CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50739

MEDICAL REVIEW(S)

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

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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 or 600 mg q 24 h	5 to 10 days 10 days
Children (age 6 months through 12 years):	14mg/kg/day 600 mg maximum	7mg/kg/dose q12h or 14 mg/kg/day q24 h	5 to 10 days 10 days

[1]The 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.

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

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 and5		Patients Microbiologically Evaluable	patients micro eval. Without 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.

II. 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 excludingIrivani	94	94	70	97	96	86
	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

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

Study No.	Indication	Location	Regimens	Number of Patients Enrolled	Patients enrolled excluding site14 and 5
983-51	Pharyngitis	NA	Cefdinir 14 mg/kg QD × 10d Cefdinir 7 mg/kg BID × 10d PenV 10 mg/kg QID × 10d	869	792
983-56	Pharyngitis	US	Cefdinir 7 mg/kg BID × 5d PenV 10 mg/kg QID × 10d	482	425

NA = North America; US = United States; PenV = 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 were conducted for each regimen. For all studies, pharyngitis was diagnosed on the basis of

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

Study	Design	Pts Enrolled	Pts enrolled without site 14 and5		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(lost57)	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.

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 (μg/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.

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	%
S. pyogenes 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 calcuation of the 95% confidence interval in Table 14. Based on the underlyig sample sizes, this is not expected to change the results to a considerable extent.*

The following is excerpted from the Sponsor' 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

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 × 5 days, and
- Penicillin 250 mg QID × 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	%	
S. pyogenes Eradication	193/218	88.5	176/214	82.2	-0.4%–12.9%

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

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%)	Cefdinir QD vs Cefdinir BID $_{252,250}(-0.0216, 0.0459)_{97.6\%,96.4\%}$ Cefdinir QD vs Penn $_{252,250}(0.0582, 0.1582)_{97.6\%,86.8\%}$ Cefdinir BID vs Penn $_{250,250}(0.0441, 0.1479)_{96.4\%,86.8\%}$
Excluding Iravani(Sites14)	222/228(97.3%)	218/227(96%)	196/227(86.3%)	Cefdinir QD vs Cefdinir BID $_{228,227}(-0.0238, 0.0505)_{97.3\%,96\%}$ Cefdinir QD vs Penn $_{228,227}(0.0566, 0.1639)_{96\%,86.3\%}$ Cefdinir BID vs Penn $_{227,227}(0.0411, 0.1527)_{96\%,86.3\%}$
Microbiologic Eradication				
All sites	233/252(92.4%)	237/250(94.8%)	177/250(70.8%)	Cefdinir QD vs Cefdinir BID $_{252,250}(-0.0701, 0.0232)_{92.4\%,94.8\%}$ Cefdinir QD vs pen $_{252,250}(0.1475, 0.2857)_{92.4\%,70.8\%}$ Cefdinir BID vs Pen $_{250,250}(0.1732, 0.3067)_{94.8\%,70.8\%}$

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

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 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 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.

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%)	$_{196,193}(0.1160, 0.274)$	

Iravani site 5

Table 55 Clinical and microbiologic outocome: 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

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

Pharyngitis Studies

Study	Population	Cefdinir								Penicillin	
		10d QD		10d BID		10d QD + BID		5d BID		10d QID	
		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.

TABLE 57. Summary of Clinical Cure Rates

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

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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:OTOCOL 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

