TABLE 26. Microbiologic Eradication Rate by Patient at TOC - Microbiologically-Clinically Evaluable Patients

	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Staphylococcus aureus	6/10	60.0	15/19	78.9	7/8	87.5
Staphylococcus salivarius	0/0	--	1/1	100.0	0/0	--
Strpetococcus agalactiae	1/1	100.0	0/0	--	2/2	100.0
Streptococcus anginosus	2/2	100.0	½	50.0	0/0	--
Streptococcus equi	1/1	100.0	0/0	--	0/0	--
Streptococcus equisimilis	0/0	--	2/2	100.0	1/1	100.0
Streptococcus pneumoniae	11/14	78.6	17/21	81.0	16/17	94.1
Streptococcus pyogenes	½	50.0	0/0	--	4/4	100.0
Streptococcus salivarius	0/0	--	1/1	100.0	0/0	--
Streptococcus Group G	0/0	--	0/1	0.0	0/0	--
Gram-Negative						
Citrobacter diversus	0/0	--	0/0	--	1/1	100.0
Escherichia coli	1/1	100.0	0/1	0.0	½	50.0
Eikenella corrodens	0/1	0.0	0/0	--	0/0	--
Haemophilus influenzae	10/13	76.9	9/12	75.0	11/17	64.7
Haemophilus parahaemolyticus	0/0	--	1/1	100.0	0/1	0.0
Haemophilus parainfluenzae	2/2	100.0	5/5	100.0	6/6	100.0
Klebsiella pneumoniae	1/1	100.0	0/0	--	1/21	100.0
Moraxella catarrhalis	8/9	88.9	7/9	77.8	7/8	87.5
Neisseria menigitidis	0/1	0.0	0/0	--	0/0	--
Proteus mirabilis	0/0	--	0/0	--	1/1	100.0
Multiple	12/16	75.0	10/14	71.4	19/23	82.6
Total Patients	56/74	75.7	64/79	81.0	74/89	83.1

n/N = Microbiologically-clinically evaluable patients with all baseline pathogens eradicated/all microbiologically-clinically evaluable patients

Medical Officer's Comment

For the pathogens generally agreed upon as the leading causes of acute maxillary sinusitis in adults and children, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, microbiologic eradication rates at the TOC visit were as follows:

Table 27. Microbiologic Eradication Rate, by Pathogen, at TOC, from All Sites.

	Cefdinir QD	Cefdinir BID	Cefdinir (combined)	Amox/Clav
S. pneumoniae	14/17 (82.4%)	14/16 (87.5%)	28/33 (84.8%)	21/22 (95.5%)
H. influenzae	16/19 (84.2%)	12/17 (70.6%)	28/36 (77.8%)	19/26 (73.1%)
M. catarrhalis	11/12 (91.7%)	9/13 (69.2%)	20/25 (80.0%)	10/11 (90.9%)

Table 28. Microbiologic Eradication Rate, by Patient, at TOC, from All Sites.

	Cefdinir QD	Cefdinir BID	Cefdinir (combined)	Amox/Clav
S. pneumoniae	11/14 (78.6%)	17/21 (81.0%)	28/35 (80.0%)	16/17 (94.1%)
H. influenzae	10/13 (76.9%)	9/12 (75.0%)	19/25 (76.0%)	11/17 (64.7%)
M. catarrhalis	8/9 (88.9%)	7/9 (77.8%)	15/18 (83.3%)	7/8 (87.5%)

Table 29. Microbiologic Eradication Rate, by Pathogen, at TOC, from All Sites Except Site 38.

	Cefdinir QD	Cefdinir BID	Cefdinir (combined)	Amox/Clav
S. pneumoniae	14/17 (82.3%)	14/16 (87.5%)	28/33 (84.8%)	20/21 (95.2%)
H. influenzae	16/19 (84.2%)	11/16(68.7%)	27/35 (77.8%)	18/25 (72.0%)
M. catarrhalis	10/11 (90.9%)	8/12 (66.7%)	18/23 (80.0%)	7/8 (87.5%)

Medical Officer's Comment

The comparison of the microbiologic eradication rates, by pathogen, with and without the data from site 38 included demonstrate the same rates of eradication of the most important three pathogens in acute maxillary sinusitis. The efficacy of cefdinir was similar to that of amoxicillin/clavulanate overall in the microbiologic eradication of these major pathogens, with acceptable levels of eradication in all three. Amoxicillin/ clavulanate was superior in the eradication of *S. pneumoniae*, both in the comparison against each cefdinir arm and in the aggregate. Cefdinir QD was superior to Amoxicillin/clavulanate in the eradication of both *H. influenzae* and *M. catarrhalis*, but Amoxicillin/clavulanate was superior to cefdinir BID in the eradication of both of these pathogens.

When the patients from site 38 were excluded, the aggregate numbers of isolates of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* treated with cefdinir were still more than sufficient to meet the recommended number of clinical isolates in trials of therapy for acute maxillary sinusitis, per the ***Points to Consider*** document. (That document recommends successful outcome [clinical, microbiological, and radiographic] in at least 100 patients, with at least 25 isolates of *S. pneumoniae*, 25 isolates of *H. influenzae*, and at least 15 isolates of *M. catarrhalis*.) There were consistently higher rates of microbiological eradication of *H. influenzae* and *M. catarrhalis* with cefdinir administered QD than with cefdinir BID. In the treatment of *S. pneumoniae*, the pathogen of highest incidence in culture-positive acute maxillary sinusitis, however, cefdinir BID consistently had higher eradication rates, by pathogen and by patient, than did cefdinir QD. The differences in eradication rates between cefdinir regimens was highest in the case of *M. catarrhalis*, in the evaluation of eradication rate by pathogen. The rate of eradication of *H. influenzae*, by patient, was nearly identical for the QD and BID cefdinir regimens.

Safety

Of the patients randomized to treatment, 2 in the cefdinir QD group and 2 in the cefdinir BID group did not receive drug and were not included in the safety summary.

Adverse Events

Overview

A total of 552 patients (45%) experienced at least 1 adverse event during the study (Table 26). The incidence was highest in patients treated with amox/clav, 50% of whom experienced an adverse event. In the cefdinir QD group, 42% of patients experienced an adverse event, and in the cefdinir BID group, 43% of patients experienced an adverse event. During the 10-day treatment period, the incidence of adverse events was 33%, 35%, and 38% for the cefdinir QD, cefdinir BID, and amox/clav treatment groups, respectively. There was no significant difference in the incidence of adverse events between the cefdinir treatment groups, but the incidence of adverse events in the cefdinir QD group was significantly lower than the amox/clav group ($p = 0.016$).

The incidence of associated adverse events showed a similar trend: 26%, 27%, and 31% of patients in the cefdinir QD, cefdinir BID, and amox/clav groups, respectively. These differences were not statistically significant.

No deaths occurred during this study. One cefdinir QD-treated patient died of lung cancer 108 days after being withdrawn from the study. His disease and death were not considered associated with cefdinir (see Patient Narratives, Appendix B.2). Only 5 patients experienced a serious adverse event. Thirty-five patients discontinued treatment as a result of an adverse event: 6 (2%) in the cefdinir QD group, 10 (2%) in the cefdinir BID group, and 19 (5%) in the amox/clav group. The rate of discontinuation was highest in the amox/clav group and lowest in the cefdinir QD group ($p = 0.011$). Twenty-nine of the discontinuations were due to an associated adverse event. Seventeen additional patients withdrew from the study because of an adverse event that occurred after completing treatment but before the LTFU visit (5 in the cefdinir QD group, 6 in the cefdinir BID group, and 6 in the amox/clav group). Seven of these withdrawals events were due to drug-associated adverse events.

