6. DISCUSSION

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

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

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

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

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

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

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

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

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

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

7. CONCLUSIONS

- Cefdinir QD and cefdinir BID are superior microbiologically and clinically to penicillin in the treatment of GABHS pharyngitis in pediatric patients.

- Although the incidence of adverse events is somewhat higher with cefdinir treatment than penicillin treatment, cefdinir is well-tolerated. Most adverse events experienced by cefdinir-treated patients are mild and do not require treatment discontinuation.

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

APPENDIX P 51
Study 983-051
Pediatric Pharyngitis -10 days

Evaluable Patients

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

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

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

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

Clinically Evaluable Patients

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

	Cefdinir QD	Cefdinir BID	Penicillin
Clinical Response Rates			
All Sites	97.3% (251/258)	96.5% (246/255)	86.2% (219/254)
Excluding Site 14	97.0% (226/233)	96.1% (222/231)	85.7% (198/231)

	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
All Sites	(6.4%, 15.7%)	<0.001	(5.4%, 15.1%)	<0.001
Excluding Site 14	(6.3%, 16.3%)	<0.001	(5.2%, 15.5%)	<0.001

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

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

Protocol 983-051
NDA Analysis - All Sites

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

Protocol 983-051 (Subset=51_noinv.txt)
All sites except Iravani

		Number (%) of Pathogens											
		Cefdinir 14 mg/kg QD				Cefdinir 7 mg/kg BID				Penicillin V-K			
		Eradication		Persistence		Eradication		Persistence		Eradication		Persistence	
		N	%	N	%	N	%	N	%	N	%	N	%
n itive	S pyogen	215	94.4	13	5.7	214	94.4	13	5.7	159	70.1	68	30.0
al	Pathogens	215	94.3	13	5.7	214	94.3	13	5.7	159	70.0	68	30.0

Protocol 983-051

Center = 983-051-014 Iravani Only

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

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

Adverse Events

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

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

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

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

CEFDINIR IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS

INTRODUCTION

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

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

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

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

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

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

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

Protocol 983-051

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

TABLE 1

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

TABLES 6 and 7

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

TABLE 8

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

TABLE 9

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

TABLE 10

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

TABLE 11

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

TABLE 12

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

TABLE 13

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

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

TABLE 14

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

TABLE 15

The number of patients with reinfections did not change.

TABLE 16

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

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

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

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

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

TABLE 17

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

TABLE 18

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

TABLES 19 and 20

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

TABLES 21 and 22

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

TABLE 23

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

TABLE 24

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

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

Protocol 983-056

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

TABLE 1

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

TABLES 6 and 7

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

TABLE 1. List of Investigators Excluding Site 14

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

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

Summary of Patient Characteristics
All Patients

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

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

(CONTINUED)

Summary Specification Table 101
(Page 1 of 2)

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

Summary of Patient Characteristics
All Patients

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

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

Summary Specification Table 101
(Page 2 of 2)

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

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

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

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

Summary Specification Table 192
(Page 1 of 1)

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

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

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

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

(CONTINUED)

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

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

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

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

Summary Specification Table 102
(Page 2 of 2)

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

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

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

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

Summary Specification Table 193
(Page 1 of 1)

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

Summary of Patient Exposure to Study Medication
All Patients

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

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

Summary Specification Table 265
(Page 1 of 1)

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

Summary of Patient Completion Status
Treatment Phase

All Patients

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

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

Summary Specification Table 269
(Page 1 of 1)

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

Summary of Patient Completion Status
Test-Of-Cure Visit

All Patients

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

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

Summary Specification Table 270
(Page 1 of 1)

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

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

All Patients

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

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

Summary Specification Table 272
(Page 1 of 1)

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

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

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

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

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(Page 1 of 1)

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

Reasons for Disqualification of Microbiologically/Clinically Evaluable Patients from Analysis
Long-Term Follow-Up Visit

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

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

Summary Specification Table 175
(Page 1 of 1)

NDA 50-739(Cefdinir)

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

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

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

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

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

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

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

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

[a] Primary efficacy analysis

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

EVALUABLE PATIENT POPULATION

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

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

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

Summary of Superinfection Rates
All Patients

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

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

Summary Specification Table 203
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Cefdinir vs Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Adverse Events
All Patients

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

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

(CONTINUED)

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

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

Summary of Adverse Events
All Patients

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

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

~Patients who did not discontinue treatment due to an AE

Summary Specification Table 148
(Page 2 of 2)

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

Summary of Associated Adverse Events
All Patients

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

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

(CONTINUED)

"Patients who did not discontinue treatment due to an AE

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

Summary of Associated Adverse Events
All Patients

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

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

~Patients who did not discontinue treatment due to an AE
Summary Specification Table 262
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TABLE 17. All and Associated Adverse Events by Body System: All Patients - Protocol 983-51

[Number (%) of Patients]

(Page 1 of 5)

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

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

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

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

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

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

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

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

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

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

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

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

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

Penicillin N = 264			
All		Assoc	
0	(0.0)	0	(0.0)
1	(0.4)	0	(0.0)
0	(0.0)	0	(0.0)
1	(0.4)	0	(0.0)
1	(0.4)	0	(0.0)
0	(0.0)	0	(0.0)
1	(0.4)	0	(0.0)
1	(0.4)	0	(0.0)
0	(0.0)	0	(0.0)
0	(0.0)	0	(0.0)
1	(0.4)	1	(0.4)
1	(0.4)	1	(0.4)

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

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

Cefdinir vs Penicillin V-K in the Treatment of Streptococcal aryngitis/Tonsillitis Infections in Pediatric Patie

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

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

(CONTINUED)

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

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

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

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

(CONTINUED)

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

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

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

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

(CONTINUED)

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

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

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

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

~ Contains only Adverse Events that occurred after the start of study drug (Study Day 1). Patients reporting multiple occurrences of an Adverse Event are counted once for each occurrence of the Adverse Event starting on a different Study Day.
Summary Specification Table 152
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Note: Dr Iravani's Data is marked out (Center 14)

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

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

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

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

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

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

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

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

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

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

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

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

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

Center	Patient Number	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinir BID (Continued)									
~~14~~	~~77~~	~~H~~	~~8 yr, M~~	~~41.4~~	~~Alkaline Phosphatase~~	~~426 U/L~~	~~365~~	~~25-350~~	~~No history noted~~
15	13	W	2 yr, M	12.4	Urine Glucose	1+	Neg	Neg	No history noted
15	72	W	5 yr, M	23.4	White Blood Cells	3.1 x 10^9/L	12.2	5.5-15.5	Reactive airway disease, cough; triamcinolone, albuterol AE: croup; prednisolone, phenylpropantine/dextromethorphan
Penicillin V-K									
[illegible]	[illegible]	W	6 yr, F	20.0	Lymphocytes	6%	9	10-66	Failure
					Polymorphonuclear Leukocytes	87%	85	20-75	
3	19	W	10 yr, F	56.8	White Blood Cells	3.2 x 10^9/L	8.3	4.5-13.5	Down's syndrome
3	21	W	8 yr, M	29.1	Lactate Dehydrogenase	460 U/L	452	118-273	No history noted
					Polymorphonuclear Leukocytes	16%	13	40-80	
3	37	W	10 yr, M	33.2	Polymorphonuclear Leukocytes	26%	67	40-80	Testicular hernia, chemosis
4	52	W	5 yr, F	16.3	Alkaline Phosphatase	516 U/L	449	25-350	Stuffy nose AE: URI
4	96	W	6 yr, F	30.5	Urine White Blood Cells	21-50/HPF	--	1-5	AE: URI
5	16	W	11 yr, F	50.5	Urine Specific Gravity	1.038	1.02	1.005-1.03	No history noted

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

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

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

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

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

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

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

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

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

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

TABLE 24. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline Excluding Site 14[a]

[Number (%) of Patients]

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

[a] This table does not include data from patients with markedly abnormal values at the STFU visit that were unchanged or improved relative to the baseline value.

[b] Three patients had no baseline values for comparison, but are included in this summary. One patient was in the cefdinir QD treatment group (Patient 138, Center 3 for Urine Specific Gravity), and 2 were in the penicillin treatment group (Patient 96, Center 4 for Urine White Blood Cells; Patient 9, Center 7 for Polymorphonuclear Leukocytes).

[c] Total number of patients in a treatment group experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) regardless of the laboratory parameter.

