients							
		Cefdinir 7 mg/kg BID				Cephalexin 10 mg/kg QID			
		Cure		Failure		Cure		Failure	
		N	%	N	%	N	%	N	%
Multiple	S aureus +								
	S pyogen	20	100.0	0	0	19	90.5	2	9.5
	S aureus +								
	E agglom	0	0	0	0	1	100.0	0	0
	S aureus +								
	E agglom +								
	E agglom (1)	1	100.0	0	0	0	0	0	0
	S aureus +								
	E cloaca	1	100.0	0	0	0	0	0	0
	S aureus +								
	E coli	0	0	0	0	1	100.0	0	0
	S aureus +								
	K oxytoc	1	100.0	0	0	0	0	0	0
	S aureus +								
	K pneumo	2	100.0	0	0	0	0	0	0
	S aureus +								
	Morax sp	0	0	0	0	1	100.0	0	0
	S pyogen +								
	E agglom	1	100.0	0	0	0	0	0	0
	S pyogen +								
	Morax sp	1	100.0	0	0	0	0	0	0

Appendix K

Baseline Pathogen(s)		Number (%) of Patients							
		Cefdinir 7 mg/kg BID				Cephalexin 10 mg/kg QID			
		Cure		Failure		Cure		Failure	
		N	%	N	%	N	%	N	%
Multiple	E cloaca +	1	100.0	0	0	0	0	0	0
	K pneumo	1	100.0	0	0	0	0	0	0
Total Patients		88	97.8	2	2.2	85	94.4	5	5.6

Appendix L

Table 23

Summary of Clinical Response Rates by Patient (By Baseline Diagnosis)
Combined Investigator/Sponsor Determination
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Diagnosis at Baseline = Abscess

Clinical Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7/10 mg/kg	
	mg/kg BID	QID	mg/kg BID	QID
	N	%	N	%
Cure	1	100.0	4	100.0
Total	1	100.0	4	100.0

Diagnosis at Baseline = Infected burn

Clinical Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7/10 mg/kg	
	mg/kg BID	QID	mg/kg BID	QID
	N	%	N	%
Cure	1	100.0	1	100.0
Total	1	100.0	1	100.0

Diagnosis at Baseline = Cellulitis

Clinical Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7/10 mg/kg	
	mg/kg BID	QID	mg/kg BID	QID
	N	%	N	%
Cure	3	100.0	2	66.7
Failure	0	0	1	33.3
Total	3	100.0	3	100.0

Diagnosis at Baseline = Infected dermatitis

Appendix L

Clinical Response	Number (%) of Patients			
	Cephalexin			
	Cefdinir 7 10 mg/kg			
	mg/kg BID QID			
	N	%	N	%
Cure	11	100.0	5	83.3
Failure	0	0	1	16.7
Total	11	100.0	6	100.0

Diagnosis at Baseline = Folliculitis

Clinical Response	Number (%) of Patients	
	Cefdinir 7	
	mg/kg BID	
	N	%
Cure	1	100.0
Total	1	100.0

Diagnosis at Baseline = Furuncle

Clinical Response	Number (%) of Patients			
	Cephalexin			
	Cefdinir 7 10 mg/kg			
	mg/kg BID QID			
	N	%	N	%
Cure	1	100.0	2	100.0
Total	1	100.0	2	100.0

Diagnosis at Baseline = Impetigo

Clinical Response	Number (%) of Patients			
	Cephalexin			
	Cefdinir 7 10 mg/kg			
	mg/kg BID QID			
	N	%	N	%
Cure	62	96.9	59	96.7
Failure	2	3.1	2	3.3
Total	64	100.0	61	100.0

Appendix L

Diagnosis at Baseline = Paronychia

Clinical Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7/10 mg/kg mg/kg BID QID	
	N	%	N	%
Cure	3	100.0	5	100.0
Total	3	100.0	5	100.0

Diagnosis at Baseline = Infected traum/surg wound

Clinical Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7/10 mg/kg mg/kg BID QID	
	N	%	N	%
Cure	4	100.0	6	100.0
Total	4	100.0	6	100.0

Diagnosis at Baseline = Other

Clinical Response	Number (%) of Patients			
	Cephalexin		Cefdinir 7/10 mg/kg mg/kg BID QID	
	N	%	N	%
Cure	1	100.0	1	50.0
Failure	0	0	1	50.0
Total	1	100.0	2	100.0