TABLE 30. Summary of Adverse Events - All Patients [Number (%) of Patients]
(Page 1 of 2)

	Cefdinir QD N = 401		Cefdinir BID N = 410		Amox/Clav N = 414	
Adverse Events During Study						
All Adverse Events	168	(41.9)	178	(43.4)	206	(49.8)
Associated[a] Adverse Events	104	(25.9)	109	(26.6)	129	(31.2)
Adverse Events During Treatment						
All Adverse Events	131	(32.7)	144	(35.1)	159	(38.4)
Adverse Events by Sex[b]						
All Adverse Events						
Male	53	(35.6)	61	(41.5)	76	(49.0)
Female	115	(45.6)	117	(44.5)	130	(50.2)
Associated Adverse Events						
Male	29	(19.5)	31	(21.1)	45	(29.0)
Female	75	(29.8)	78	(29.7)	84	(32.4)
Adverse Events by Race[c]						
All Adverse Events						
White	152	(42.7)	162	(44.5)	177	(49.7)
Hispanic	8	(34.8)	6	(27.3)	12	(52.2)
Black	6	(31.6)	7	(38.9)	15	(46.9)
Asian	0	(0.0)	1	(100.0)	0	(0.0)
Other	2	(66.7)	2	(40.0)	2	(66.7)
Associated Adverse Events						
White	96	(27.0)	102	(28.0)	113	(31.7)
Hispanic	4	(17.4)	3	(13.6)	6	(26.1)
Black	2	(10.5)	3	(16.7)	8	(25.0)
Asian	0	(0.0)	0	(0.0)	0	(0.0)
Other	2	(66.7)	1	(20.0)	2	(66.7)
Adverse Events by Age[d]						
All Adverse Events						
6 to <13 years	0	(0.0)	0	(0.0)	0	(0.0)
13 to <18 years	15	(46.9)	16	(51.6)	15	(45.5)
18 to <65 years	146	(41.8)	153	(43.5)	182	(50.1)
≥65 years	7	(36.8)	9	(33.3)	9	(50.0)
Associated Adverse Events						
6 to <13 years	0	(0.0)	0	(0.0)	0	(0.0)
13 to <18 years	7	(21.9)	4	(12.9)	9	(27.3)
18 to <65 years	93	(26.6)	102	(29.0)	114	(31.4)
≥65 years	4	(21.1)	3	(11.1)	6	(33.3)

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

TABLE 30. Summary of Adverse Events - All Patients
[Number (%) of Patients]
(Page 2 of 2)

	Cefdinir QD N = 401		Cefdinir BID N = 410		Amox/Clav N = 414	
Adverse Events by Maximum Intensity[c]						
All Adverse Events						
Mild	117	(29.2)	127	(31.0)	148	(35.7)
Moderate	61	(15.2)	64	(15.6)	79	(19.1)
Severe	12	(3.0)	14	(3.4)	20	(4.8)
Associated Adverse Events						
Mild	75	(18.7)	77	(18.8)	92	(22.2)
Moderate	30	(7.5)	31	(7.6)	43	(10.4)
Severe	6	(1.5)	6	(1.5)	11	(2.7)
Serious Adverse Events	1	(0.2)	3	(0.7)	1	(0.2)
Deaths	0	(0.0)	0	(0.0)	0	(0.0)
Discontinuation of Treatment Due to Adverse Events						
All Adverse Events	6	(1.5)	10	(2.4)	19	(4.6)
Associated Adverse Events	6	(1.5)	6	(1.5)	17	(4.1)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	5	(1.2)	6	(1.5)	6	(1.4)
Associated Adverse Events	1	(0.2)	3	(0.7)	3	(0.7)

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

Adverse Events by Age

Among patients treated with cefdinir, the overall incidence of adverse events was slightly higher in the youngest age group (13 to <18 years of age). However, the incidence of associated adverse events was higher in the intermediate age group (18 to <65 years of age). The incidence of adverse events among cefdinir-treated patients, both all and associated, was similar for patients 18 to <65 and ≥65 years old. However, there were too few patients in the ≥65 age group to make any definitive comparison.

Whereas 20% of patients 18 to <65 years old who were treated with cefdinir QD experienced diarrhea, only 3% of patients 13 to <18 years old experienced this adverse event. Similarly, 21% of patients 18 to <65 years old who were treated with cefdinir BID experienced diarrhea versus 7% of patients 13 to <18 years old. All of the cases of vaginal moniliasis experienced by cefdinir-treated patients were also in the 18 to <65 age group. Two adverse events that occurred more frequently in younger patients treated with cefdinir QD were abdominal pain and

pharyngitis. In the cefdinir QD treatment group, 13% of patients 13 to <18 years old experienced abdominal pain, versus 2% of patients 18 to <65 years old; and 9% of patients 13 to <18 experienced pharyngitis, versus 2% of patients 18 to <65. Patients ≥65 years of age had a similar toxicity profile to patients in the 18 to <65 age group. The only notable difference was that elderly patients treated with cefdinir BID had a lower rate of diarrhea (7%) than patients in the intermediate age group (21%). The rates of diarrhea were similar between these 2 age groups for cefdinir QD- and amox/clav-treated patients.

For patients treated with amox/clav, the overall incidence of adverse events and associated adverse events was somewhat greater in the 18 to <65 age group than in younger patients. The incidence of diarrhea was also greater in the 18 to <65 age group (21%) than in the 13 to <18 age group (12%). There were no other noteworthy differences in incidence of specific adverse events among age groups, including elderly patients.

Adverse Events by Sex

Overall, females had a slightly higher incidence of adverse events than males in all treatment groups. This was largely because females had a higher incidence of adverse events related to the urogenital system, such as vaginal moniliasis, vaginitis, and dysmenorrhea. There were no clinically relevant differences in adverse event profiles between the sexes.

Adverse Events by Race

Over 88% of patients in the study were white. No clinically important differences in adverse event profiles were apparent based on race.

Adverse Events by Intensity

Most patients experienced only mild or moderate adverse events. Twelve patients (3%) in the cefdinir QD group, 14 patients (3%) in the cefdinir BID group, and 20 patients (5%) in the amox/clav group experienced at least 1 severe adverse event. Diarrhea was the most common severe adverse event (18 patients), followed by headache (8 patients), and nausea (5 patients). Six patients in the cefdinir QD group, 6 patients in the cefdinir BID group, and 11 patients in the amox/clav group experienced a treatment-associated severe adverse event. These included abdominal pain, headache, diarrhea, nausea, dyspepsia, rectal disorder, vomiting, and bilirubinemia. With the exception of a patient in the cefdinir QD group who died of lung cancer unrelated to treatment after the study ended (Patient 204, Center 38) (see Appendix B.2, Patient Narratives), all severe adverse events were completely reversible.

Adverse Events by Day of Onset

Most adverse events began during the first 5 days of treatment, regardless of treatment regimen.

Medical Officer's Comment

The most common adverse events in this study were diarrhea, nausea, vomiting, headache, abdominal pain, and vaginal moniliasis. A summary of these AE s, condensed from Table 27 of the sponsor's report, shows the incidences of these and the comparable frequencies of occurrence between treatment groups. There was no trend of greater frequency or severity of adverse events in patients receiving therapy with cefdinir when compared with those receiving amoxicillin/clavulanate.

Table 31. Summary of Most Frequent Adverse Events, All Patients [Number (%) of Patients].

	Cefdinir				Amox/ Clav	
Adverse Event	600 mg QD, N=401		300 mg BID, N=410		N= 414	
	All	Assoc	All	Assoc	All	Assoc
Diarrhea	75 (18.7)	62 (15.5)	77 (18.8)	73 (17.8)	84 (20.3)	78 (18.8)
Nausea	17 (4.2)	12 (3.0)	13 (3.2)	8 (2.0)	26 (6.3)	23 (5.6)
Headache	12 (3.0)	5 (1.2)	15 (3.7)	5 (1.2)	19 (4.6)	1 (0.2)
Abdominal Pain	10 (2.5)	4 (1.0)	11 (2.7)	7 (1.7)	14 (3.4)	12 (2.9)
Vaginal Moniliasis	13 (5.1)	13 (5.1)	11 (4.2)	10 (3.8)	15 (5.8)	15 (5.8)
Rash	4 (1.0)	2 (0.5)	6 (1.5)	3 (0.7)	9 (2.2)	6 (1.4)

Medical Officer's Comments

The most frequently seen adverse events with cefdinir therapy occurred no more often than with the use of amoxicillin/clavulanate in comparable use on a comparable patient population. These treatment-emergent signs and symptoms were no more often associated with cefdinir therapy than with amoxicillin/clavulanate therapy. Overall incidences of adverse events were slightly lower in the cefdinir arms than in the amoxicillin/clavulanate therapy arm. The incidence of withdrawal from therapy due to adverse events, both overall and with likely association of the adverse events with study therapy, was slightly lower in the cefdinir arms of the study than in the amoxicillin/ clavulanate arm. None of these differences was statistically significant.

Medical Officer's Conclusions From Trial #983-6

APPEARS THIS WAY
ON ORIGINAL

TRIAL #983-37

OBJECTIVE/RATIONALE

The objective of this study was to evaluate the efficacy and safety of cefdinir treatment (600 mg QD or 300 mg BID) for 10 days versus amox/clav (500 mg TID, expressed as the amoxicillin component) for 10 days in the treatment of adult patients with acute maxillary sinusitis.

Cefdinir is active in vitro against organisms commonly associated with sinus infections, including *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, *Streptococcus pyogenes*, anaerobic gram-positive cocci, and many other gram-negative bacteria.[10] This study was designed to compare the efficacy and safety of cefdinir with amoxicillin/clavulanate (amox/clav, Augmentin®) in patients with acute maxillary sinusitis. Amox/clav contains both amoxicillin, an ampicillin analog, and clavulanic acid, a β-lactam that protects amoxicillin from degradation by β-lactamases.

STUDY DESIGN

This was an investigator-blinded, randomized, comparative, multi center study with 3 parallel-treatment groups.

The protocol and CRFs specified the test-of-cure (TOC) visit occur 7 to 14 days post-therapy (i.e, Days 17 through 24 for patients completing treatment on Day 10). For many patients, the TOC visit beginning on Day 17 was actually 6 days post-therapy since patients who started BID or TID treatment late on Day 1 ended treatment on Day 11. For analysis purposes, the TOC window was widened to 6 to 15 days post-therapy to include these patient data. The long-term follow-up (LTFU) window (21 to 35 days post-therapy) was not changed.