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

1. OBJECTIVES

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

2. STUDY MANAGEMENT

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

TABLE 1. List of Investigators

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

* Investigator received drug but did not enroll patients

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

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

3. MATERIALS AND METHODS

3.1. Study Design

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

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

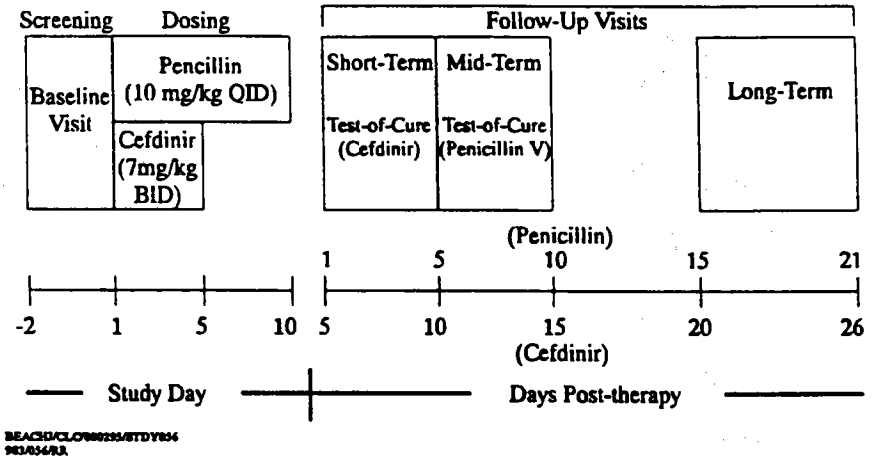

FIGURE 1. Study Design

3.1.1. Treatment

3.1.1.1. Materials

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

TABLE 2. Study Medication

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

* All suspensions supplied in 100-mL bottles

3.1.1.2. Drug Administration

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

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

3.1.1.3. Methods of Assigning Patients to Treatment

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

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

3.2. Patient Selection

3.2.1. Inclusion Criteria

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

3.2.2. Exclusion Criteria

- *Serum creatinine >1.5 × ULN;*

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

Medical Officer's Note: The schedule of clinical observations and laboratory measurements is indicated below (Table 4).This is similar to protocol 58.

TABLE 4. Clinical Observations and Laboratory Measurements

						Posttherapy Visits		
	Baseline	Day 1	Days 3-5	Day 5	Day 10	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[d]	X					X	X	X
Adverse Events and Concurrent Medications	X	X	X			X	X	X
Telephone Call to Patient			X					
Clinical Laboratory Tests[d]	X					X	X[e]	X[e]
Dosing (Cefdinir)		X			X			
Dosing (Penicillin V-K)		X			X			

[a] Test-of-cure (TOC) visit, cefdinir
[b] Test-of-cure (TOC) visit, penicillin
[c] Must be positive for patients to enter study
[d] Perform also after early treatment discontinuation or withdrawal (see Section 4.2.4).
[e] If abnormalities detected at the STFU visit

3.3.4. Data Acceptability and Evaluability

3.3.4.1. Method of Assigning Study Days

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

3.3.4.2. Data Acceptability

3.3.4.3. Patient Populations for Analysis

3.3.5. Statistical Methodology

Medical Officer's Note: Please note that the random number's generated are located in protocol 7.

3.3.5.1. Sample Size

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

3.3.5.2. Methods

3.3.5.2.1. Efficacy

3.3.5.2.2. Safety

4. PATIENT DEMOGRAPHICS, TREATMENT, AND DISPOSITION

4.1. Patient Characteristics

4.1.1. Patient Sample

Patient characteristics were similar across treatment groups with respect to sex, age, and race for all and evaluable patient populations (Tables 6 and 7).

Approximately equal numbers of males and females participated in the study. The mean age across treatment groups was 7.5 years; 73% of the patients were between 6 to 12 years old. Eighty-nine percent of patients were white.

TABLE 6. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir N = 240		Penicillin N = 242		Total N = 482	
Sex						
Male	128	(53.3)	122	(50.4)	250	(51.9)
Female	112	(46.7)	120	(49.6)	232	(48.1)
Race						
White	214	(89.2)	214	(88.4)	428	(88.8)
Black	8	(3.3)	12	(5.0)	20	(4.1)
Asian	4	(1.7)	0	(0.0)	4	(0.8)
Other	14	(5.8)	16	(6.6)	30	(6.2)
Age, years						
Median	7.4		7.7		7.5	
Range	(1-13)		(2-18)		(1-18)	
Distribution:						
<2	2	(0.8)	1	(0.4)	3	(0.6)
2 to <6	65	(27.1)	62	(25.6)	127	(26.3)
6 to <13	173	(72.1)	177	(73.1)	350	(72.6)
13 to <18 years	0	(0.0)	2	(0.8)	2	(0.4)

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

Variable	Cefdinir N = 224		Penicillin N = 216		Total N = 440		CMH p-value
Sex							0.642
Male	118	(52.7)	109	(50.5)	227	(51.6)	
Female	106	(47.3)	107	(49.5)	213	(48.4)	
Race							0.742
White	199	(88.8)	194	(89.8)	393	(89.3)	
Black	8	(3.6)	9	(4.2)	17	(3.9)	
Asian	4	(1.8)	0	(0.0)	4	(0.9)	
Other	13	(5.8)	13	(6.0)	26	(5.9)	
Age, years							0.762
Median	7.4		7.6		7.5		
Range (Min, Max)	(2-13)		(2-16)		(2-16)		
Distribution:							
<2	1	(0.4)	1	(0.5)	2	(0.5)	
2 to <6	59	(26.3)	55	(25.5)	114	(25.9)	
6 to <13	164	(73.2)	159	(73.6)	323	(73.4)	
13 to <18	0	(0.0)	1	(0.5)	1	(0.2)	

[a] Microbiologically and clinically

Medical Officer's Note: Excluding the Iravani data did not substantially change the demographic characteristics of either the total patient population or the evaluable patient population. The number of

black patients decreased from 20 to 11, but this was a very small subgroup; white patients constituted 91% of the population. See table 6 and 7 in appendix P56.

Statistical Reviewer's Notes:

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

4.1.2. Confirmed Microbiologic Diagnosis and Baseline Susceptibility

At the baseline visit, *S. pyogenes* was isolated from throat swabs from 472 of 482 (98%) patients randomized to treatment. All *S. pyogenes* isolates were susceptible to both cefdinir and penicillin.

4.1.3. Clinical Signs and Symptoms

Of the patients randomized to treatment, all but 1 cefdinir-treated patient (pain absent) had both pharyngeal pain and erythema. Most patients also had tonsillar swelling, dysphagia, and cervical lymph node tenderness. Baseline signs and symptoms were similar between treatment groups and patient populations.

4.1.4. Medical History and Secondary Diagnoses

There were no differences in significant medical/surgical history between the 2 treatment groups. Approximately a third of the patients in each treatment group experienced pharyngitis/tonsillitis within 1 year prior to the study.

4.1.5. Prior Medications for Pharyngitis

Sixteen cefdinir-treated patients and 17 penicillin-treated patients had received prior anti-infective medications for pharyngitis or tonsillitis within 30 days of the study. The most frequently used were penicillin and amoxicillin.

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

Overall, acetaminophen (20% of patients) and cefadroxil monohydrate (8%) were the most frequently used concurrent medications. No clinically relevant concurrent nondrug therapies, elective surgeries, or elective procedures were used or performed during this study.

4.2. Patient Treatment

The majority of cefdinir-treated patients (175) completed therapy on Day 5; most penicillin-treated patients (150) completed therapy on Day 11 (Table 8). Cefdinir-treated patients who began treatment in the late afternoon or evening of Day 1 completed their course of therapy on Day 6 instead of Day 5. Similarly, penicillin-treated patients who began therapy in the latter part of Day 1 completed therapy on Day 11.

TABLE 8. Patient Exposure to Study Medication - All Patients
(Number of Patients)

Days of Study Medication	Cefdinir N = 240	Penicillin N = 242
1	2	0
2	1	1
3	1	0
4	0	1
5	175	3
6	61	1
7	0	2
8	0	0
9	0	2
10	0	75
11	0	150
12	0	3
Unknown	0	4
Median (Days)	5	11

Medical Officer's Note: Patient exposure to study medication remained the same, with the majority of cefdinir patients finishing study medication on Day 5 and most penicillin patients finishing medication on Day 11. Please see table (appendix 8) in appendix P56.

4.3. Patient Disposition

Of the 482 patients who entered the study, 461 (90%) completed the treatment phase (Table 9). Ninety-eight percent of cefdinir-treated patients completed the TOC follow-up visit compared with 83% of penicillin-treated patients.

The investigators assessed if patients took the full 10 days (penicillin) or 5 days (cefdinir) of study medication as prescribed. Analysis of this indicator of treatment compliance indicated that 93% of cefdinir-treated patients took medication as prescribed compared with 76% of penicillin-treated patients. This suggests that the 5-day course of therapy and/or the BID dosing schedule may improve compliance.