Appendix M

Table 33

Summary of All Adverse Events
Patients Who Received Study Medication - cefdinir

	All Cefdinir N=142	Cefdinir 7 mg/kg BID N=142		
	N	%	N	%
Number of Patients Reporting AE	66	46.5	66	46.5
Number of Patients Reporting Mild AE	46	32.4	46	32.4
Number of Patients Reporting Moderate AE	30	21.1	30	21.1
Number of Patients Reporting Severe AE	2	1.4	2	1.4
Number of Patients < 2 Years Old Reporting AE	17	89.5	17	89.5
Number of Patients 2 to < 6 Years Old Reporting AE	27	50.0	27	50.0
Number of Patients 6 to < 13 Years Old Reporting AE	22	31.9	22	31.9
Number of Male Patients Reporting AE	35	46.1	35	46.1
Number of Female Patients Reporting AE	31	47.0	31	47.0
Number of Premenarchal Females Reporting AE	31	47.0	31	47.0
Number of Whites Reporting AE	44	50.0	44	50.0
Number of Blacks Reporting AE	8	40.0	8	40.0
Number of Hispanics Reporting AE	13	39.4	13	39.4
Number of Other Races Reporting AE	1	100.0	1	100.0
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	2	1.4	2	1.4
Number of Patients Withdrawn from Study Due to AE~	9	6.3	9	6.3

Appendix M

Number of Patients with Renal Impairment Reporting AE	1 100.0	1 100.0
Number of Patients without Renal Impairment Reporting AE	65 46.1	65 46.1
Number of Patients without Hepatic Impairment Reporting AE	66 46.5	66 46.5

Summary of All Adverse Events Patients Who Received Study Medication - cephalalexin

	All Comparators in N=147 N=147			
	N	%	N	%
Number of Patients Reporting AE	45	30.6	45	30.6
Number of Patients Reporting Mild AE	32	21.8	32	21.8
Number of Patients Reporting Moderate AE	16	10.9	16	10.9
Number of Patients Reporting Severe AE	1	0.7	1	0.7
Number of Patients < 2 Years Old Reporting AE	11	52.4	11	52.4
Number of Patients 2 to < 6 Years Old Reporting AE	24	37.5	24	37.5
Number of Patients 6 to < 13 Years Old Reporting AE	10	16.1	10	16.1
Number of Male Patients Reporting AE	22	28.9	22	28.9
Number of Female Patients Reporting AE	23	32.4	23	32.4
Number of Premenarchal Females Reporting AE	23	32.4	23	32.4
Number of Whites Reporting AE	22	27.5	22	27.5
Number of Blacks Reporting AE	5	20.8	5	20.8

Appendix M

Number of Hispanics Reporting AE	14	38.9	14	38.9
Number of Other Races Reporting AE	4	66.7	4	66.7
Number of Patients Withdrawn from Study Due to AE~	2	1.4	2	1.4
Number of Patients without Renal Impairment Reporting AE	45	30.6	45	30.6
Number of Patients without Hepatic Impairment Reporting AE	45	30.6	45	30.6

Summary of Associated Adverse Events Patients Who Received Study Medication - cefdinir

	All Cefdinir ,17 mg/kg BID N=142		Cefdinir N=142	
	N	%	N	%
Number of Patients Reporting AE	25	17.6	25	17.6
Number of Patients Reporting Mild AE	17	12.0	17	12.0
Number of Patients Reporting Moderate AE	10	7.0	10	7.0
Number of Patients < 2 Years Old Reporting AE	6	31.6	6	31.6
Number of Patients 2 to < 6 Years Old Reporting AE	10	18.5	10	18.5
Number of Patients 6 to < 13 Years Old Reporting AE	9	13.0	9	13.0
Number of Male Patients Reporting AE	13	17.1	13	17.1
Number of Female Patients Reporting AE	12	18.2	12	18.2
Number of Premenarchal Females Reporting AE	12	18.2	12	18.2
Number of Whites Reporting AE	13	14.8	13	14.8

Appendix M

Number of Blacks Reporting AE	5	25.0	5	25.0
Number of Hispanics Reporting AE	7	21.2	7	21.2
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	1	0.7	1	0.7
Number of Patients with Renal Impairment Reporting AE	1	100.0	1	100.0
Number of Patients without Renal Impairment Reporting AE	24	17.0	24	17.0
Number of Patients without Hepatic Impairment Reporting AE	25	17.6	25	17.6

Summary of Associated Adverse Events Patients Who Received Study Medication - cephalixin

	All Comparators		Cephalixin	
	N=147		N=147	
	N	%	N	%
Number of Patients Reporting AE	16	10.9	16	10.9
Number of Patients Reporting Mild AE	12	8.2	12	8.2
Number of Patients Reporting Moderate AE	5	3.4	5	3.4
Number of Patients < 2 Years Old Reporting AE	8	38.1	8	38.1
Number of Patients 2 to < 6 Years Old Reporting AE	6	9.4	6	9.4
Number of Patients 6 to < 13 Years Old Reporting AE	2	3.2	2	3.2
Number of Male Patients Reporting AE	7	9.2	7	9.2