Medical Officer's Comment

This study was identical to trial #983-6 in rationale, objective, and design, with one, important difference: this study was intended to enroll only patients who were eligible for both clinical and microbiological examination and outcome evaluation. All enrolled patients were to undergo diagnostic sinus aspiration.

STUDY MANAGEMENT

Sixteen centers throughout Europe participated in this study, which was monitored by the sponsor, Parke-Davis Pharmaceutical Research (Table 1). Investigators met to review the protocol on September 25, 1992. Identical protocols and case report forms (CRFs) were used by all centers. The study was conducted in compliance with the United States Food and Drug Administration's (FDA) good clinical practice guidelines and according to the Declaration of

Helsinki. Individual ethics committee (EC) approvals were obtained before the study began at each center and written informed patient consents were obtained from each center prior to patient enrollment.

The first patient began treatment on December 10, 1992, and the last patient visit occurred on August 25, 1994. A central laboratory was used by Centers 1, 2, 3, and 21, and local laboratories were used by the rest of the centers to analyze the microbiological and clinical laboratory specimens collected during the study. Randomization codes for all patients were released to the study manager on March 23, 1995.

Cefdinir capsules and amox/clav tablets were packaged and provided by Parke-Davis Pharmaceutical Research (Table 2).

TABLE 32. Study Medication

	Lot	Formulation
Cefdinir 300-mg Capsules	CM 0660492 9	134393-25
	CM 0700492 9	134393-25
	CM 106061 9	134393-25
	CM 1781292 9	134393-25
Amox/Clav 500-mg Tablets[a]	TM2947 9	Marketed
	TS0111 9	Marketed
	WT0924	Marketed

[a] Each tablet contains 500 mg amoxicillin and 125 mg clavulanate.

Methods of Assigning Patients to Treatment

An independent randomization schedule was prepared for each study center. A block size of 6 patients was used with 2 treatment replicates per block, consistent with the planned treatment group ratio of 1:1:1 for cefdinir 600 mg QD, cefdinir 300 mg BID, and amox/clav 500 mg TID, respectively.

POPULATION

The inclusion and exclusion criteria employed in this trial were identical to those used in Trial #983-6, described above.

Evaluability criteria were identical to those used in protocol #983-6.

The scheme of medical history, physical examinations, clinical assessments, sinus aspiration(s), laboratory testing, radiography, adverse events monitoring, and dosing assessments was identical to that in protocol #983-6. The scheme is displayed in Table 5 of Parke-Davis Research Report (RR) 720-03416.

Medical Officer's Comment
The reviewer agrees with the design of the clinical study as presented by the applicant.

Statistical Methodology

Sample Size

This investigator-blind, randomized, comparative multi center study of cefdinir versus amox/clav was designed with a sample size of 112 evaluable patients per randomized group (336 total evaluable patients).

A microbiologic eradication rate of 90% across all randomized groups was assumed in the sample size calculations. Equivalence was to be assessed by comparing a 95% lower confidence limit for the difference (cefdinir minus amox/clav) in microbiologic eradication rates to a set of predetermined, fixed criteria (defined below). The sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and amox/clav microbiologic eradication rates at the TOC visit, using this confidence limit method.

Analyses

Efficacy and safety data summaries were generated and statistical analyses were performed for the cefdinir QD, cefdinir BID, and amox/clav treatment groups. These investigative statistical methods are described below. All summaries and analyses were carried out using SAS (Version 6).

Efficacy

The efficacy objectives of this study were to estimate the microbiologic and clinical response rates of cefdinir QD, cefdinir BID, and amox/clav in the treatment of acute maxillary sinusitis, and to evaluate the equivalence of the response rates of cefdinir QD and cefdinir BID each versus amox/clav at the TOC visit, based on predefined fixed criteria.

The primary outcome measures were the microbiologic eradication rate by pathogen, the microbiologic eradication rate by patient, and the clinical cure rate by patient in the evaluable

population at TOC. Data from the LTFU visit were summarized and presented as supporting information, but no inferential analyses were performed on LTFU data.

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

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

At TOC, the primary end point, the microbiologic eradication rates by pathogen and by patient were calculated for each treatment group in the evaluable, MITT, and ITT patient populations. Clinical cure rates and mean clinical signs/symptoms scores were calculated for each treatment group in the evaluable, clinically evaluable, and ITT patient populations.

At LTFU, the secondary end point, the microbiologic eradication rates by pathogen and by patient (i.e, the "no relapse" rates) were calculated for each treatment group in the qualified and ITT patient populations. The clinical cure rates (i.e, the "no recurrence" rates) and mean clinical signs/symptoms scores were calculated for each treatment group in the qualified and ITT patient populations.

Two methods of investigating treatment equivalence at TOC were used. One method was based on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient (or each pathogen, for the by-pathogen case) in the analysis, and were calculated as the total number of cures or eradications in the study population, divided by the total number of cases.

The second method used a categorical modeling procedure to obtain center-adjusted estimates of the response rates and their standard errors. The model contained terms for study center, treatment group, and center-by-treatment interaction. The resulting parameter estimates were used to construct estimates of the treatment group response rates and standard errors in which each center was given equal weight.

Pairwise treatment differences were defined as cefdinir QD or BID minus amox/clav. The estimated response rate differences and their standard errors were used to construct a 95% lower confidence limit (i.e, a one-tailed test) for each treatment difference, using a standard normal approximation.[19] Each 95% lower confidence limit was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the 2 rates (pooled or center-adjusted) under comparison (Table 7). To demonstrate equivalence, each 95% lower confidence limit must be below 0 and above the indicated bounds. Two-tailed 95% confidence intervals were also calculated for the evaluable population.

TABLE 33. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Cefdinir is Equivalent to or Better Than Amox/Clav if 95% Lower Confidence Limit for Treatment Difference Is Greater Than
90% or greater	-10%
80%-89%	-15%
70%-79%	-20%

Results of the 2 methods were compared for consistency. When the 2 methods agreed, the pooled analysis was presented as the final analysis. If results from the 2 methods disagreed, the differences were addressed and a conclusion was drawn based on the overall weight of the evidence across both methods. A comparison of the 2 analyses can be found in Appendix D.1.

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

Study centers contributing 12 or fewer patients, or 2 or fewer patients in any treatment group, were pooled for center-adjusted analyses (except that for the ITT analysis by pathogen, the same pooling rule applied to the number of available pathogens). Pooling was performed independently for each analysis population after any required data exclusions were made.

Patient Population

The participating investigators, and their enrollment numbers, are listed in Table 34.

TABLE 34. List of Investigators

Center	Investigator	Country	Number of Patients		
			Randomized to Treatment	Completed Treatment	Evaluable[a]
1	M. Sorri	Finland	106	95	59
2	S. Savolainen	Finland	56	56	39
3	M. Pietola	Finland	57	52	23
5	H. Meyer-Bothling	Germany	33	28	13
6	M. Fischer	Germany	25	24	19
7	B. Bertrand	Belgium	5	3	0
8	P. Rivas	Spain	69	62	31
9	J. Daele	Belgium	11	11	5
10	C. Benning	Germany	21	20	12
12	P. Comte	Switzerland	11	11	7
13	R. Nyffenegger	Switzerland	49	49	32
14	H. Stierlen	Germany	15	13	9
15	M. Pentilla	Finland	55	53	24
17	P. Schenk	Austria	43	38	19
20	V. Kuhlicke	Germany	3	3	1
21	J. Väyrynen	Finland	10	9	2
	Total		569	527	295

[a] Microbiologically and clinically evaluable

The demographic characteristics of the enrolled patients are listed in Table 35.

TABLE 35. Patient Characteristics - All Patients

[Number (%) of Patients]

Variable	Cefdinir QD N = 182	Cefdinir BID N = 198	Amox/Clav N = 189	Total N = 569
Sex				
Male	107 (58.8)	115 (58.1)	114 (60.3)	336 (59.1)
Female	75 (41.2)	83 (41.9)	75 (39.7)	233 (40.9)
Race				
White	182 (100.0)	198 (100.0)	186 (98.4)	566 (99.5)
Asian	0 (0.0)	0 (0.0)	3 (1.6)	3 (0.5)
Age, yr				
Median	30.0	32.0	29.0	31.0
Range	14-74	13-73	13-73	13-74
Distribution				
13 to <18	4 (2.2)	4 (2.0)	6 (3.2)	14 (2.5)
18 to <65	169 (92.9)	184 (92.9)	175 (92.6)	528 (92.8)
≥65	9 (4.9)	10 (5.1)	8 (4.2)	27 (4.7)

The demographic characteristics of the clinically evaluable patients are listed in Table 36.