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

Disposition	Cefdinir		Penicillin		Total	
Randomized to Treatment	240		242		482	
Withdrawn Prior to End of Treatment						
Lack of Compliance	2	(0.8)	10	(4.1)	12	(2.5)
Failure at End of Therapy	0	(0.0)	1	(0.4)	1	(0.2)
No Baseline Pathogen	0	(0.0)	1	(0.4)	1	(0.2)
Adverse Event	0	(0.0)	2	(0.8)	2	(0.4)
Other/Administrative	2	(0.8)	3	(1.2)	5	(1.0)
Completed Treatment[a]	236	(98.3)	225	(93.0)	461	(95.6)
Completed Follow-Up Visits						
TOC[b]	235	(97.9)	200	(82.6)	435	(90.2)
LTFU	182	(75.8)	169	(69.8)	351	(72.8)

[a] Based on investigator assessment at end of treatment.
[b] Short-term follow-up visit for cefdinir-treated patients; mid-term follow-up visit for penicillin-treated patients.

Medical Officer's Note: The overall percentages of patients completing the treatment phase, TOC visit phase, and LTFU visit phase of the study remained relatively constant at 96.2%, 89.1%, and 70.6% respectively. The percentage of patients completing the treatment phase increased by 0.6% when patients from Dr Iravani's site were excluded. See table (Appendix 9) in appendix P56.

5. RESULTS

5.1. Protocol Variations

The most common protocol variation was the enrollment of patients whose baseline clinical laboratory results showed 2 times the upper limit of normal in AST or ALT levels; this affected 6 patients.

5.1.1. Efficacy Evaluations

The most common reasons for exclusion from the evaluable analysis at TOC were that the clinical assessment and throat culture were out of the appropriate study day range (Table 10). A summary of the number of patients included in the efficacy analysis for each population is given in Table 11.

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

	Cefdinir	Penicillin
Reasons For Exclusion From Evaluable Analyses at TOC		
Clinical Assessment Out of Range	7	15
Culture Out of Range	7	15
Medication Not as Prescribed	7	12
No Proven Pathogen	5	5
Concurrent Antibacterial	3	2
Culture Missed	2	8
Clinical Assessment Missed	1	4
No Baseline Signs or Symptoms	0	1
Total Not Evaluable[a]	16	26
Reasons For Disqualification From Qualified Analyses at LTFU[a]		
Culture Missed	27	55
Clinical Assessment Missed	25	53
Culture Out of Range	21	15
Clinical Assessment Out of Range	20	16
Concurrent Antibacterial	1	4
Total Disqualified[a]	48	73

[a] Patients may have multiple reasons for exclusion or disqualification.

Medical Officer's Note: No substantial change was seen in the frequency distribution of reasons for exclusion from evaluable analyses at TOC and reasons for disqualification from qualified analyses at LTFU. Please see table (appendix 10) in appendix P56.

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

Patient Population	Cefdinir	Penicillin
Intent-to-Treat (ITT)	240	242
Modified Intent-to-Treat (MITT)	235	229
Clinically Evaluable	228	220
Microbiologically-Clinically Evaluable	224	216
Qualified at LTFU	176	143

Medical Officer's Note: Please see appendix P56 for the above revised table.
Also note that when Dr. 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 P56 page 1,2 and 3 . The table below is recalulated by the statistical reviewer with Yates' continuity correction.

SUMMARY OF CURE RATES IN PROTOCOL 56

Criteria	*Cefdinir BID*	*Penicillin*	*95% Confidence Interval (with continuity correction)*
Clinical Efficacy (all evaluable patients)			
All sites	*205/224(91.5%)*	*196/216(90.7%)*	$_{224,216}(-0.0499, 0.0655)_{91.5\%,90.7\%}$
Sites excluding Dr Iravani	*179/196(91.3%)*	*173/193(89.6%)*	$_{196,193}(-0.0465, 0.0804)_{91.3\%,89.6\%}$
Microbiologic Eradication (all evaluable patients)			
All sites	*201/224(89.7%)*	*155/216(71.7%)*	$_{224,216}(0.1031, 0.2563)_{89.7\%,71.7\%}$
Sites excluding Dr. Iravani	*176/196(89.7%)*	*135/193(69.9%)*	$_{196,193}(0.1160, 0.2809)_{89.7\%,69.9\%}$
Clinical Efficacy (clinically evaluable patients)			
All sites	*209/228(91.6%)*	*200/220(90.9%)*	$_{228,220}(-0.0491, 0.0642)_{91.6\%,90.9\%}$
Sites excluding Dr Iravani	*182/199(91.4%)*	*175/195(89.7%)*	$_{199,195}(-0.0455, 0.0798)_{91.4\%,89.7\%}$

Statistical Reviewer's notes:

With respect to clinical efficacy in all evaluable patients, Cefdinir is therapeutically equivalent to penicillin, with or without data from Dr. Iravani's site. With respect to microbiologic eradication in all evaluable patients, Cefdinir is statistically superior to penicillin, with or without Dr. Iravani's information. With respect to clinical efficacy in clinically evaluable patients only, Cefdinir is therapeutically equivalent to penicillin, with or without data from Dr. Iravani's site.

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5.1.2. Safety Evaluations

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

5.2. Efficacy

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

Outcomes Changed by Medical Officer			
Patient Number	**Applicant**	**FDA**	**Reason:**
1	MICRO: TOC/LTFU (persistence/Not Asse Clin: TOC/LTFU cure/cure	MICRO: TOC/LTFU Not assessable/not assessible Clin: toc/ltfu: not assess/not assessable	Ths patient had his test of cure visit at 1 day vs. 7 day with a positive culture. If he had a culture further on, it potentially could have been negative.
115	MICRO: TOC/LTFU (Not Asse/Not Asse	MICRO: TOC/LTFU (Erad/Eradication	S. pyogenes was isolated at baseline with a non pathogen(S. Aureus) and was not considered

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

5.2.1. Evaluable Analyses and Qualified Analyses

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

5.2.1.1.1. Microbiologic Eradication

The microbiologic eradication rates were 89.7% (201/224) for the cefdinir group and 71.8% (155/216) for the penicillin group. The 95% CI about the difference between cefdinir vs penicillin (cefdinir minus penicillin) was (10.8%, 25.2%), indicating that cefdinir treatment was superior to penicillin because the interval lies above zero. The exploratory CMH test showed that the eradication rate for cefdinir was significantly higher ($p < 0.001$) than that for penicillin.

5.2.1.1.2. Clinical Cure

The clinical response rates were 91.5% (205/224) for the cefdinir group and 90.7% (196/216) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (-4.5%, 6.1%) indicating that cefdinir treatment was equivalent to penicillin based on the fixed criteria for equivalence

(-10%, +10%). The exploratory CMH tests showed no significant difference between the clinical cure rate for cefdinir and penicillin (p = 0.80).

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

The response rates were based on the combined investigator/sponsor assessment of clinical cure. Only 1 patient was considered Not Assessable by the investigator and thus was assessed according to the sponsor definition.

5.2.1.1.3. Microbiologic Versus Clinical Response Rates

Most patients (87%) had the same clinical as microbiologic response. Among those who had different responses for clinical and microbiologic assessment, McNemar's test showed no significant pattern to the discordant assessments in the cefdinir group (p = 0.29). However, a significant pattern to the discordant results was seen in the penicillin group (p <0.001); 42 of 43 patients with discordant results experienced a clinical cure, yet had a persistent pathogen. Clinical improvement in the penicillin group did not reliably indicate streptococcal eradication.

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

(Number of Patients)

Microbiologic Response	Clinical Response	
	Cure	Failure
Cefdinir		
Eradication	196	5
Persistence	9	14
Penicillin		
Eradication	154	1
Persistence	42	19

Medical Officer's Note: *The pattern of microbiologic and clinical outcomes remains unchanged, with good correlation, but with a relatively large number of penicillin patients with clinical cure but microbiological persistence. Cefdinir still shows superiority microbiologically. Please see table (appendix 12) in appendix P56.*

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

5.2.1.2.1. Microbiologic Eradication

Of the qualified patients who had *S. pyogenes* eradicated at the TOC visit, 95.9% (164/171) in the cefdinir group and 97.7% (127/130) in the penicillin group also had microbiologic eradication at the LTFU visit.

5.2.1.2.2. Clinical Cure

In qualified patients who were clinically cured at TOC, the clinical cure rate at LTFU was 94.9% (166/175) for the cefdinir group and 96.5% (138/143) for the penicillin group. Clinical cure rates were based on the combined investigator/sponsor determination, which was identical to the investigator determination in this case.

5.2.2. Modified Intent-to-Treat (MITT) Analyses

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

In the MITT population, the microbiologic eradication rates were 89.8% (211/235) for the cefdinir group and 72.9% (167/229) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (9.9%, 23.8%), indicating that the cefdinir treatment was superior to penicillin because the interval lies above zero. The exploratory CMH test showed that the eradication rate for cefdinir treatment was significantly higher ($p < 0.001$) than that for penicillin treatment.