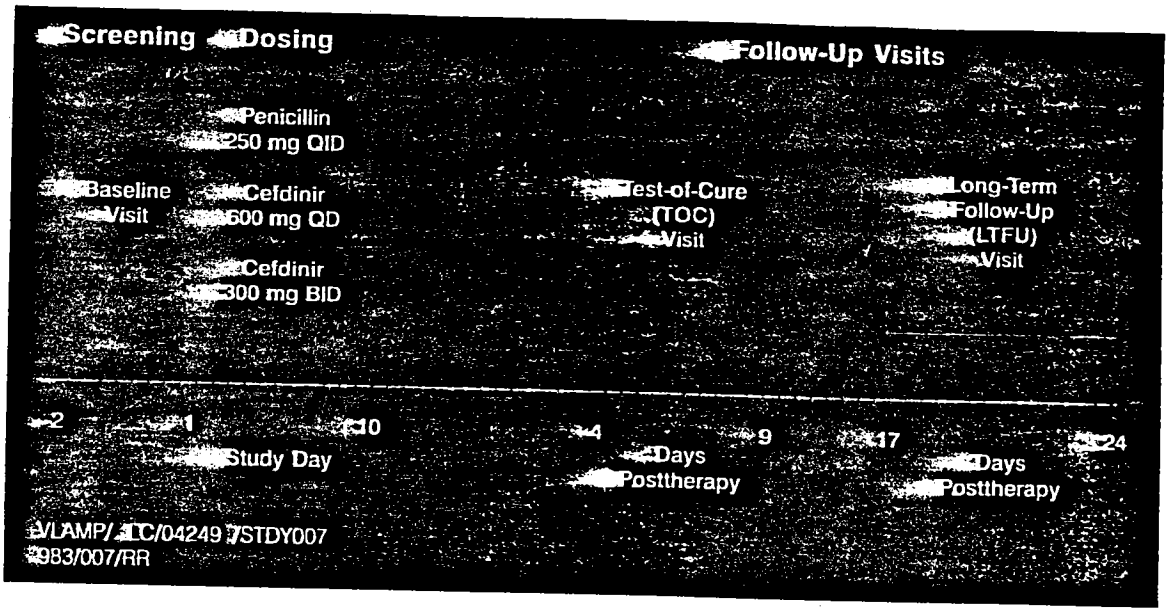
Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable
1	J. Adelglass	45	35	35
2	R. Chiulli	17	12	11
3	H. Collins	32	27	24
4	V. Elinoff	35	30	24
5	W. Gooch	108	87	78
6	D. Henry	90	79	73
7	J. Hedrick	45	44	43
8	E. Dattani	9	7	6
9	R. Knight	12	8	6
10	J. McCarty	108	99	86
11	S. McLinn	7	7	2
12	B. Cochran J. McCarty	23	22	13
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,) 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 identifiation 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 unitpenicillin disk. Susceptibility was defined on the basis of zone diameter inhibition as follows

Diameter of Zones of Inibition

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).

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

APPEARS THIS WAY
ON ORIGINAL

DETERMINATION OF CLINICAL SCORE

Score = Sum of (|Symptom Weight| × |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[1]	2
Cervical Lymph Node Tenderness	2
Dysphagia	1

[1] Oral body temperature > [illegible]°F or 38°C

Parke-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:

Total Score = (2) (Pain) + (2) (Erythema) + (2) (Exudate) + (2) (Swelling) + (2) (Fever) + (2) (Cervical Lymph Node Tenderness) + (Dysphagia)

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

% Change = 100 × (Observation Score - Baseline Score) ÷ (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 ≥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.

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 ≥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 CANDA 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		

[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.

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.

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% ≤ reponse 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 QD N = 210		Cefdinir BID N = 217		Penicillin N = 217		Total 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[b]	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]	257	(84.3)	253	(83.2)	262	(84.5)	772	(84.0)
Completed Follow-Up Visits[c]								
TOC	251	(82.3)	252	(82.9)	253	(81.6)	756	(82.3)
LTFU	214	(70.2)	219	(72.0)	199	(64.2)	632	(68.8)

[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 withSerratia 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 ±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 ±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 CANDA 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 ±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 ±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 ±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 ±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 ±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 ±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			
Streptococcus agalactiae	0	0	1
Staphylococcus aureus	0	0	1
Streptococcus pyogenes[a]	1	1	0
Streptococcus Group C	0	3	3
Streptococcus Group F	1	0	0
β-Hemolytic *Streptococcus*, not Group A, B, C, F, or G	0	0	1

[a] 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			
Streptococcus pyogenes[a]	1	1	2
Streptococcus Type C	0	2	0
β-Hemolytic *Streptococcus*, not Group A, B, C, F, or G	1	0	2
Multiple			
Streptococcus pyogenes[a] + *Streptococcus* Type C	0	0	1

[a] 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.

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

	Cefdinir				Penicillin	
	QD N = 305		BID N = 304		N = 310	
Adverse Events During Study						
All Adverse Events	169	(55.4)	157	(51.6)	140	(45.2)
Associated[a] 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)

[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.

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

	Cefdinir QD N = 305		Cefdinir BID N = 304		Penicillin N = 310	
Adverse Events by Maximum Intensity[a]						
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)

[a] 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[a]	Relationship to Study Medication[b]	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

[a] Investigator term (COSTART preferred term)
[b] Investigator assessment

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.

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.[27] 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.

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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X. 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.

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. Drehobl	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.