TABLE 36. Patient Characteristics - Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 93	Cefdinir BID N = 96	Amox/Clav N = 106	Total N = 295
Sex				
Male	63 (67.7)	58 (60.4)	63 (59.4)	184 (62.4)
Female	30 (32.3)	38 (39.6)	43 (40.6)	111 (37.6)
Race				
White	93 (100.0)	96 (100.0)	105 (99.1)	294 (99.7)
Asian	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
Age, yr				
Median	30.0	29.0	25.5	27.0
Range	17-72	13-72	13-69	13-72
Distribution				
13 to <18	1 (1.1)	2 (2.1)	5 (4.7)	8 (2.7)
18 to <65	87 (93.5)	90 (93.8)	96 (90.6)	273 (92.5)
≥65	5 (5.4)	4 (4.2)	5 (4.7)	14 (4.7)

Medical Officer's Comment
The population studied in this trial differed significantly from the population in trial #983-6 in gender predominance, racial proportion, and median age. In both the entire enrolled population and in the clinically evaluable group, men predominated, in about the same proportion between treatment groups; the study population was almost entirely white; and the median ages in the treatment groups were 25.5 to 32.0 years.

Confirmed Microbiologic Diagnosis and Baseline Susceptibility[1]

The sponsor reviewed the list of pathogens from the central and local laboratories and identified some as organisms not to be considered pathogenic in acute maxillary sinusitis. These organisms are listed in Appendix C.6.

During the study, one or more baseline pathogens were isolated from the maxillary sinus aspirates of 375 (66%) patients (Table 37). Forty-eight percent (274/569) of patients had 1 pathogen and 18% (101/569) had multiple pathogens isolated at baseline. These isolates

(1) Appendix C.6, Organisms Not Considered Pathogenic; C.7, Distribution of Patients by Baseline Pathogen

included 21 anaerobic species.

H. influenzae was the most common baseline pathogen isolated (148 isolates); it occurred as a single pathogen in 14% (77/569) of patients. *S. pneumoniae* (110 isolates), *M. catarrhalis* (49), and *S. aureus* (45) were the next most common pathogens isolated at baseline.

TABLE 37. Distribution of Patients by Baseline Pathogen - All Patients With Baseline Pathogens
(Number of Patients)

Baseline Pathogen	Cefdinir QD N = 182	Cefdinir BID N = 198	Amox/Clav N = 189
Gram-Positive			
Corynebacterium pyogenes	0	0	1
Gemella morbillorum	1	0	3
Staphylococcus aureus	11	14	7
Staphylococcus epidermidis	3	3	2
Streptococcus mitis	0	1	0
Streptococcus pneumoniae	22	25	19
Streptococcus pyogenes	2	2	3
Streptococcus Group C	1	0	1
Streptococcus Group F	1	0	0
Streptococcus, β-hemolytic[a]	2	1	0
Gram-Negative			
Acinetobacter junii	1	0	0
Citrobacter diversus	0	0	1
Comamonas acidovorans	0	0	1
Enterobacter amnigenus[b]	0	0	1
Enterobacter cloacae	1	0	0
Escherichia coli	2	1	2
Haemophilus aphrophilus	0	1	0
Haemophilus ducreyi	1	0	0
Haemophilus influenzae	20	28	29
Haemophilus parainfluenzae	1	1	8
Haemophilus sp	0	1	0
Klebsiella pneumoniae	1	0	0
Moraxella catarrhalis	10	9	10
Moraxella lacunata	1	0	0
Proteus mirabilis	3	5	4
Serratia marcescens	0	0	1
Serratia proteamaculans	0	1	0
Anaerobic			
Actinomyces israelii	0	1	0
Bacteroides eggerthii	1	0	0
Prevotella loescheii	1	0	0

Prevotella oralis	0		0		1	
Multiple[c]	31		33		37	
Total	117	(64.3)	127	(64.1)	131	(69.3)

[a] Not otherwise speciated
[b] Biotype 1
[c] Appendix C.7 has a complete summary.

Medical Officer's Comment
The frequency of isolation of various pathogens in this trial reflected the predominant roles of *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis*, in that order of decreasing frequency, as the responsible pathogens in acute maxillary sinusitis.

At baseline, 5% (23/499) of pathogens were resistant to cefdinir and 3% (15/495) were resistant to amox/clav (Table 11). No statistically significant differences were observed in the numbers of cefdinir- and amox/clav-resistant isolates for all pathogens ($p = 0.117$), *H. influenzae* ($p = 0.317$), *S. pneumoniae* ($p = 0.157$), or *M. catarrhalis* ($p = 0.317$).

The majority of *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis* isolates were susceptible to study medication at baseline regardless of their β-lactamase status. Three β-lactamase-negative *H. influenzae* isolates were cefdinir-resistant and 1 was amoxicillin-resistant. One β-lactamase-positive *M. catarrhalis* isolate was also cefdinir-resistant.

TABLE 38. Distribution of Baseline Pathogens by Susceptibility to Study Medication - Pathogens From All Patients With Baseline Pathogens (Number of Pathogens)
(Page 1 of 3)

Baseline Pathogen	N	Cefdinir				Amox/Clav			
		S	I	R	U	S	I	R	U
Gram-Positive									
Corynebacterium pyogenes	2	2	0	0	0	2	0	0	0
Corynebacterium spp	2	1	0	0	1	1	0	0	1
Enterococcus faecalis	1	0	0	1	0	1	0	0	0
Gemella morbillorum	4	3	0	1	0	4	0	0	0
Staphylococcus aureus	45	45	0	0	0	42	0	3	0
Staphylococcus epidermidis	15	12	1	2	0	14	0	1	0
Staphylococcus hominis	1	1	0	0	0	1	0	0	0
Staphylococcus lugdunensis	1	1	0	0	0	1	0	0	0
Staphylococcus, Coagulase-Negative	1	1	0	0	0	1	0	0	0
Streptococcus agalactiae	1	1	0	0	0	1	0	0	0
Streptococcus anginosus	5	4	0	1	0	5	0	0	0
Streptococcus mitis	3	3	0	0	0	3	0	0	0
Streptococcus pneumoniae	110	106	2	2	0	107	0	0	3
Streptococcus pyogenes	8	8	0	0	0	8	0	0	0
Streptococcus Group C	3	3	0	0	0	3	0	0	0

Streptococcus Group F	2	2	0	0	0	2	0	0	0
Streptococcus, α-hemolytic[a]	2	1	0	0	1	1	0	0	1
Streptococcus, β-hemolytic[a]	3	3	0	0	0	3	0	0	0
Total	209	197	3	7	2	200	0	4	5

N = Number of Pathogens; S = Susceptible; I = Moderate or intermediate susceptibility; R = Resistant; U = Unknown susceptibility.

[a] Not otherwise speciated

TABLE 38. Distribution of Baseline Pathogens by Susceptibility to Study Medication - Pathogens From All Patients With Baseline Pathogens (Number of Pathogens)
(Page 2 of 3)

Baseline Pathogen	N	Cefdinir				Amox/Clav			
		S	I	R	U	S	I	R	U
Gram-Negative									
Acinetobacter calcoaceticus var *anitratus*	2	1	0	1	0	2	0	0	0
Acinetobacter junii	1	0	1	0	0	0	1	0	0
Citrobacter diversus	2	2	0	0	0	1	0	1	0
Citrobacter freundii	1	1	0	0	0	0	0	1	0
Comamonas acidovorans	1	0	1	0	0	1	0	0	0
Eikenella corrodens	3	3	0	0	0	3	0	0	0
Enterobacter amnigenus	1	0	0	1	0	0	0	1	0
Enterobacter cloacae	1	0	1	0	0	0	0	1	0
Escherichia coli	7	7	0	0	0	7	0	0	0
Escherichia vulneris	1	1	0	0	0	0	0	1	0
Haemophilus aphrophilus	1	1	0	0	0	1	0	0	0
Haemophilus ducreyi	1	1	0	0	0	0	0	1	0
Haemophilus influenzae, β-lactamase +	16	16	0	0	0	16	0	0	0
Haemophilus influenzae, β-lactamase -	132[b]	126[b]	3	3	0	131[b]	0	1	0
Haemophilus parainfluenzae, β-lactamase -	17	16	1	0	0	16	0	0	1
Haemophilus spp	2	1	0	1	0	2	0	0	0
Klebsiella oxytoca	1	1	0	0	0	1	0	0	0
Klebsiella pneumoniae	3	3	0	0	0	3	0	0	0
Moraxella catarrhalis, β-lactamase +	31	29	1	1	0	31	0	0	0
Moraxella catarrhalis, β-lactamase -	18	18	0	0	0	17	1	0	0
Moraxella lacunata	1	0	0	1	0	1	0	0	0
Proteus mirabilis	16	15	1	0	0	16	0	0	0
Proteus vulgaris	1	1	0	0	0	1	0	0	0
Serratia marcescens	2	0	0	2	0	0	0	2	0
Serratia proteamaculans	2	0	0	2	0	0	0	2	0
Total	264	243	9	12	0	250	2	11	1
Anaerobic									
Actinomyces israelii	1	1	0	0	0	1	0	0	0
Actinomyces odontolyticus	1	1	0	0	0	1	0	0	0
Bacteroides eggerthii	1	0	0	1	0	1	0	0	0
Bacteroides fragilis	1	1	0	0	0	0	1	0	0
Bacteroides sp	1	0	0	0	1	0	0	0	1
Eubacterium sp	1	1	0	0	0	1	0	0	0
Fusobacterium nucleatum	5	4	0	0	1	4	0	0	1
Fusobacterium sp	1	0	0	0	1	0	0	0	1
Lactobacillus sp	1	1	0	0	0	1	0	0	0
Peptostreptococcus anaerobius	2	2	0	0	0	2	0	0	0
Peptostreptococcus micros	5	5	0	0	0	5	0	0	0
Prevotella buccae	1	1	0	0	0	1	0	0	0

N = Number of Pathogens; S = Susceptible; I = Moderate or intermediate susceptibility; R = Resistant; U = Unknown susceptibility.