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

5.2.3. Intent-to-Treat (ITT) Analyses

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

5.2.3.1.1. Microbiologic Eradication

The ITT microbiologic eradication rates were 87.9% (211/240) for the cefdinir group, and 69.0% (167/242) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (11.8%, 26.0%), indicating that the cefdinir treatment was superior to penicillin treatment because the interval lies above zero. The exploratory CMH test showed that the eradication rate for cefdinir was significantly higher ($p < 0.001$) than that for penicillin.

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

5.2.3.1.2. Clinical Cure

The ITT clinical response rates were 91.3% (219/240) for the cefdinir group and 90.1% (218/242) for the penicillin group. According to the sponsor, the 95% CI about the difference between cefdinir vs penicillin was (-4.0%, 6.4%), indicating that cefdinir treatment was equivalent to penicillin treatment based on the fixed criteria for equivalence (-10%, +10%). The exploratory CMH test showed that the clinical response rates were not significantly different ($p = 0.67$) for the 2 treatment groups

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

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

The microbiologic eradication rates for the cefdinir and penicillin groups were 78.3% and 59.1%, respectively. The clinical cure rates for the cefdinir and penicillin treatment groups were 80.8% and 66.9%, respectively.

5.2.4. Other Population Analyses

5.2.4.1. Clinically Evaluable Patients

In the clinically evaluable patient population, the clinical response rate was 91.7% (209/228) for the cefdinir group and 90.9% (200/220) for the penicillin group. According to the sponsor, the 95% CI about the difference between treatment groups was (-4.5%, 6.0%), indicating that cefdinir treatment was equivalent to penicillin treatment based on the fixed criteria for equivalence (-10%, +10%). The exploratory CMH test showed that there was no significant difference (p = 0.79) between clinical response rates for cefdinir and penicillin treatment groups.

Statistical Reviewer's notes:

The sponsor's results and consequently the inferences based on it are acceptable.

5.2.4.2. Patients Who Took Iron During Treatment

Two cefdinir-treated patients took iron supplements (multivitamin or iron tablets) during treatment. *S. pyogenes* was eradicated at the TOC visit for 1 patient (evaluable) and persisted for the other patient (not evaluable). It is not clear what effect the iron tablets had on this outcome.

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

One cefdinir-treated patient took a magnesium-containing antacid (Rolaids™) during treatment. *S. pyogenes* was eradicated at the TOC visit for this evaluable patient.

5.2.5. Summary of Efficacy Results

A summary of the efficacy analyses at the TOC visit is given below (Table 13).

TABLE 13. Summary of Efficacy Analyses at TOC

Efficacy Parameter/Population	Rates (%)		95% CI[a]	Interpretation[b] (Superior, Equivalent, Not Equivalent)	CMH[c] (p-Value)
	Cefdinir	Penicillin			
Microbiologic Eradication					
Evaluable[d]	90	72	(10.8, 25.2)	Superior	<0.001
MITT	90	73	(9.9, 23.8)	Superior	<0.001
ITT	88	69	(11.8, 26.0)	Superior	<0.001
Clinical Response					
Evaluable	92	91	(-4.5, 6.1)	Equivalent	0.80
Clinically Evaluable	92	91	(-4.5, 6.0)	Equivalent	0.79
ITT	91	90	(-4.0, 6.4)	Equivalent	0.67

[a] CI about difference between cefdinir vs penicillin (cefdinir minus penicillin)
[b] Treatments were equivalent if the 95% CI fell within the fixed criteria for equivalence and contained zero. Cefdinir treatment was superior where indicated.
[c] Exploratory CMH; cefdinir vs penicillin
[d] Primary efficacy analysis

Medical Officer's Note: *The response rates and analysis results for all patient populations are shown in Table 13. Excluding Site 5 had very little effect on response rates. Cefdinir and penicillin are still shown to be equivalent in clinical response rate across patient populations. Cefdinir remains statistically superior to penicillin for microbiological response rate across populations. Please see table 13 in appendix P56.*

Statistical Reviewer's notes:
Table 13, as reported by the sponsor, is acceptable.

5.2.6. Appearance of New Pathogens During the Study

5.2.6.1. Superinfections

Two cefdinir-treated patients developed superinfections caused by *S. pyogenes* (different strains than present at baseline); both pathogens were susceptible to cefdinir.

5.2.6.2. Reinfections

Four cefdinir-treated patients developed reinfections with *S. pyogenes* (different strains than present at baseline). All pathogens were susceptible to cefdinir. No penicillin-treated patients developed reinfections.
Medical Officer's Note: *I agree with the different outcome responses by the sponsor.*

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 P56 page 4.

5.3.1. Adverse Events

5.3.1.1. Overview

Thirty-eight percent of cefdinir-treated patients and 33% of penicillin-treated patients experienced at least 1 adverse event during the study (Table 14); these rates were not significantly different ($p = 0.212$). Five percent of patients in both treatment groups experienced an adverse event considered associated with study medication. Thirteen percent of cefdinir-treated patients and 14% of penicillin-treated patients experienced an adverse event while receiving study medication.

Statistical Reviewer's notes:

The safety report in this study is based on the sponsor's results. It was felt that the statistical validity of the analysis plan was acceptable, so further reanalysis was not required.

The number of withdrawals after treatment due to adverse events was similar between treatment groups; 2 penicillin-treated patients and no cefdinir-treated patients discontinued treatment due to adverse events. Two serious adverse events occurred during the study; neither was related to study therapy. No deaths occurred during the study.

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TABLE 14. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 1 of 2)

	Cefdinir N = 240		Penicillin N = 242	
Adverse Events During Study				
All Adverse Events	92	(38.3)	80	(33.1)
Associated[a] Adverse Events	13	(5.4)	11	(4.5)
Adverse Events During Treatment				
All Adverse Events	30	(12.5)	33	(13.6)
Adverse Events by Sex[b]				
All Adverse Events				
Male	49	(38.3)	40	(32.8)
Female	43	(38.4)	40	(33.3)
Associated Adverse Events				
Male	6	(4.7)	5	(4.1)
Female	7	(6.3)	6	(5.0)
Adverse Events by Race[c]				
All Adverse Events				
White	84	(39.3)	73	(34.1)
Hispanic	3	(27.3)	4	(36.4)
Black	1	(12.5)	3	(25.0)
Asian	2	(50.0)	0	(0.0)
Other	2	(66.7)	0	(0.0)
Associated Adverse Events				
White	13	(6.1)	10	(4.7)
Hispanic	0	(0.0)	0	(0.0)
Black	0	(0.0)	1	(8.3)
Asian	0	(0.0)	0	(0.0)
Other	0	(0.0)	0	(0.0)
Adverse Events by Age[d]				
All Adverse Events				
<2 years	1	(50.0)	1	(100.0)
2 to <6 years	31	(47.7)	24	(38.7)
6 to <13 years	60	(34.7)	55	(31.1)
13 to <18 years	0	(0.0)	0	(0.0)
Associated Adverse Events				
<2 years	0	(0.0)	0	(0.0)
2 to <6 years	4	(6.2)	7	(11.3)
6 to <13 years	9	(5.2)	4	(2.3)
13 to <18 years	0	(0.0)	0	(0.0)

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

	Cefdinir N = 240		Penicillin N = 242	
Adverse Events by Maximum Intensity[a]				
All Adverse Events				
Mild	70	(29.2)	67	(27.7)
Moderate	36	(15.0)	24	(9.9)
Severe	1	(0.4)	1	(0.4)
Associated Adverse Events				
Mild	9	(3.8)	8	(3.3)
Moderate	3	(1.3)	4	(1.7)
Severe	1	(0.4)	0	(0.0)
Serious Adverse Events	1	(0.4)	1	(0.4)
Deaths	0	(0.0)	0	(0.0)
Discontinuation of Treatment Due to Adverse Events				
All Adverse Events	0	(0.0)	2	(0.8)
Associated Adverse Events	0	(0.0)	1	(0.4)
Withdrawals After Treatment Due to Adverse Events				
All Adverse Events	6	(2.5)	5	(2.1)
Associated Adverse Events	0	(0.0)	0	(0.0)

[a] Patients with multiple adverse events were counted once in each applicable category.

Medical Officer's Note: Again, Dr Iravani's site reported a lower incidence of adverse events than the overall reported rates: 21% for cefdinir BID and 11% for penicillin. Because of this, the incidence of all adverse events increased proportionally in both the cefdinir and penicillin groups when data from his site were excluded. As shown below, rates of all adverse events increased from 38.3% to 40.8% (a factor of 1.07) in the cefdinir group and from 33.1% to 36.0% (a factor of 1.09) in the penicillin group. Likewise, rates of drug-associated adverse events increased from 5.4% to 6.2% (a factor of 1.15) in the cefdinir group and from 4.5% to 5.1% (a factor of 1.13) in the penicillin group. No significant differences in the number of adverse events or drug-associated adverse events reported by patients receiving either cefdinir or penicillin were detected; p values are reported below.