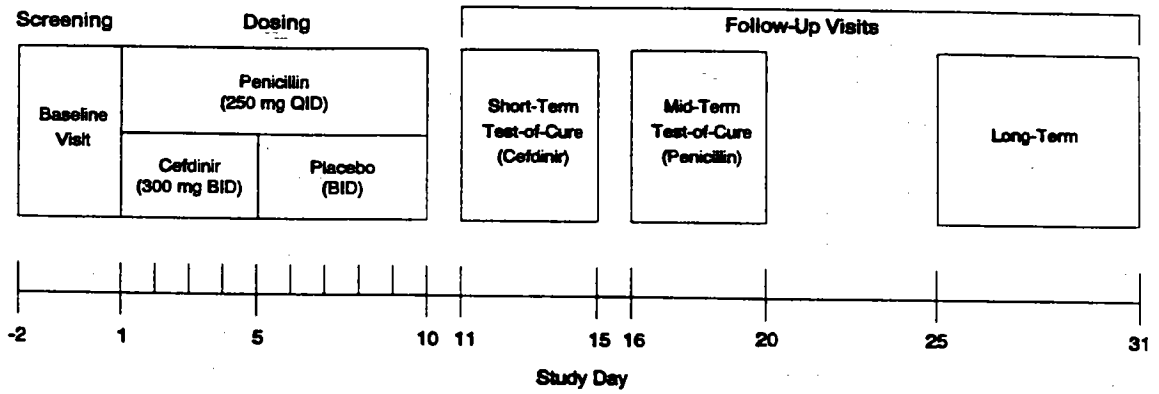

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FIGURE 1. Study Design

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
	8MA9ON	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).

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 Days 11-15[a]	MTFU Days 16-20[b]	LTFU 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	X						X	X	X
Adverse Events and Concurrent Medications	X	X	X	----	----	X	X	X	
Telephone Call to Patient			X						
Clinical Laboratory Tests[e,f]	X						X	X[d]	X[d]
Dosing (Cefdinir)		X	----	X					
Dosing (Placebo)					X	X			
Dosing (Penicillin)		X	----	----	----	X			

STFU = Short-term follow-up visit.
MTFU = Mid-term follow-up visit.
[a] Test-of-cure (TOC) visit, cefdinir
[b] Test-of-cure (TOC) visit, penicillin
[c] Must be positive for patients to enter study
[d] Performed also after early treatment discontinuation or withdrawal (see Section 4.2.4).
[e] See protocol, Appendix A.2.
[f] If abnormalities detected at the TOC visit

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	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[a]	(2.5)	6	(2.1)	13	(2.3)
Other/Administrative[b]	6	(2.2)	8	(2.9)	14	(2.5)
Completed Treatment[c]	242	(87.1)	237	(84.6)	479	(85.8)
Completed Follow-Up Visits						
TOC[d]	249	(89.6)	212	(75.7)	461	(82.6)
LTFU	193	(69.4)	185	(66.1)	378	(67.7)

[a] Includes 2 patients who were withdrawn during placebo phase of treatment.

[b] 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).

[c] Based on investigator assessment of patient status at end of treatment

[d] 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 ≥2 × 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[a]		
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[a]		
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[a]	50	54

[a] 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 (±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 (±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 sponor, 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, ±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 (±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 (±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 ($p = 0.74$).

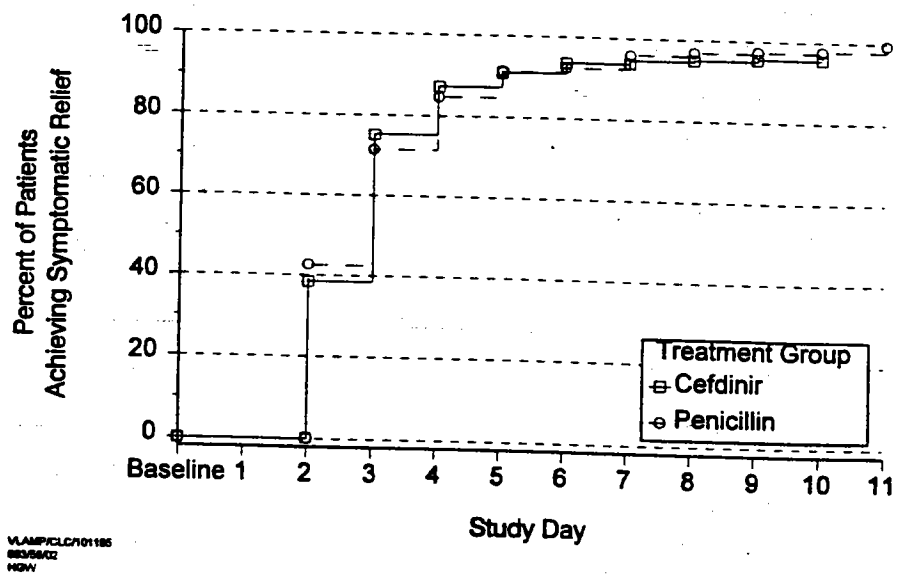

FIGURE 2. Time to Onset of Symptomatic Relief

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

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.)