[b] Two isolates included in these totals were not tested for β-lactamase activity.

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TABLE 38. Distribution of Baseline Pathogens by Susceptibility to Study Medication - Pathogens From All Patients With Baseline Pathogens (Number of Pathogens)
(Page 3 of 3)

Baseline Pathogen	N	Cefdinir				Amox/Clav			
		S	I	R	U	S	I	R	U
Anaerobic (continued)									
Prevotella intermedia	1	1	0	0	0	1	0	0	0
Prevotella loescheii	2	1	0	1	0	2	0	0	0
Prevotella melaninogenica	2	1	0	0	1	1	0	0	1
Prevotella oralis	2	1	0	1	0	2	0	0	0
Prevotella oris	2	1	0	1	0	2	0	0	0
Prevotella ruminicola	1	1	0	0	0	1	0	0	0
Prevotella sp	1	1	0	0	0	1	0	0	0
Anaerobic Streptococcus[a]	2	0	0	0	2	0	0	0	2
Anaerobic Gram-Positive Bacillus[a]	1	0	0	0	1	0	0	0	1
Total	35	24	0	4	7	27	1	0	7
Total	508	464	12	23	9	477	3	15	13

N = Number of Pathogens; S = Susceptible; I = Moderate or intermediate susceptibility; R = Resistant; U = Unknown susceptibility.
[a] Not otherwise speciated

5.1.3. Clinical Signs and Symptoms[2]

Patient signs and symptoms were similar for each of the patient populations and treatment groups at baseline (Table 12). At baseline, patient clinical scores could range from 0 through 5, and the score in at least 1 sinus had to range from 2 through 21. Actual patient, left sinus, and right sinus clinical scores at baseline ranged from 2.2 to 2.5 across patient populations and treatment groups.

(2) Appendices C.8 through C.13, Patient and Sinus Clinical Signs and Symptoms

TABLE 39. Signs and Symptoms at Baseline
(Percentage of Patients)

Signs and Symptoms	All Patients			Evaluable Patients		
	Cefdinir		Amox/Clav	Cefdinir		Amox/Clav
	QD N = 182	BID N = 198	N = 189	QD N = 93	BID N = 96	N = 106
Patient						
Headache	83.0	88.9	84.1	80.6	88.5	84.0
Alteration of Smell	59.9	61.1	59.3	61.3	65.6	66.0
Fever	17.0	14.1	11.6	21.5	18.8	14.2
Sinus						
Left Purulent Nasal Discharge	86.3	83.8	88.9	87.1	86.5	91.5
Right Purulent Nasal Discharge	83.5	85.9	85.2	84.9	82.3	85.8
Left Facial Pain	67.0	66.7	64.0	60.2	68.8	67.9
Right Facial Pain	60.4	65.7	63.0	57.0	60.4	66.0
Left Facial Tenderness	57.1	63.1	55.6	52.7	68.8	58.5
Right Facial Tenderness	57.7	61.1	61.9	58.1	56.3	63.2
Left Nasal Obstruction	87.9	88.4	93.1	86.0	89.6	93.4
Right Nasal Obstruction	87.9	88.9	83.6	90.3	83.3	85.8

Medical History and Secondary Diagnoses

One hundred patients (34 cefdinir QD-treated patients, 39 cefdinir BID-treated patients, and 27 amox/clav-treated patients) had a history of sinusitis. Nine (5%) cefdinir QD-treated patients, 14 (7%) cefdinir BID-treated patients, and 15 (8%) amox/clav-treated patients reported medical history items considered by the medical monitor to predispose them to acute maxillary sinusitis. Common predisposing conditions included medical histories of allergic rhinitis, nasal surgical procedures (eg, ethmoid surgery), fractured nasal bones, and nasal polyps.

Almost half of the patients in each of the treatment groups reported a significant medical history item (cefdinir QD, 46%; cefdinir BID, 49%; and amox/clav, 46%). Measles and mumps were the most common history items reported. Tonsillectomy and appendectomy were the most common procedures reported.

Prior Medications for Sinusitis

Doxycycline (3% of patients), amox/clav and amoxicillin (both 2%), and penicillin and cefaclor (both 1%) were the most frequently used antibacterial agents for sinusitis within 30 days of study

start.

Concurrent Medications

Xylometazoline (42% of patients), xylometazoline hydrochloride (13%), and oxymetazoline (10%) were reported as the most common concurrent medications. They were nasal decongestants that could be used up to 4 days after the sinus puncture procedure. Acetylcysteine (10% of patients) was also a common concurrent medication.

Disulfiram (Antabuse®) was not used by patients during the study.

Patient Treatment

The median patient exposure was 10 days for cefdinir QD- and BID-treated patients and 11 days for amox/clav-treated patients for each patient population (Table 13). Patients starting cefdinir BID or amox/clav late on Day 1 finished medication on Day 11, thereby contributing to the large number of patients with 11 days exposure. In all treatment groups, patients who missed doses during treatment and took them at the end of therapy also contributed to the number of patients who took study medication longer than the prescribed 10-day treatment period.

TABLE 40. Patient Exposure to Study Medication - ~~All~~ Patients (Number of Patients)

Days of Study Medication	Cefdinir QD N = 182	Cefdinir BID N = 198	Amox/Clav N = 189
1	0	1	1
2	1	2	1
3	1	0	0
4	0	3	1
5	2	4	0
6	0	0	2
7	0	3	1
8	0	0	2
9	0	0	6
10	174	126	78
11	0	52	94
Median	10	10	11
Unknown[a]	4	7	3

[a] Includes 1 cefdinir QD- and 1 cefdinir BID-treated patient who received no study medication

Medical Officer's Comment

The population enrolled was appropriate by history. The occurrence of predisposing medical history, such as prior sinus surgery, was expected and did not compromise evaluability of the patients. The coincident use of nasal decongestants was allowed by protocol. The use of antibiotics within 30 days of entrance into the study was also not frequent enough to pose a problem.

Patient Disposition

Of the 569 patients who entered the study, 527 (93%) completed treatment (according to the investigator), 549 (97%) completed the TOC visit, and 500 (88%) completed the LTFU visit (Table 14). Two centers (Centers 1 and 2) that were military installations probably contributed to the high completion rates observed in this study.

TABLE 41. Patient Disposition - All Patients
[Number (%) of Patients]

Disposition	Cefdinir QD	Cefdinir BID	Amox/Clav	Total
Randomized to Treatment	182	198	189	569
Withdrawn Prior to End of Treatment				
Adverse Event	2 (1.1)	12 (6.1)	12 (6.3)	26 (4.6)
Lack of Compliance	1 (0.5)	4[a] (2.0)	3 (1.6)	8 (1.4)
No Baseline Pathogen	2[a] (1.1)	0 (0.0)	0 (0.0)	2 (0.4)
Resistant Baseline Pathogen	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.4)
Lack of Efficacy	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Other[b]	0 (0.0)	1 (0.5)	2 (1.1)	3 (0.5)
Completed Treatment[c]	176 (96.7)	181 (91.4)	170 (89.9)	527 (92.6)
Completed Follow-Up Visits[c]				
TOC	175 (96.2)	193 (97.5)	181 (95.8)	549 (96.5)
LTFU	166 (91.2)	170 (85.9)	164 (86.8)	500 (87.9)

[a] Two patients (1 cefdinir QD- and 1 cefdinir BID-treated) were randomized but did not receive study medication.

[b] Patients in this category either lost their study medication, had it stolen, or the patient was lost to follow-up.

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

Medical Officer's Comment

The population of patients randomized to treatment was more than sufficient by the statistical goals of the protocol design. The proportions of patients completing treatment and completing TOC and LTFU visits, in all arms, were high.

Protocol variations that did not exclude patients from the evaluable analyses included patients who had no ongoing purulent nasal discharge at baseline (6 patients); had endoscopy also performed at baseline (69 patients); had a history of sensitivity to β-lactams (3); had abnormal hepatic enzyme levels at baseline (7); had patient numbers mistakenly assigned out of order (6); had an investigator assessment done on a different day than the assessment of clinical signs and symptoms (5); and were less than the center-specified (but not protocol-specified) age limit (1). Appendix A.8 contains a complete list of these patients.