	Cefdinir BID	*Penicillin*	*CMH p-Value*
All Adverse Events			
All Sites	*38.3% (92/240)*	*33.1% (80/242)*	*0.212*
Excluding Site 5	*40.8% (86/211)*	*36.0% (77/214)*	*0.314*
Drug-Associated Adverse Events			
All Sites	*5.4% (13/240)*	*4.5% (11/242)*	*0.678*
Excluding Site 5	*6.2% (13/211)*	*5.4% (11/214)*	*0.678*

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

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5.3.1.2. All and Drug-Associated Adverse Events

In general, the adverse event profile of cefdinir was similar to the adverse event profile of penicillin. Adverse events relating to the body as a whole occurred with the highest frequency for both treatment groups . Infection occurred in 10% of cefdinir-treated patients and 5% of penicillin-treated patients; these infections consisted mainly of upper respiratory infections and cold symptoms. Fifteen percent of cefdinir-treated patients and 10% of penicillin-treated patients experienced adverse events related to the respiratory system mainly due to reports of cough and rhinitis commonly associated with upper respiratory infections.

Approximately 10% of patients in each treatment group experienced an adverse event related to the digestive system; the most frequently occurring event in this system was diarrhea which occurred in 5% of cefdinir-treated patients and 4% of penicillin-treated patients (not significantly different, p = 0.638). Vomiting occurred in 3% of cefdinir-treated patients and 5% of penicillin-treated patients.

The adverse events most frequently associated with study treatment was diarrhea (2.1%) for cefdinir-treated patients and rash (1.2%) for penicillin-treated patients.

Medical Officer's Note: Small increases were also seen in most individual adverse event rates and drug-associated adverse event rates as a result of a smaller denominator. The largest increase in rates for a particular event was seen in the cefdinir group for infection, where the rate increased by 0.9%, and for increased cough, where the rate increased by 0.8%. Lesser increases in the rates of diarrhea were seen, by 0.1% in the cefdinir group and by 0.6% in the penicillin group. Rates of drug-associated diarrhea increased by 0.3% in the cefdinir group and by 0.1% in the penicillin group. Please see table 15 in appendix P56.

5.3.1.9. Serious Adverse Events

Two serious adverse events occurred during the study. A cefdinir-treated patient developed possible rheumatic fever after completing treatment and withdrew from the study. The narrative for this patient follows:

Patient 048 (983-056-003), a 7-year-old white girl with GABHS pharyngitis, developed possible rheumatic fever 4 days post treatment with cefdinir. The patient had received cefdinir (7 mg/kg BID) for 5 days for treatment of her pharyngitis, beginning on the first day of her sore throat. Four days after completion of cefdinir, swelling of the left knee appeared and was attributed to trauma. *Streptococcus pyogenes* was eradicated from the pharynx at the TOC culture. The initial swelling resolved, but arthralgia involving the knee and both upper extremities appeared along with a fever of 101.3 and an elevated sedimentation rate, 62 mm/hr. The patient was admitted to the hospital, was treated with aspirin and Penicillin V-K and was discharged 3 days later.

After discharge from the hospital, the patient was sent to a streptococcal infection specialist who felt that the clinical findings were compatible with, but not diagnostic of rheumatic fever. No evidence of cardiac involvement was seen and a bone scan was normal. The possible rheumatic fever resolved on Day 30. Follow-up 4 months poststudy also indicated that there was no cardiac involvement and that the patient had fully recovered. She was also receiving acetaminophen and ibuprofen. The patient had a past history of sinusitis and otitis media. The investigator considered this event moderate in intensity and unlikely to be related to cefdinir.

A penicillin-treated patient was hospitalized for dehydration after 4 days of treatment. Study medication was discontinued and the patient was treated with IV fluids and antibiotics. The event was considered unrelated to therapy.

5.3.1.10. Withdrawals Due to Adverse Events

Two penicillin-treated patients and no cefdinir-treated patients discontinued study medication because of an adverse event (Table 16). This difference was not statistically different ($p = 0.157$). One of these adverse events (stomach cramps, nausea) was considered treatment-associated.

Six cefdinir-treated patients and 5 penicillin-treated patients withdrew from the study after completing treatment. Otitis media was the most common reason patients withdrew from the study. There were no withdrawals due to diarrhea.

Narratives for patients who discontinued treatment or withdrew from the study are in Appendix B.2.

TABLE 16. Withdrawals Due to Adverse Events - All Patients

Center	Patient Number	Age, Sex	Adverse Event	Relationship to Study Medication[a]	Study Day of Onset	Study Day Drug Discontinued	Outcome
Cefdinir							
3	48	7 yr, F	Possible Rheumatic Fever[b,c]	Unlikely	9	Completed	Recovered
2	29	19 mo, F	Otitis media	Definitely not	12	Completed medication	Unknown
7	14	5 yr, M	Otitis media	Definitely not	18	Completed medication	Recovered
8	7	11 yr, M	Otitis media, sinusitis	Definitely not	17	Completed medication	Recovered
9	36	6 yr, M	Otitis media	Definitely not	7	Completed medication	Recovered
14	3	10 yr, M	Sinusitis	Definitely not	16	Completed medication	Recovered
Penicillin							
5[c]	33	2 yr, F	Dehydration[b]	Definitely not	4	4	Recovered
3	58	8 yr, F	Stomach cramps, nausea	Possibly	2	2	Recovered
4	21	2 yr, M	Smashed thumb	Definitely not	2	Completed medication	Recovered
10	38	10 yr, F	Urinary tract infection	Definitely not	15	Completed medication	Recovered
10	47	9 yr, F	Otitis media	Definitely not	11	Completed medication	Recovered
11	9	2 yr, F	Sinusitis, conjunctivitis	Unlikely	18	Completed medication	Recovered
12	6	5 yr, M	Impetigo	Definitely not	18	Completed medication	Recovered

[a] As assessed by the investigator
[b] Serious adverse event
[c] Preferred term: infection

Medical Officer's Note: Please see table 16 in Appendix P56. Patient 33 at site 5(struck out) discontinued penicillin and was hospitalized due to dehydration. This was reported as a serious adverse event. The event was considered by the investigator to be definitely not related to study medication.

5.3.3. Clinical Laboratory Measurements

5.3.3.1. Changes From Baseline

5.3.3.2. Category Shifts

Medical officer's Note. These tables (17 and 18)in the sponsor's study report, which looked at changes from baseline and category shifts have not been revised as this lab data was run on a different set of programs with extensive reworking required to exclude patients in site 5.

5.3.3.3. Markedly Abnormal Clinical Laboratory Values

Medical Officer's Note: The table19, which shows markedly abnormal clinical laboratory values, from the original NDA has been included, with patients from center 5 lined out. See table 19 in appendix S56.

Medical Officer's Note: The total number of patients experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) decreased from 23 to 20 in the cefdinir treatment group and from 22 to 19 in the penicillin group, but the overall percentages remained relatively constant at 9.5% and 8.9% respectively The largest change among the individual parameters was seen in polymorphonuclear leukocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal increase, and in lymphocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal decrease. Please see table 20 in appendix P56

6. DISCUSSION

Patients treated with a 5-day course of cefdinir showed a significantly higher microbiologic eradication rate ($p < 0.001$) compared with patients treated with a 10-day course of penicillin. Clinical response rates for the 2 treatment groups were statistically equivalent at the TOC visit.

The higher eradication rate resulting from cefdinir treatment has important implications in the treatment of GABHS pharyngitis in children. The main objective of antimicrobial intervention in this type of infection is the prevention of more serious complications, such as rheumatic fever. Since the reduction of the incidence of rheumatic fever and other nonsuppurative complications of GABHS pharyngitis is not a practical endpoint for a study, the eradication of *S. pyogenes* becomes the accepted surrogate endpoint for efficacy. The superior eradication rate demonstrated by cefdinir may be a result of its stability in the presence of β-lactamases produced by normal flora in the pharynx. The 5-day, BID dosing regimen for cefdinir therapy may also have contributed to the superior microbiological eradication rate by improving treatment compliance; the percent of patients who took the full course of treatment as prescribed was greater (93%) for cefdinir treatment compared with penicillin treatment (76%).

One cefdinir-treated patient developed what was considered "possible" rheumatic fever. It is uncertain whether this patient did indeed have rheumatic fever. The supposed onset was atypically soon after the development of pharyngitis (Study Day 9). The strain of *S. pyogenes* isolated from the pharynx was not a rheumatogenic strain, but was serotyped as T-Type 11 and M- (Opacity Factor) Type 11; this strain was eradicated by cefdinir treatment. It is also not clear that the patient fulfilled all of the modified Jones criteria for polyarthritis; an evaluation of the patient by an internationally recognized infectious disease specialist resulted in this same conclusion (Appendix B.3). If this patient did have rheumatic fever, it was likely due to an antecedent (nonstudy) infection and does not represent the failure of cefdinir.