Appendix M

Number of Female Patients Reporting AE	9	12.7	9	12.7
Number of Premenarchal Females Reporting AE	9	12.7	9	12.7
Number of Whites Reporting AE	5	6.3	5	6.3
Number of Blacks Reporting AE	3	12.5	3	12.5
Number of Hispanics Reporting AE	7	19.4	7	19.4
Number of Other Races Reporting AE	1	16.7	1	16.7
Number of Patients without Renal Impairment Reporting AE	16	10.9	16	10.9
Number of Patients without Hepatic Impairment Reporting AE	16	10.9	16	10.9

Appendix N

TABLE 34. All and Associated* Adverse Events by Body System - Patients
Receiving Study Medication Without Sites 3 and 11
[Number (%) of Patients]
(Page 1 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir ^b N = 142				Cephalexin N = 147			
	All		Associated		All		Associated	
BODY AS A WHOLE	20 ^c	(14.1)	2	(1.4)	18	(12.2)	0	(0.0)
Infection	12	(8.5)	0	(0.0)	13	(8.8)	0	(0.0)
Headache	4	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Accidental Injury	2	(1.4)	0	(0.0)	3	(2.0)	0	(0.0)
Fever	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Asthenia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
DIGESTIVE SYSTEM	19	(13.4)	16	(11.3)	13	(8.8)	10	(6.8)
Diarrhea	15	(10.6)	15	(10.6)	10	(6.8)	9	(6.1)
Gastroenteritis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Vomiting	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Dyspepsia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Constipation	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
HEMIC AND LYMPHATIC SYSTEM	5	(3.5)	4	(2.8)	0	(0.0)	0	(0.0)
Leukopenia	4	(2.8)	4	(2.8)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1	(0.7)	0	(0.0)	1	(0.7)	1	(0.7)
Alkaline Phosphatase Increased	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood Urea Nitrogen Increased	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
NERVOUS SYSTEM	3	(2.1)	1	(0.7)	2	(1.4)	0	(0.0)
Nervousness	2	(1.4)	1	(0.7)	0	(0.0)	0	(0.0)
Incoordination	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vestibular Disorder	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Insomnia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
RESPIRATORY SYSTEM	16	(11.3)	0	(0.0)	10	(6.8)	0	(0.0)
Rhinitis	5	(3.5)	0	(0.0)	3	(2.0)	0	(0.0)
Cough Increased	4	(2.8)	0	(0.0)	2	(1.4)	0	(0.0)
Pharyngitis	4	(2.8)	0	(0.0)	3	(2.0)	0	(0.0)
Lung Disorder	2	(1.4)	0	(0.0)	2	(1.4)	0	(0.0)
Sinusitis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Asthma	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Bronchitis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)

* Possibly, probably, or definitely related to treatment

^b All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.

^c The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Appendix N

TABLE 34. All and Associated^a Adverse Events by Body System - Patients
Receiving Study Medication Without Sites 3 and 11
[Number (%) of Patients]
(Page 2 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir ^a N = 142				Cephalexin N = 147			
	All		Associated		All		Associated	
SKIN AND APPENDAGES	20	(14.1)	4	(2.8)	16	(10.9)	6	(4.1)
Rash	7	(4.9)	2	(1.4)	6	(4.1)	3	(2.0)
Eczema	3	(2.1)	0	(0.0)	2	(1.4)	0	(0.0)
Pustular Rash	3	(2.1)	0	(0.0)	2	(1.4)	1	(0.7)
Contact Dermatitis	2	(1.4)	1	(0.7)	2	(1.4)	0	(0.0)
Cutaneous Moniliasis	2	(1.4)	2	(1.4)	2	(1.4)	2	(1.4)
Nail Disorder	2	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Fungal Dermatitis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Furunculosis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes Simplex	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vesiculobullous Rash	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Acne	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dry Skin	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
SPECIAL SENSES	9	(6.3)	0	(0.0)	2	(1.4)	0	(0.0)
Otitis Media	4	(2.8)	0	(0.0)	2	(1.4)	0	(0.0)
Conjunctivitis	3	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Disorder	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Pain	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
UROGENITAL SYSTEM	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Hematuria	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Urine Abnormality	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

^a Possibly, probably, or definitely related to treatment

^b All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.