Efficacy Evaluations

Patients were most frequently excluded from the evaluable efficacy (TOC) analyses because no pathogen was proven at baseline, medication was not taken as prescribed (i.e, insufficient duration of treatment, significant number (>30%) of missed doses, or an overdose), a follow-up sinus x-ray was missed, or baseline pathogens were resistant to either study medication (Table 15).

Patients were most frequently disqualified from the qualified efficacy (LTFU) analyses because of concurrent use of antibacterial agents and clinical assessment performed outside the specified range of study days. A complete list of reasons for excluding patients from the clinically evaluable and MITT analyses appear in the appendices.

Table 16 provides a comparison of the numbers of patients in each of the patient populations for analysis.

TABLE 42. Reasons Patients Were Not Evaluable at TOC or Disqualified at LTFU[a] (Number of Patients)

	Cefdinir		Amox/Clav
	QD	BID	
Reasons Patients Were Not Clinically Evaluable for TOC Analyses			
Medication Not Taken as Prescribed[b]	8	20	9
Follow-Up X-ray Missed	8	14	13
Baseline Pathogen Resistant to Either Study Drug	9	11	10
Clinical Assessment Out of Range[b]	7	11	8
Clinical Assessment Missed	4	7	4
Concurrent Antibacterial Agent	5	2	3
Disallowed Prior Antibacterial	1	1	2
Baseline X-ray Missed	1	0	2
No Baseline Signs or Symptoms	0	1	0
Total Patients Not Clinically Evaluable	31	43	31
Additional Reasons Patients Were Not Evaluable for TOC Analyses			
No Proven Baseline Pathogen	66	71	58
Culture Out of Range[b]	4	6	3
No Baseline Susceptibility Tests	4	3	2
Total Patients Not Evaluable	89	102	83
Patients Who Were Evaluable at TOC	93	96	106
Reasons Clinically Evaluable Patients Were Disqualified From LTFU Analyses			
Concurrent Antibacterial Agent[b]	9	12	7
Clinical Assessment Out of Range[b]	6	8	13
Clinical Assessment Missed	6	7	8
Total Patients Clinically Disqualified	20	27	26
Reasons Evaluable Patients Were Disqualified from LTFU Analyses			
Concurrent Antibacterial Agent[b]	5	9	5
Clinical Assessment Out of Range[b]	3	4	8
Culture Out of Range[b]	1	3	1
Clinical Assessment Missed	0	0	1
Total Patients Disqualified	8	14	14

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Patients Who Were Qualified at LTFU	85	82	92

[a] Patients who had multiple reasons for being nonevaluable or disqualified were counted for each reason that applied.

[b] Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early recurrences were not removed from the analyses for these reasons. Patients who had a culture done early because they were early recurrences were not removed from the microbiologically-clinically evaluable analyses for this reason.

TABLE 43. Patients Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir				Amox/Clav	
	QD		BID			
Intent-to-Treat (ITT)	182	(100.0)	198	(100.0)	189	(100.0)
Modified Intent-to-Treat (MITT)	116	(63.7)	124	(62.6)	127	(67.2)
Clinically Evaluable	151	(83.0)	155	(78.3)	158	(83.6)
Evaluable	93	(51.1)	96	(48.5)	106	(56.1)
Qualified[a]	85	(91.4)	82	(85.4)	92	(86.8)

[a] As a percentage of Evaluable patients.

6.2.2.1.1. Microbiologic Eradication by Pathogen[3]

For evaluable patients, the microbiologic eradication rates by pathogen were 98% (121/123) for the cefdinir QD treatment group, 90% (118/131) for cefdinir BID, and 93% (128/138) for amox/clav (Table 17).

The 95% lower confidence limit for the difference between cefdinir QD versus amox/clav was +1.5% under the pooled analysis and -0.3% under the center-adjusted analysis (fixed criteria, -10%). These lower confidence limits showed that cefdinir QD is superior to amox/clav under the pooled analysis because the limit lies above 0, and equivalent to or better than amox/clav under the center-adjusted analysis. The 95% lower confidence limit for the difference between cefdinir BID versus amox/clav was -8.3%, showing that cefdinir BID was equivalent to or better than amox/clav (fixed criteria, -10%). The exploratory CMH tests showed a significant difference

(3) Appendices C.29 and C.30, Microbiologic Response Rates at TOC

between cefdinir QD versus amox/clav ($p = 0.039$) in favor of cefdinir QD and no significant difference between cefdinir BID versus amox/clav ($p = 0.496$).

TABLE 44. Microbiologic Eradication Rate by Pathogen at TOC - Pathogens From Evaluable Patients

(Page 1 of 2)

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Corynebacterium pyogenes	0/0	-	0/0	-	1/1	100.0
Corynebacterium sp	0/0	-	1/1	100.0	0/0	-
Gemella morbillorum	1/1	100.0	0/0	-	2/2	100.0
Staphylococcus aureus	15/15	100.0	13/15	86.7	7/10	70.0
Staphylococcus epidermidis	3/3	100.0	5/5	100.0	3/3	100.0
Staphylococcus hominis	1/1	100.0	0/0	-	0/0	-
Streptococcus agalactiae	0/0	-	0/1	0.0	0/0	-
Streptococcus anginosus	2/2	100.0	0/0	-	1/1	100.0
Streptococcus mitis	0/0	-	2/2	100.0	0/0	-
Streptococcus pneumoniae	35/35	100.0	30/31	96.9	25/26	96.1
Streptococcus pyogenes	3/3	100.0	1/1	100.0	2/2	100.0
Streptococcus Group C	2/2	100.0	0/0	--	1/1	100.0
Streptococcus Group F	1/1	100.0	0/0	--	1/1	100.0
Streptococcus, α-hemolytic[a]	1/1	100.0	0/0	--	0/0	--
Streptococcus, β-hemolytic[a]	2/2	100.0	1/1	100.0	0/0	--
Gram-Negative						
Acinetobacter calcoaceticus var *anitratus*	0/0	--	0/0	--	1/1	100.0
Citrobacter diversus	1/1	100.0	0/0	--	0/0	--
Eikenella corrodens	0/0	--	0/1	0.0	0/0	--
Escherichia coli	3/3	100.0	1/1	100.0	2/2	100.0
Haemophilus aphrophilus	0/0	--	1/1	100.0	0/0	--
Haemophilus influenzae, β-lactamase +	3/4	75.0	2/2	100.0	6/6	100.0
Haemophilus influenzae, β-lactamase -	19/19	100.0	34/39[b]	87.2	46/50[b]	92.0
Haemophilus parainfluenzae, β-lactamase -	7/7	100.0	1/1	100.0	5/6	83.3
Haemophilus sp	1/1	100.0	0/0	--	0/0	--
Klebsiella oxytoca	0/0	--	0/0	--	1/1	100.0
Klebsiella pneumoniae	3/3	100.0	0/0	--	0/0	--
Moraxella catarrhalis, β-lactamase +	7/8	87.5	8/8	100.0	9/9	100.0
Moraxella catarrhalis, β-lactamase -	3/3	100.0	8/8	100.0	4/4	100.0
Proteus mirabilis	2/2	100.0	2/3	66.7	6/7	85.7
Proteus vulgaris	0/0	--	0/0	--	1/1	100.0

n/N = Number of pathogens eradicated/total number of pathogens.

[a] Not otherwise speciated

[b] Two pathogens, 1 from a cefdinir BID-treated patient and 1 from an amox/clav-treated patient, were not tested for β-lactamase production but are included in these totals.

TABLE 44. Microbiologic Eradication Rate by Pathogen at TOC - Pathogens From Evaluable Patients

(Page 2 of 2)

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Anaerobic						
Actinomyces israelii	0/0	–	1/1	100.0	0/0	–
Actinomyces odonata	0/0	–	1/1	100.0	0/0	–
Bacteroides fragilis	1/1	100.0	0/0	–	0/0	–
Eubacterium sp	0/0	–	1/1	100.0	0/0	–
Fusobacterium nucleatum	0/0	–	2/2	100.0	0/0	–
Lactobacillus sp	0/0	–	1/1	100.0	0/0	–
Peptostreptococcus anaerobius	1/1	100.0	0/0	–	0/0	–
Peptostreptococcus micros	1/1	100.0	½	50.0	1/1	100.0
Prevotella buccae	0/0	–	0/0	–	1/1	100.0
Prevotella intermedia	1/1	100.0	0/0	–	0/0	–
Prevotella loescheii	1/1	100.0	0/0	–	0/0	–
Prevotella melaninogenica	1/1	100.0	0/0	–	0/0	–
Prevotella oralis	0/0	–	0/0	–	1/1	100.0
Prevotella oris	0/0	–	0/0	–	1/1	100.0
Prevotella ruminicola	0/0	–	0/1	0.0	0/0	–
Prevotella sp	0/0	–	1/1	100.0	0/0	–
Total	121/123	98.4	118/131	90.1	128/138	92.8

n/N = Number of pathogens eradicated/total number of pathogens.