Cefdinir therapy was well-tolerated by the pediatric patient population in this study. The safety profile of cefdinir was similar to that of penicillin with 38% of cefdinir-treated patients and 33% of penicillin-treated patients experiencing adverse events over the course of the study. Thirteen percent of cefdinir-treated patients and 14% of penicillin-treated patients experienced adverse events during the treatment phase. The most frequently reported adverse events for cefdinir-treated patients were consistent with upper respiratory symptoms (infection 10%, cough, rhinitis 5%). Diarrhea was reported for 5% of cefdinir-treated patients; 2% were

considered associated with treatment. Vomiting (5%) was the most frequently reported adverse event for penicillin-treated patients, which is not unexpected given that stomach upset is commonly associated with penicillin treatment. Withdrawals due to adverse events were similar for both treatments.

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

In the study comparing 5 days treatment of BID cefdinir to 10 days treatment with penicillin, cefdinir was again superior to penicillin in eradication of S. pyogenes from the pharynx, by both CI and CMH testing. Clinical response for the 2 regimens was equivalent by CI testing.

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

7. CONCLUSIONS

- Five days of cefdinir therapy (BID) is more effective microbiologically than 10 days of penicillin therapy (QID) in the treatment of pediatric patients with GABHS pharyngitis. Clinical response rate is equivalent for cefdinir and penicillin therapy.
- Cefdinir therapy is well-tolerated by pediatric patients; adverse event profiles are similar for cefdinir- and penicillin-treated patients.

Medical Officer's Note: The reviewer agrees with the design and conduct of the study

APPENDIX P56 ,Study 983-56,Pediatric Pharyngitis -5 days

Evaluable Patients

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding site 5 (Iravani).

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.5% (205/224)	90.7% (196/216)	(-4.5%, 6.1%)	0.798
Excluding Site 5	91.3% (179/196)	89.6% (173/193)	(-4.1%, 7.5%)	0.567
Microbiological Response by Patient				
All Sites	89.7% (201/224)	71.8% (155/216)	(10.8%, 25.2%)	<0.001
Excluding Site 5	89.8% (176/196)	69.9% (135/193)	(12.1%, 27.6%)	<0.001

Excluding site 5 had very little effect on the response rates. Cefdinir is still shown to be equivalent to penicillin in clinical response rate, and superior to penicillin for microbiological response by patient, for the evaluable population.

Clinically Evaluable Patients

The table below presents the clinical response rates and analysis results for the clinically evaluable patient population, both including and excluding site 5.

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.7% (209/228)	90.9% (200/220)	(-4.5%, 6.0%)	0.787
Excluding Site 5	91.5% (182/199)	89.7% (175/195)	(-4.1%, 7.5%)	0.552

Excluding site 5 had very little effect on the clinical response rates. Cefdinir and penicillin are still shown to be equivalent for the clinically evaluable population.

1

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

Protocol 983-056

NDA Analysis- All sites

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Penicillin V	
	N	%	N	%
Patients w/ eradication	201	89.7	155	71.8
Patients w/ persistence	23	10.3	61	28.2
Total	224	100.0	216	100.0

Protocol 983-056 (Subset=56_noinv.txt)

All sites except Iravani

Pathogen		Number (%) of Pathogens							
		Cefdinir 7 mg/kg BID				Penicillin V			
		Eradication		Persistence		Eradication		Persistence	
		N	%	N	%	N	%	N	%
Gram Positive	Bhsa mor1	1	100.0	0	0	0	0	0	0
	Bhsa mor2	1	100.0	0	0	0	0	0	0
	S pyogen	175	89.8	20	10.3	135	69.9	58	30.0
Total	Pathogens	177	89.8	20	10.2	135	69.9	58	30.1

Protocol 983-056

Center = 983-056-005 Iravani Only

Pathogen		Number (%) of Pathogens							
		Cefdinir 7 mg/kg BID				Penicillin V			
		Eradication		Persistence		Eradication		Persistence	
		N	%	N	%	N	%	N	%
Gram Positive	Bhsa mor1	0	0	0	0	1	100.0	0	0
	Bhsa mor2	0	0	0	0	1	100.0	0	0
	S pyogen	25	89.3	3	10.7	19	82.6	3	13.6
Total	Pathogens	25	89.3	3	10.7	21	87.5	3	12.5

[1] The preceding page lists the microbiological eradication rates by pathogen/patient according to the NDA analyses (all patients, all sites except Iravani); and Iravani alone.

Adverse Events

The table below presents the adverse event rates and drug-associated adverse event rates, and the analysis results, for patients who took drug both including and excluding site 5.

	Cefdinir BID	Penicillin	CMH p-value
All Adverse Events			
All Sites	38.3% (92/240)	33.1% (80/242)	0.212
Excluding Site 5	40.8% (86/211)	36.0% (77/214)	0.314
Drug-Associated Adverse Events			
All Sites	5.4% (13/240)	4.5% (11/242)	0.678
Excluding Site 5	6.2% (13/211)	5.4% (11/214)	0.678

Excluding site 5 had very little effect on adverse event rates. No significant difference in the number of all adverse events or drug-associated adverse events in patients receiving cefdinir or penicillin was detected.

Dr. Iranvani reported one serious adverse event in this study. A penicillin-treated patient was hospitalized after 4 days of treatment with penicillin. The study medication was discontinued, and the patient treated with IV fluids and antibiotics. The investigator considered the event definitely not related to study therapy.

Protocol 983-056

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

TABLE 1

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

TABLES 6 and 7

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

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TABLE 8

Patient exposure to study medication remained the same, with the majority of cefdinir patients finishing study medication on Day 5 and most penicillin patients finishing medication on Day 11.

TABLE 9

The overall percentages of patients completing the treatment phase, TOC visit phase, and LTFU visit phase of the study remained relatively constant at 96.2%, 89.1%, and 70.6% respectively. The percentage of patients completing the treatment phase increased by 0.6% when patients from Dr Iravani's site were excluded.

TABLE 10

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

TABLE 11

The revised numbers of patients included in the efficacy summaries are presented.

TABLE 12

The pattern of microbiologic and clinical outcomes remains unchanged, with good correlation, but with a relatively large number of penicillin patients with clinical cure but microbiological persistence. Cefdinir still shows superiority microbiologically.

TABLE 13

The response rates and analysis results for all patient populations are shown in Table 13. Excluding Site 5 had very little effect on response rates. Cefdinir and penicillin are still shown to be equivalent in clinical response rate across patient

populations. Cefdinir remains statistically superior to penicillin for microbiological response rate across populations.

TABLE 14

Again, Dr Iravani's site reported a lower incidence of adverse events than the overall reported rates: 21% for cefdinir BID and 11% for penicillin. Because of this, the incidence of all adverse events increased proportionally in both the cefdinir and penicillin groups when data from his site were excluded. As shown below, rates of all adverse events increased from 38.3% to 40.8% (a factor of 1.07) in the cefdinir group and from 33.1% to 36.0% (a factor of 1.09) in the penicillin group. Likewise, rates of drug-associated adverse events increased from 5.4% to 6.2% (a factor of 1.15) in the cefdinir group and from 4.5% to 5.1% (a factor of 1.13) in the penicillin group. No significant differences in the number of adverse events or drug-associated adverse events reported by patients receiving either cefdinir or penicillin were detected; p values are reported below.

	Cefdinir BID	Penicillin	CMH p-Value
All Adverse Events			
All Sites	38.3% (92/240)	33.1% (80/242)	0.212
Excluding Site 5	40.8% (86/211)	36.0% (77/214)	0.314
Drug-Associated Adverse Events			
All Sites	5.4% (13/240)	4.5% (11/242)	0.678
Excluding Site 5	6.2% (13/211)	5.4% (11/214)	0.678

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

TABLE 15

For ease of comparison, this revised table includes data from both the NDA study report and the revised data excluding Dr Iravani's site.

Small increases were also seen in most individual adverse event rates and drug-associated adverse event rates as a result of a smaller denominator. The largest increase in rates for a particular event was seen in the cefdinir group for infection, where the rate increased by 0.9%, and for increased cough, where the rate increased by 0.8%. Lesser increases in the rates of diarrhea were seen, by 0.1% in the cefdinir group and by 0.6% in the penicillin group. Rates of drug-associated diarrhea increased by 0.3% in the cefdinir group and by 0.1% in the penicillin group

TABLE 16

Patient 33 at Dr Iravani's site discontinued penicillin and was hospitalized due to dehydration. This was reported as a serious adverse event. The event was considered by the investigator to be definitely not related to study medication.