^c The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Appendix O''

Table 38

Summary of Treatment Discontinuations Due to Adverse Events
Patients Who Received Study Medication - Cefdinir

Body System / Costart Term		Number (%) of Patients			
		Cefdinir			
		All	1r 7		
		Cefdinir	mg/kg BID		
		N=142	N=142		
		N	%	N	%
Respiratory system	*** TOTAL ***	1	0.7	1	0.7
	Bronchitis	1	0.7	1	0.7
Skin and appendages	*** TOTAL ***	1	0.7	1	0.7
	Rash	1	0.7	1	0.7

Appendix O

Listing of Withdrawals from Study due to Adverse Events

Treatment Group: Cefdinir 7 mg/kg BID
Protocol 983-013-

Center	Patient Number	Sex	Age	Adverse Event*	Relationship to Study Medication	Study Day of Last Dose	Start Day of Adverse Event	Adverse Event Outcome
4	18	M	1.04	*NEW IMPETIGINOUS LESION (Pustular rash)	Def. Not	10	22	Not yet recovered
	24	M	1.29	*BILATERAL OTITIS MEDIA (Otitis media)	Unlikely	10	15	Recovered
				*SINUSITIS	Unlikely		15	Recovered
	27	M	8	*SINUSITIS	Def. Not	10	19	Unknown
	36	F	1.54	*CONJUNCTIVITIS	Unlikely	10	20	Not yet recovered
	44	F	2	*BILATERAL OTITIS MEDIA (Otitis media)	Def. Not	10	17	Recovered
8	59	M	10	*BURNED RIGHT FOOT WITH IRON (Accidental injury)	Def. Not	11	15	Unknown
	64	M	2	*RT. CONJUNCTIVITIS (Conjunctivitis)	Def. Not	11	8	Recovered
9	2	M	4	*HIVEY RASH (Rash)	Probably	2	2	Recovered
	8	F	1.83	*RIGHT OTITIS MEDIA (Otitis media)	Def. Not	11	22	Not yet recovered
	9	M	10	*LEFT OTITIS MEDIA (Otitis media)	Def. Not	10	13	Recovered
18	3	M	4	*BRONCHITIS	Def. Not	9	9	Not yet recovered

*When the investigator term and COSTART term differ, the COSTART adverse event appears in parentheses.

*Treatment Emergent Sign or Symptom - First occurrence

Appendix O

Listing of Withdrawals from Study due to Adverse Events

Treatment Group: Cephalexin
Protocol 983-013-

Center	Patient Number	Sex	Age	Adverse Event*	Relationship to Study Medication	Study Day of Last Dose	Start Day of Adverse Event	Adverse Event Outcome
7	1	F	7	*RT OTITIS MEDIA (Otitis media)	Def. Not	11	19	Recovered
12	6	M	9	*BURN RIGHT HAND (Accidental injury)	Def. Not	11	23	Recovered

*When the investigator term and COSTART term differ, the COSTART adverse event appears in parentheses.

*Treatment Emergent Sign or Symptom - First occurrence

Appendix P

TABLE 42. Summary of Markedly Abnormal Laboratory Values More
Abnormal at TOC Than at Baseline Without Sites 3 and 11^a
[Number (%) of Patients]

Parameter	Direction of Change	Cefdinir N = 142	Cephalexin N = 147
Hematology			
Hemoglobin ^b	Decrease	1 (0.7)	0 (0.0)
Hematocrit	Decrease	0 (0.0)	1 (0.7)
White Blood Cells	Decrease	3 (2.1)	0 (0.0)
Lymphocytes	Increase	1 (0.7)	2 (1.4)
Eosinophils ^b	Increase	2 (1.4)	6 (4.1)
Platelets	Decrease	1 (0.7)	0 (0.0)
Blood Chemistry			
Alkaline Phosphatase	Increase	6 (4.2)	2 (1.4)
Lactate Dehydrogenase ^b	Increase	2 (1.4)	3 (2.0)
AST ^b	Increase	0 (0.0)	1 (0.7)
ALT	Increase	0 (0.0)	1 (0.7)
Potassium ^b	Increase	0 (0.0)	3 (2.0)
Calcium	Decrease	0 (0.0)	1 (0.7)
Phosphorus	Increase	3 (2.1)	2 (1.4)
Bicarbonate ^b	Decrease	1 (0.7)	3 (2.0)
	Increase	0 (0.0)	1 (0.7)
	Decrease	0 (0.0)	1 (0.7)
Urinalysis			
Protein	Increase	1 (0.7)	1 (0.7)
pH ^b	Increase	6 (4.2)	4 (2.7)
Any Parameter^c		24 (16.9)	27 (18.4)

^a This table does not include data from patients with markedly abnormal values at the TOC visit that were improved relative to the baseline value.

^b Four patients had no baseline values for comparison, but are included in this summary. Of these, 1 was a cefdinir-treated patient (Patient 33, Center 8, for eosinophils) and 3 were cephalexin-treated (Patient 12, Center 4, for bicarbonate, AST, potassium, and lactate dehydrogenase; Patient 30, Center 4, for urine pH; and Patient 55, Center 8, for eosinophils).

^c Total number of patients in a treatment group experiencing a markedly abnormal laboratory value (more abnormal than at baseline) regardless of the laboratory parameter.