Microbiologic Eradication by Patient

For evaluable patients, the microbiologic eradication rates by patient were 98% (91/93) for the cefdinir QD treatment group, 89% (85/96) for cefdinir BID, and 93% (99/106) for amox/clav (Table 18).

The 95% lower confidence limit for the difference between cefdinir QD versus amox/clav was -0.2%. This result shows that cefdinir QD was equivalent to or better than amox/clav (fixed criteria, -10%). For cefdinir BID, analysis by the 2 different methods resulted in differing conclusions. In the pooled analysis, the lower confidence limit for the difference between cefdinir BID and amox/clav was -11.5 showing amox/clav is better than cefdinir BID (fixed criteria, -10%). In the center-adjusted analysis, the lower confidence limit was -9.1 showing that cefdinir BID is equivalent to or better than amox/clav (fixed criteria, -10%). The fact that the

lower confidence limit in the pooled analysis was very close to the -10% cutoff and the center-adjusted lower confidence limit was within the -10% cutoff indicates that cefdinir BID and amox/clav are marginally equivalent. The CMH tests showed no significant differences between cefdinir QD versus amox/clav (p = 0.169) or between cefdinir BID versus amox/clav (p = 0.243).

TABLE 45. Microbiologic Eradication Rate by Patient (According to Baseline Pathogen) at TOC - Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Gemella morbillorum	1/1	100.0	0/0	–	2/2	100.0
Staphylococcus aureus	10/10	100.0	10/12	83.3	4/7	57.1
Staphylococcus epidermidis	2/2	100.0	3/3	100.0	2/2	100.0
Streptococcus mitis	0/0	–	1/1	100.0	0/0	–
Streptococcus pneumoniae	18/18	100.0	19/20	95.0	18/18	100.0
Streptococcus pyogenes	2/2	100.0	1/1	100.0	2/2	100.0
Streptococcus Group C	1/1	100.0	0/0	–	1/1	100.0
Streptococcus Group F	1/1	100.0	0/0	–	0/0	–
Streptococcus, β-hemolytic[a]	2/2	100.0	1/1	100.0	0/0	–
Gram-Negative						
Escherichia coli	2/2	100.0	1/1	100.0	2/2	100.0
Haemophilus aphrophilus	0/0	–	1/1	100.0	0/0	–
Haemophilus influenzae	16/17	94.1	14/19	73.7	25/25	100.0
Haemophilus parainfluenzae	1/1	100.0	1/1	100.0	4/5	80.0
Klebsiella pneumoniae	1/1	100.0	0/0	–	0/0	–
Moraxella catarrhalis	8/9	88.9	8/8	100.0	9/9	100.0
Proteus mirabilis	2/2	100.0	2/3	66.7	3/4	75.0
Anaerobic						
Actinomyces israelii	0/0	–	1/1	100.0	0/0	–
Prevotella loescheii	1/1	100.0	0/0	–	0/0	–
Prevotella oralis	0/0	–	0/0	–	1/1	100.0
Multiple[b]	23/23	100.0	22/24	91.7	26/28	92.9
Total	91/93	97.8	85/96	88.5	99/106	93.4

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

[a] Not otherwise speciated

[b] Appendix C.31 has a complete summary of patients with multiple pathogens.

Four patients each had a *S. pneumoniae* isolate that was either intermediately susceptible or resistant to cefdinir in in vitro assays. Two of the patients were treated with cefdinir QD, 1 with cefdinir BID, and 1 with amox/clav. All 4 of these patients were classified as clinical cures and all 4 *S. pneumoniae* isolates were eradicated.

At TOC, 2 evaluable cefdinir QD-treated patients, 11 cefdinir BID-treated patients, and 7 amox/clav-treated patients had 2, 13, and 10 persistent pathogens, respectively (Appendix E.2). For cefdinir QD-treated patients with persistent pathogens, 1 *H. influenzae* isolate remained susceptible to study medication at TOC and 1 *M. catarrhalis* was not tested. For cefdinir BID-treated patients, 8 persistent pathogens remained susceptible, and 5 were not tested; for amox/clav-treated patients, 4 remained susceptible and 6 were not tested. *H. influenzae* and *S. aureus* were the most common persistent pathogens at TOC for the cefdinir BID (5 and 2 isolates, respectively) and amox/clav (4 and 3 isolates, respectively) treatment groups.

Clinical Cure

The clinical cure rates presented below are based on combined investigator/sponsor assessments. At the TOC visit, all evaluable patients in each of the 3 treatment groups had the same clinical assessment on both the investigator and combined assessment scales of clinical response (Table 46).

TABLE 46. Investigator vs Combined Investigator/Sponsor Clinical Response Determination at the TOC Visit - Evaluable Patients

Investigator Determination	Combined Investigator/Sponsor Determination					
	Cefdinir QD N = 93		Cefdinir BID N = 96		Amox/Clav N = 106	
	Cure	Failure	Cure	Failure	Cure	Failure
Cure	88	0	86	0	102	0
Failure	0	5	0	10	0	4
Not Assessable	0	0	0	0	0	0

For evaluable patients, the clinical cure rates by patient were 95% (88/93) for the cefdinir QD treatment group, 90% (86/96) for cefdinir BID, and 96% (102/106) for amox/clav (Table 20).

The 95% lower confidence limit for the difference between cefdinir QD versus amox/clav was

-6.5% and between cefdinir BID versus amox/clav was -12.6% showing that cefdinir QD was equivalent to or better than amox/clav while amox/clav was better than cefdinir BID (fixed criteria, -10%). The CMH tests showed no significant differences between cefdinir QD versus amox/clav (p = 0.594) or between cefdinir BID versus amox/clav (p = 0.074).

TABLE 47. Clinical Cure Rate by Patient (According to Their Baseline Pathogens) at TOC - Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Gemella morbillorum	1/1	100.0	0/0	–	2/2	100.0
Staphylococcus aureus	10/10	100.0	11/12	91.7	7/7	100.0
Staphylococcus epidermidis	2/2	100.0	3/3	100.0	2/2	100.0
Streptococcus mitis	0/0	–	1/1	100.0	0/0	–
Streptococcus pneumoniae	18/18	100.0	18/20	90.0	18/18	100.0
Streptococcus pyogenes	2/2	100.0	1/1	100.0	2/2	100.0
Streptococcus Group C	1/1	100.0	0/0	–	1/1	100.0
Streptococcus Group F	1/1	100.0	0/0	–	0/0	–
Streptococcus, β-hemolytic[a]	2/2	100.0	1/1	100.0	0/0	–
Gram-Negative						
Escherichia coli	2/2	100.0	1/1	100.0	2/2	100.0
Haemophilus aphrophilus	0/0	–	1/1	100.0	0/0	–
Haemophilus influenzae	15/17	88.2	14/19	73.7	24/25	96.0
Haemophilus parainfluenzae	1/1	100.0	1/1	100.0	4/5	80.0
Klebsiella pneumoniae	0/1	0.0	0/0	–	0/0	–
Moraxella catarrhalis	7/9	77.8	8/8	100.0	9/9	100.0
Proteus mirabilis	2/2	100.0	3/3	100.0	4/4	100.0
Anaerobic						
Actinomyces israelii	0/0	–	1/1	100.0	0/0	–
Prevotella loescheii	1/1	100.0	0/0	–	0/0	–
Prevotella oralis	0/0	–	0/0	–	1/1	100.0
Multiple[b]	23/23	100.0	22/24	91.7	26/28	92.9
Total	88/93	94.6	86/96	89.6	102/106	96.2

n/N = Number of patients who were cured (according to the combined investigator/sponsor clinical assessment)/total number of patients.

[a] Not otherwise speciated

[b] Appendix C.33 has a complete summary of patients with multiple pathogens.

Microbiologic Versus Clinical Response Rates

Most (91%, 268/295) evaluable patients had successful microbiologic and clinical outcomes (i.e, microbiologic eradication plus clinically cured); another 12 had failing responses (i.e, persistent pathogens plus clinical failure) (Table 21). For those patients who had inconsistent microbiologic and clinical outcomes (i.e, eradication plus failure or persistence plus cure), McNemar's test did not detect a significant pattern to the discordant assessments for any treatment group (cefdinir QD, p = 0.083; cefdinir BID, p = 0.705; amox/clav, p = 0.180).