TABLES 17 and 18

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

TABLE 19

This table is a list of patients with markedly abnormal values at the first posttherapy visit. The table from the original NDA has been included, with patients from Dr Iravani's site (Center 5) lined out.

TABLE 20

The total number of patients experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) decreased from 23 to 20 in the cefdinir treatment group and from 22 to 19 in the penicillin group, but the overall percentages remained relatively constant at 9.5% and 8.9% respectively.

The largest change among the individual parameters was seen in polymorphonuclear leukocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal increase, and in lymphocytes, where 2 fewer patients in the cefdinir group experienced a markedly abnormal decrease.

DISCUSSION

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

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

In the study comparing 5 days treatment of BID cefdinir to 10 days treatment with penicillin, cefdinir was again superior to penicillin in eradication of *S. pyogenes* from the pharynx, by both CI and CMH testing. Clinical response for the 2 regimens was equivalent by CI testing.

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

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

Two of the streptococcal pharyngitis studies were conducted in adolescents/adults, and 2 in children. The efficacy results across all 4 studies are shown in the tables on the following 2 pages. As the pathophysiology of the infection in children and adults is similar, the pathogen identical, and the pharmacokinetics of cefdinir in the populations very similar, study results in adolescents/adults and children can be used

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.

Microbiological Response by Patient and Clinical Response Rates - Evaluable Patients
(% of Patients)

Study	983-7			983-58		983-51			983-51 (Excluding Iravani)			983-56		983-56 (Excluding Iravani)	
Treatment	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef BID	Pen
Microbiological Response by Patient	91.4	91.7	83.4	88.5	82.2	92.5	94.8	70.8	94.3	94.3	70.0	89.7	71.8	89.8	69.9
Clinical Response Rates	93.8	95.9	89.4	89.0	84.6	97.6	96.4	86.8	97.4	96.0	86.3	91.5	90.7	91.3	89.6

Cef = Cefdinir, Pen = Penicillin.

Clinical Response Rates - Clinically Evaluable Patients
(% of Patients)

Study	983-7			983-58		983-51			983-51 (Excluding Iravani)			983-56		983-56 (Excluding Iravani)	
Treatment	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef QD	Cef BID	Pen	Cef BID	Pen	Cef BID	Pen
Clinical Response Rates	90.9	93.3	85.2	86.7	81.6	97.3	96.5	86.2	97.0	96.1	85.7	91.7	90.9	91.5	89.7

Cef = Cefdinir; Pen = Penicillin.

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TABLE 1. List of Investigators Excluding Site 5

Center 983-56-	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Evaluable
1	Gerson Aronovitz, MD	12	12	11
2	W. Manford Gooch III, MD, PC	50	47	44
3	James A. Hedrick, MD	59	56	53
4	Dan Henry, MD	47	45	45
6	Kevin Ludwig, MD*	0	0	0
7	James McCarty, MD	33	31	28
8	Samuel McLinn, MD	30	29	29
9	Michael Pichichero, MD	48	48	46
10	Edward Rothstein, MD	53	53	51
11	Sandra Wiederhold, MD	25	24	24
12	Malcolm Sperling, MD	20	19	19
13	Richard Schwartz, MD	32	32	31
14	Margaret Drehobl, MD	16	13	13
Total		425	409	394

* Investigator received drug but did not enroll patients

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efdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients		
		Cefdinir 7 mg/kg BID	Penicillin V	Total
Total	Patients	211	214	425
Sex				
Male	N	112	109	221
	Percent	53.1	50.9	52.0
Female	N	99	105	204
	Percent	46.9	49.1	48.0
Race				
White	N	193	193	386
	Percent	91.5	90.2	90.8
Black	N	3	8	11
	Percent	1.4	3.7	2.6
Asian	N	4	0	4
	Percent	1.9	0	0.9
Other	N	11	13	24
	Percent	5.2	6.1	5.6
Age (Years)				
< 2	N	2	1	3
	Percent	0.9	0.5	0.7
2 to < 6	N	54	48	102

(CONTINUED)

Summary Specification Table 101
(Page 1 of 2)

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediat... Patients

Summary of Patient Characteristics
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients		
		Cefdinir 7 mg/kg BID	Penicillin V	Total
Age (Years)				
2 to < 6	Percent	25.6	22.4	24.0
6 to < 13	N	155	163	318
	Percent	73.5	76.2	74.8
13 to < 18	N	0	2	2
	Percent	0	0.9	0.5
Age Range	Max	13	18	18
	Min	1	2	1
Baseline Diagnosis				
Pharyngitis	N	60	63	123
	Percent	28.4	29.4	28.9
Tonsillitis	N	22	15	37
	Percent	10.4	7.0	8.7
Pharyngitis & tonsillitis	N	129	136	265
	Percent	61.1	63.6	62.4

Summary Specification Table 101
(Page 2 of 2)

dinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

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

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID			Penicillin V			Total		
	Min	Med	Max	Min	Med	Max	Min	Med	Max
Baseline Parameters									
Age (Years)	1.0	7.5	12.8	1.7	7.8	18.0	1.0	7.8	18.0
Weight (kg)	11.3	25.5	86.6	10.3	26.4	86.4	10.3	26.4	86.6
Height (cm)	78.7	124.5	168.9	82.8	128.3	168.9	78.7	127.0	168.9
Systolic BP (mm Hg)	70.0	100.0	140.0	70.0	98.0	128.0	70.0	98.0	140.0
Diastolic BP (mm Hg)	36.0	60.0	80.0	30.0	60.0	84.0	30.0	60.0	84.0
Temperature (C)	35.4	37.3	40.0	35.3	37.3	39.8	35.3	37.3	40.0

Summary Specification Table 192
(Page 1 of 1)

dinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients		
		Cefdinir 7 mg/kg BID	Penicillin V	Total
Total	Patients	196	193	389
Sex				
Male	N	103	98	201
	Percent	52.6	50.8	51.7
Female	N	93	95	188
	Percent	47.4	49.2	48.3
Race				
White	N	179	176	355
	Percent	91.3	91.2	91.3
Black	N	3	6	9
	Percent	1.5	3.1	2.3
Asian	N	4	0	4
	Percent	2.0	0	1.0
Other	N	10	11	21
	Percent	5.1	5.7	5.4
Age (Years)				
< 2	N	1	1	2
	Percent	0.5	0.5	0.5
2 to < 6	N	48	44	92

(CONTINUED)

Summary Specification Table 102
(Page 1 of 2)

dinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric atients

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients		
		Cefdinir 7 mg/kg BID	Penicillin V	Total
Age (Years)				
2 to < 6	Percent	24.5	22.8	23.7
6 to < 13	N	147	147	294
	Percent	75.0	76.2	75.6
13 to < 18	N	0	1	1
	Percent	0	0.5	0.3
Age Range	Max	13	16	16
	Min	2	2	2
Baseline Diagnosis				
Pharyngitis	N	58	54	112
	Percent	29.6	28.0	28.8
Tonsillitis	N	20	15	35
	Percent	10.2	7.8	9.0
Pharyngitis & tonsillitis	N	118	124	242
	Percent	60.2	64.2	62.2

Summary Specification Table 102
(Page 2 of 2)

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

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID			Penicillin V			Total		
	Min	Med	Max	Min	Med	Max	Min	Med	Max
Baseline Parameters									
Age (Years)	1.6	7.7	12.6	1.7	7.8	15.7	1.6	7.8	15.7
Weight (kg)	11.3	26.0	86.6	10.3	26.4	71.8	10.3	26.4	86.6
Height (cm)	82.8	126.5	168.9	82.8	127.0	168.9	82.8	127.0	168.9
Systolic BP (mm Hg)	70.0	100.0	140.0	70.0	98.0	128.0	70.0	98.0	140.0
Diastolic BP (mm Hg)	36.0	60.0	80.0	30.0	60.0	84.0	30.0	60.0	84.0
Temperature (C)	35.4	37.3	40.0	35.3	37.3	39.8	35.3	37.3	40.0

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Exposure to Study Medication
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

Days on Study Medication	Number (%) of Patients			
	Cefdinir 7 mg/kg BID (Median=5.0)		Penicillin V (Median=11.0)	
	N	%	N	%
1	2	0.9	0	0
2	1	0.5	1	0.5
3	1	0.5	0	0
5	157	74.4	3	1.4
6	50	23.7	1	0.5
7	0	0	2	0.9
9	0	0	1	0.5
10	0	0	68	31.8
11	0	0	132	61.7
12	0	0	3	1.4
Unknown	0	0	3	1.4
Total	211	100.0	214	100.0

Summary Specification Table 265
(Page 1 of 1)

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Summary of Patient Completion Status
Treatment Phase