TABLE 13. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 1 of 2)

	Cefdinir N = 278		Penicillin N = 280	
Adverse Events During Study				
All Adverse Events	161	(57.9)	143	(51.1)
Associated[a] Adverse Events	61	(21.9)	47	(16.8)
Adverse Events During Treatment				
All Adverse Events	106	(38.1)	94	(33.6)
Adverse Events by Sex[b]				
All Adverse Events				
Male	65	(54.2)	51	(48.6)
Female	96	(60.8)	92	(52.6)
Associated Adverse Events				
Male	21	(17.5)	14	(13.3)
Female	40	(25.3)	33	(18.9)
Adverse Events by Race[c]				
All Adverse Events				
White	144	(60.0)	131	(52.8)
Black	8	(72.7)	2	(33.3)
Asian	1	(20.0)	3	(60.0)
Hispanic	7	(35.0)	7	(36.8)
Other	1	(50.0)	0	(0.0)
Associated Adverse Events				
White	53	(22.1)	45	(18.1)
Black	4	(36.4)	0	(0.0)
Asian	1	(20.0)	0	(0.0)
Hispanic	3	(15.0)	2	(10.5)
Other	0	(0.0)	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

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[d]				
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[e]				
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)

[d] Percentages equal the 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] Includes 2 patients on placebo.
[g] 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).

5.3.1.8. Deaths

No deaths occurred during this study.

5.3.1.9. Serious Adverse Events

[2]

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.[29,30] 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[31,32], and 1 study reported that β-lactamase-producing anaerobic bacteria were recovered from 45% of patients with recurrent tonsillitis.[33] In addition, a correlation between the presence of pharyngeal β-lactamase-producing streptococci and failure of penicillin treatment has been demonstrated.[34] 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[35,36], 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.[19,20] 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.

- 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.

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. Iravani	77	72	70
15	S. McLinn	90	76	63
Total		869	805	752

Medical Officer's Note: Eliminating data from Dr. Irivani'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.

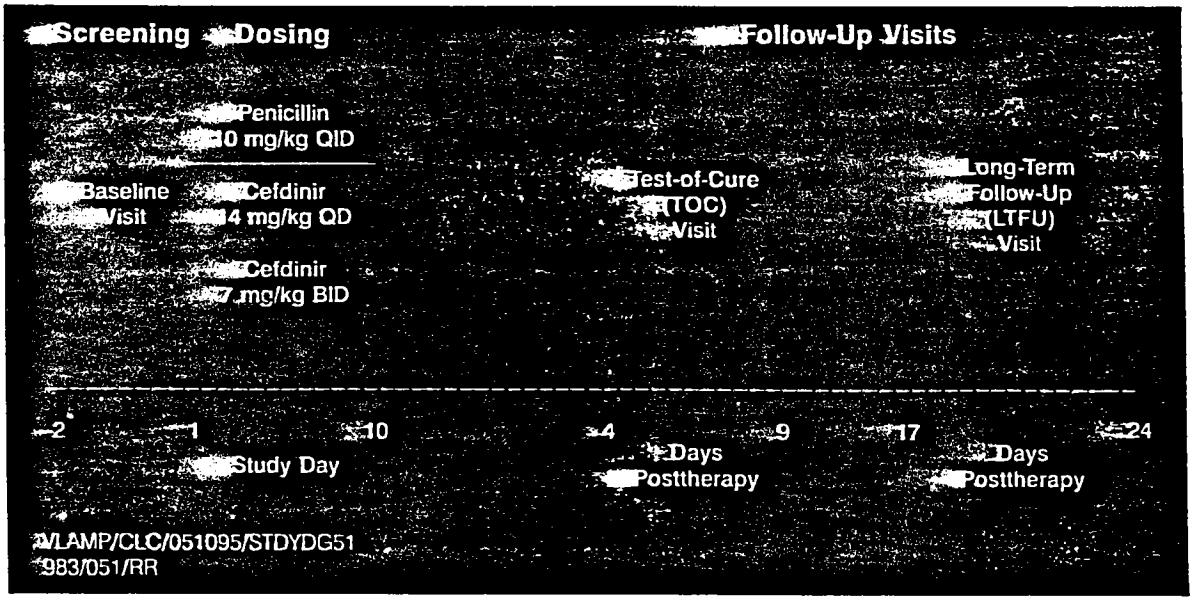

FIGURE 1. Study Design

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

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 QD N = 252		Cefdinir BID N = 250		Penicillin N = 250		Total 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 QD N = 289	Cefdinir BID N = 290	Penicillin 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[a]	5

[a] 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)[a]
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]	271	(93.8)	266	(91.7)	268	(92.4)	805	(92.6)
Completed Follow-Up Visits[c]								
TOC	272	(94.1)	270	(93.1)	268	(92.4)	810	(93.2)
LTFU	250	(86.5)	237	(81.7)	202	(69.7)	689	(79.3)

[a] Twenty-six other patients were withdrawn due to an adverse event after treatment but before the LTFU visit.
[b] 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).
[c] 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%)*	*Cefdinir QID vs Cefdinir BID* $_{252,250}(-0.0216, 0.0459)_{97.6\%,96.4\%}$ *Cefdinir QID vs Penn* $_{252,250}(0.0582, 0.1582)_{97.6\%,86.8\%}$ *Cefdinir BID vs Penn* $_{250,250}(0.0441, 0.1479)_{96.4\%,86.8\%}$
Sites14 excluding Iravani	*222/228(97.3%)*	*218/227(96%)*	*196/227(86.3%)*	*Cefdinir QID vs Cefdinir BID* $_{228,227}(-0.0238, 0.0505)_{97.3\%,96\%}$ *Cefdinir QID vs Penn* $_{228,227}(0.0566, 0.1639)_{96\%,86.3\%}$ *Cefdinir BID vs Penn* $_{227,227}(0.0411, 0.1527)_{96\%,86.3\%}$
		Microbiologic Eradication		
All sites	*233/252(92.4%)*	*237/250(94.8%)*	*177/250(70.8%)*	*Cefdinir QD vs Cefdinir BID* $_{252,250}(-0.0701, 0.0232)_{92.4\%,94.8\%}$ *Cefdinir QD vs pen* $_{252,250}(0.1475, 0.2857)_{92.4\%,70.8\%}$ *Cefdinir BID vs Pen* $_{250,250}(0.1732, 0.3067)_{94.8\%,70.8\%}$
Sites 14 excluding Iravani	*215/228(94.3%)*	*214/227(94.3%)*	*159/227(70%)*	*Cefdinir QD vs Cefdinir BID* $_{228,227}(-0.0468, 0.0473)_{94.3\%,94.3\%}$ *Cefdinir QD vs Pen* $_{228,227}(0.1713, 0.3137)_{94.3\%,70\%}$ *Cefdinir BID vs Pen* $_{227,227}(0.1711, 0.3135)_{94.3\%,70\%}$

Statistical Reviewer's Comments:

For both clinical efficacy as well as for microbiologic eradication, Cefdinir QD is therapeutically equivalent to Cefdinir BID. Both CefdinirQD 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*	*S. pyogenes was isolated at baseline with a non pathogen (S. Aureus) 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*	*S. pyogenes was isolated at baseline with a non pathogen (P. aeruginosa) 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*	*S. pyogenes was isolated at baseline with a non pathogen (Citrobacter freundii) 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			
Streptococcus pyogenes[a]	2	1	0
Streptococcus Type G	0	1	0
Gram Negative -			
Enterobacter sakazakii	0	0	1

[a] 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 reinfecting 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			
Streptococcus pyogenes[a]	2	4	3
Gram Negative			
Acinetobacter calcoaceticus var *lwoffi*	1	0	1

[a] 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. 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. . 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 QD N = 289		Cefdinir BID N = 289		Penicillin N = 290	
Adverse Events During Study						
All Adverse Events	119	(41.2)	129	(44.6)	110	(37.9)
Associated[a] 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)

[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

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

	Cefdinir QD N = 289		Cefdinir BID N = 289		Penicillin N = 290	
Adverse Events by Intensity[e]						
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)

[e] 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[a] - 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)

[a] 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.