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicillin V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		207	98.1	202	94.4	409	96.2
Reason for Withdrawal	Lack of Compliance	2	0.9	6	2.8	8	1.9
	Adverse Event	0	0	1	0.5	1	0.2
	Failure at end of therapy	0	0	1	0.5	1	0.2
	No Baseline Pathogen	0	0	1	0.5	1	0.2
	Other/Administrative	2	0.9	3	1.4	5	1.2

Summary Specification Table 269
(Page 1 of 1)

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

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

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicillin V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		206	97.6	208	97.2	414	97.4
Reason for Withdrawal	Lack of Compliance	2	0.9	3	1.4	5	1.2
	Failure at end of therapy	1	0.5	0	0	1	0.2
	No Baseline Pathogen	0	0	1	0.5	1	0.2
	Other/Administrative	2	0.9	2	0.9	4	0.9

Summary Specification Table 270
(Page 1 of 1)

TABLE 17. All and Associated Adverse Events by Body System: All Patients - Protocol 983-51
[Number (%) of Patients]
(Page 4 of 5)

BODY SYSTEM[a]/ Adverse Event	Sites Excluding Iravani									
	Cefdinir						Penicillin N = 264			
	14 mg/kg QD N = 264				7 mg/kg BID N = 263					
	All		Assoc		All		Assoc		All		Assoc	
SKIN AND APPENDAGES (Continued)												
Seborrhea	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Skin Disorder	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)	1	(0.4)
Dry Skin	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Eczema	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pruritus	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HEMIC AND LYMPHATIC SYSTEM	5	(1.9)	0	(0.0)	7	(2.7)	0	(0.0)	5	(1.9)	0	(0.0)
Lymphadenopathy	4	(1.5)	0	(0.0)	7	(2.7)	0	(0.0)	4	(1.5)	0	(0.0)
Eosinophilia	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphocytosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
UROGENITAL SYSTEM	4	(1.5)	2	(0.8)	6	(2.3)	2	(0.8)	1	(0.4)	0	(0.0)
Urinary Tract Infection	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
Vaginitis[b]	1	(0.4)	1	(0.4)	2	(0.8)	1	(0.4)	0	(0.0)	0	(0.0)
Hematuria	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Leukorrhea	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dysuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Penis Disorder[c]	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urine Abnormality	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vaginal Moniliasis[b]	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
NERVOUS SYSTEM	2	(0.8)	0	(0.0)	3	(1.1)	0	(0.0)	3	(1.1)	1	(0.4)
Abnormal Dreams	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Emotional Lability	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperkinesia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)	1	(0.4)

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

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

[b] The denominators used are for females only: Cefdinir QD, N = 134; Cefdinir BID, N = 135 for all sites and Cefdinir QD, N = 123; Cefdinir BID, N = 131 for sites excluding Iravani.

[c] The denominator used is for males only: Cefdinir QD, N = 155 for all sites and Cefdinir QD, N = 141 for sites excluding Iravani.

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

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

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicillin V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		178	84.4	173	80.8	351	82.6
Reason for Withdrawal	Lack of Compliance	4	1.9	3	1.4	7	1.6
	Adverse Event	4	1.9	4	1.9	8	1.9
	Failure at EOT or previous visit	19	9.0	26	12.1	45	10.6
	No Baseline Pathogen	1	0.5	3	1.4	4	0.9
	Other/Administrative	5	2.4	5	2.3	10	2.4

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fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

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

All Patients

Protocol 983-056 (Subset=56_noinv.txt)

		Number of Patients					
		Cefdinir 7 mg/kg BID N=211		Penicillin V N=214		Total N=425	
		N	%	N	%	N	%
Completed Phase		157	74.4	143	66.8	300	70.6
Reason for Withdrawal	Lack of Compliance	7	3.3	5	2.3	12	2.8
	Adverse Event	6	2.8	6	2.8	12	2.8
	Failure at EOT or previous visit	36	17.1	52	24.3	88	20.7
	No Baseline Pathogen	1	0.5	3	1.4	4	0.9
	Other/Administrative	4	1.9	5	2.3	9	2.1

Summary Specification Table 272
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dinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

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

Protocol 983-056 (Subset=56_noinv.txt)

		Number (%) of Patients					
		Cefdinir 7 mg/kg BID		Penicillin V		Total	
		N	%	N	%	N	%
Exclusions from Clinical Analyses	*** Total ***	12	5.7	19	8.9	31	7.3
	Clin asmt missed	1	0.5	3	1.4	4	0.9
	Clin out of range	7	3.3	14	6.5	21	4.9
	Concurrent antibac	3	1.4	2	0.9	5	1.2
	Med not as prescrb	7	3.3	10	4.7	17	4.0
Additional Exclusions from Microbiological Analyses	*** Total ***	3	1.4	2	0.9	5	1.2
	Cult out of range	7	3.3	14	6.5	21	4.9
	Culture missed	2	0.9	7	3.3	9	2.1
	No proven pathogn	4	1.9	3	1.4	7	1.6
Total	*** TOTAL ***	15	7.1	21	9.8	36	8.5

Cefdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

Reasons for Disqualification of Microbiologically/Clinically Evaluable Patients from Analysis
Long-Term Follow-Up Visit

Protocol 983-056 (Subset=56_noinv.txt)

Disqualification	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Penicillin V	
	N	%	N	%
*** Total ***	44	22.4	70	36.3
Clin asmt missed	23	11.7	52	26.9
Clin out of range	19	9.7	14	7.3
Concurrent antibac	1	0.5	4	2.1
Cult out of range	19	9.7	13	6.7
Culture missed	25	12.8	54	28.0

TABLE 11. Patients (With Data) Included in Efficacy Summaries Excluding Site 5 (Protocol 983-56) [Number (%) of Patients]

Patient Population	Cefdinir	Penicillin
Intent-to-Treat (ITT)	211	214
Modified Intent-to-Treat (MITT)	207	204
Clinically Evaluable	199	195
Microbiologically-Clinically Evaluable	196	193
Qualified at LTFU	152	123

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients

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

Protocol 983-056 (Subset=56_noinv.txt)

Microbiologic Response	Clinical Response							
	Cefdinir 7 mg/kg BID				Penicillin V			
	Cure		Failure		Cure		Failure	
	N	%	N	%	N	%	N	%
Patients w/ eradication	172	87.8	4	2.0	134	69.4	1	0.5
Patients w/ persistence	7	3.6	13	6.6	39	20.2	19	9.8

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TABLE 13. Summary of Efficacy Analyses at TOC Excluding Site 5

Efficacy Parameter/ Population	Rates (%)		95% CI[a]	Interpretation[b] (Superior, Equivalent, Not Equivalent)	CMH[c] (p-Value)
	Cefdinir	Penicillin			
Microbiologic Eradication					
Evaluable[d]	90	70	(12.1, 27.6)	Superior	<0.001
MITT	90	72	(10.9, 25.7)	Superior	<0.001
ITT	88	68	(12.3, 27.5)	Superior	<0.001
Clinical Response					
Evaluable	91	90	(-4.1, 7.5)	Equivalent	0.57
Clinically Evaluable	92	90	(-4.1, 7.5)	Equivalent	0.55
ITT	91	89	(-3.9, 7.4)	Equivalent	0.55

[a] CI about difference between cefdinir vs penicillin (cefdinir minus penicillin)
[b] Treatments were equivalent if the 95% CI fell within the fixed criteria for equivalence and contained zero. Cefdinir treatment was superior where indicated.
[c] Exploratory CMH; cefdinir vs penicillin
[d] Primary efficacy analysis

fdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patient

Summary of Adverse Events
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID (N=211)		Penicillin V (N=214)	
	N	%	N	%
Number of Patients Reporting AE	86	40.8	77	36.0
Number of Patients Reporting Mild AE	65	30.8	65	30.4
Number of Patients Reporting Moderate AE	33	15.6	22	10.3
Number of Patients Reporting Severe AE	1	0.5	0	0.0
Number of Male Patients Reporting AE	45	40.2	40	36.7
Number of Female Patients Reporting AE	41	41.4	37	35.2
Number of Patients < 2 Years Old Reporting AE	1	50.0	1	100.0
Number of Patients 2 to < 6 Years Old Reporting AE	28	51.9	23	47.9
Number of Patients 6 to < 13 Years Old Reporting AE	57	36.8	53	32.5
Number of Patients 13 to < 18 Years Old Reporting AE	0	0.0	0	0.0
Number of White Patients Reporting AE	80	41.5	70	36.3
Number of Black Patients Reporting AE	0	0.0	3	37.5
Number of Asian Patients Reporting AE	2	50.0	0	0.0
Number of Hispanic Patients Reporting AE	2	25.0	4	40.0
Number of Other Patients Reporting AE	2	66.7	0	0.0

(CONTINUED)

~Patients who did not discontinue treatment due to an AE