TABLE 48. Microbiologic Versus Clinical Response at the Test-of-Cure Visit - Evaluable Patients [Number (%) of Patients]

Microbiologic Response	Clinical Response	
	Cure[a]	Failure
Cefdinir QD, N = 93		
Patients With Eradication	88	3
Patients With Persistence	0	2
Cefdinir BID, N = 96		
Patients With Eradication	82	3
Patients With Persistence	4	7
Amox/Clav, N = 106		
Patients With Eradication	98	1
Patients With Persistence	4	3

[a] Combined investigator/sponsor clinical determination

Medical Officer's Comment

The clinical and microbiological outcomes demonstrated comparable efficacy between cefdinir and amoxicillin/clavulanate. Eradication of the three main pathogens (*Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis*) appeared to be greater with cefdinir qd than with cefdinir bid

Safety

Adverse Events

Overview

Safety was evaluated using data from the 567 patients who received study medication. Forty-one percent (75/181) of these patients in the cefdinir QD treatment group, 45% (88/197) in the cefdinir BID group, and 50% (94/189) in the amox/clav group experienced at least 1 adverse event (Table 30). Thirty-three percent (60/181) of the patients in the cefdinir QD group, 36% (70/197) in the cefdinir BID group, and 39% (74/189) in the amox/clav group had adverse events considered by the investigator to be drug-associated.

Two percent (3 patients) of the cefdinir QD group and 6% each (12 patients) of the cefdinir BID and amox/clav groups discontinued treatment due to an adverse event. One additional cefdinir BID-treated patient withdrew from the study due to an adverse event after completing treatment. Nine patients (1 in the cefdinir QD group, 3 in the cefdinir BID group, and 5 in the amox/clav group) experienced a serious adverse event. No deaths occurred during the study.

All and Drug-Associated Adverse Events

Most adverse events that occurred were related to the digestive system and body as a whole for each of the 3 treatment groups (Table 31). Most of the adverse events that related to the digestive and urogenital systems, skin and appendages, and to the metabolic and nutritional area were considered drug-associated by investigators.

Although most adverse events occurred in the amox/clav treatment group, there were no significant differences between the numbers of patients experiencing adverse events when the cefdinir QD and amox/clav groups ($p = 0.074$) or the cefdinir BID and amox/clav groups ($p = 0.473$) were compared. In addition, there were no significant difference between the cefdinir QD and amox/clav groups ($p = 0.140$) or the cefdinir BID and amox/clav groups ($p = 0.550$) when the numbers of patients experiencing drug-associated adverse events were compared.

The most frequent adverse events experienced were diarrhea (29%), vaginal moniliasis/vaginitis (based on total number of females only, 4%), and headache (3%) in the cefdinir QD group; diarrhea (33%), vaginal moniliasis/vaginitis (females only, 6%), and headache (3%) in the cefdinir BID group; and diarrhea (30%), vaginal moniliasis/vaginitis (females only, 9%), abdominal pain (4%), urticaria (3%), headache (2%), and pain (2%) in the amox/clav group. All

other adverse events occurred in <2% of patients. There were no significant differences in the incidence of diarrhea when the cefdinir QD and amox/clav groups (p = 0.603) or the cefdinir BID and amox/clav groups (p = 0.364) were compared.

Diarrhea rates varied by country. In particular, high rates were seen in Finland (approximately 40%), where many of the patients were military conscripts. It is postulated that the increased reporting of diarrhea in this patient population was due to the fact that a report of diarrhea would excuse a soldier from the strenuous physical activities involved in military duty.

During treatment, the most frequent adverse events were diarrhea (27%) and headache (2%) in the cefdinir QD group; diarrhea (29%) in the cefdinir BID group; and diarrhea (29%), abdominal pain (3%), vaginal moniliasis (3%), headache (2%), and urticaria (2%) in the amox/clav group. All other adverse events during treatment occurred in <2% of patients.

Medical Officer's Comment

The adverse effects profile of cefdinir in this trial was comparable to its profile in trial #983-6.

Medical Officer's Conclusions

1. Cefdinir is effective and safe in both the 300 mg bid and 600 mg qd regimens for the treatment of acute maxillary sinusitis.

2. The pathogens for which approval is recommended are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

3. The once-daily regimen appears to have a slightly lower incidence of adverse events, and with the exception of *Streptococcus pneumoniae*, a higher rate of microbiologic eradication. The clinical pharmacokinetic profile of the drug, however, suggest that twice-daily use should be a useful alternative regimen.

/S/

Andrew M. Bonwit, M.D.
Medical Officer 3 June 1999

cc:
Original NDA 50-739
Original NDA 50-749
HFD-520/Division Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/SMO/J. Soreth
HFD-340
HFD-40/DDMAC

Concurrence:
HFD-520/DivDir/G. Chikami
7/1/99

Joint Medical & Statistical Review of NDA 50-739, 50-749

General Information

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Drusilla Scott, Ph.D.

Submission/review dates

Date of Submission:

September 3, 1996 (NDA 50-739)
December 30, 1996 (NDA 50-749)
Date of major amendment, June 23, 1997

CDER Stamp Dates:

September 4, 1996 (NDA 50-739)
December 31, 1996 (NDA 50-749)
Date of major amendment, June 24, 1997

Date Received by Reviewer:

October, 1996

Date Review Begun:

November, 1996

Drug Identification

Generic Name:

Cefdinir 300 mg Capsules (NDA 50-739)
Cefdinir Oral Suspension 125 mg/5ml (NDA 50-749)

Proposed Trade Name:

OMNICEF™ Capsules and Oral Suspension

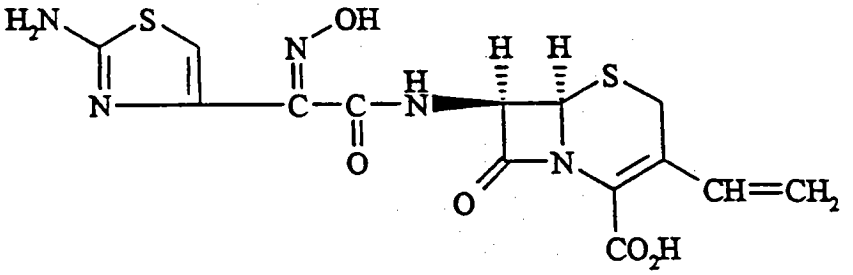
Chemical Name:

[6R-[6α,7β(Z)]]-7][[(2-amino-4-thiazolyl)(hydroxyimin)acetyl] a,omp-3-ethynyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Chemical Structure:

$C_{14}H_{13}N_5O_5S_2$

Molecular Formula:



Cefdinir

Molecular Weight:

395.42

Pharmacologic Category:

Semisynthetic cephalosporin

Route of Administration:

Oral

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

Related Drugs:

NA

Material Reviewed

NDA Volumes Reviewed:

Volume 1 through 427

Regulatory Background:

The following is the regulatory background as provided by Mr. Carmen DeBellas (DAIDP project manager) :

- **May 2, 1990** – IND submitted.
- **May 31, 1990 to June 5, 1990** – Three teleconference discussions of minor deficiencies between FDA and Applicant. DAIDP recommended that study be allowed to begin.
- **June 26, 1990** – Teleconference discussion concerning dose escalation in studies.
- **August 3, 1990** – Teleconference regarding comments on preliminary review for Phase I pharmacokinetic study.
- **August 20, 1990** – Teleconference initiated by Applicant regrading Phase I pharmacokinetic trial in healthy volunteers.
- **August 31, 1990** – Teleconference providing comments on review of preliminary laboratory data.
- **September 26, 1990** – Request for information on two drug interactions from studies.
- **October 12, 1990** – Discussion of dosing schedule for pharmacokinetic studies.
- **October 19, 1990** – Teleconference regarding initiation of the urinary tract infection study before comment on the protocol is made.
- **November 27, 1990** – Meeting with Applicant to discuss Phase II/III protocols.
- **January 23, 1991** – Teleconference clarifying Applicant's meeting minutes.
- **January 23, 1991** – Teleconference providing comments on multiple recent submissions.
- **January 28, 1991** – Applicant initiated teleconference for clarification of lower respiratory tract infection protocols.
- **February 8, 1991** – Teleconference for further discussion of deficiencies in lower respiratory tract infection protocols.
- **February 20, 1991** – Teleconference providing comments on Phase II/III protocols with emphasis on lower respiratory tract infection.
- **March 23, 1991** – Teleconference discussing otitis media protocol
- **April 10, 1991** – Teleconference providing comments on protocol dealing with effect of iron on CI-983.
- **May 28, 1991** – Letter to sponsor reiterating some comments not addressed since the meeting on November 27, 1990.
- **July 8, 1991** – Teleconference providing comments on pediatric studies.

- **July 30, 1991** -- Teleconference providing comments on lower respiratory tract infection protocol and pharmacokinetic study.
- **August 8, 1991** -- Two teleconferences to discuss comments on pharmacokinetic studies in pediatric patients.
- **November 6 and 8, 1991** -- Teleconferences providing comments on protocols for the community acquired pneumonia and skin and skin structure protocols.
- **December 16, 1991** -- Teleconference providing comments on otitis media and skin and skin structure protocols.
- **January 13, 1992** -- Phase II meeting occurred.
- **October 2, 1992** -- Teleconference providing comments on the pharmacokinetic study evaluating subjects with different degrees of renal function.
- **February 17, 1993** -- Teleconference discussing sinusitis protocol.
- **November 24, 1993** -- Meeting regarding discussion of CANDA.
- **September 22, 1994** -- Meeting presenting clinical development plan for cefdinir.
- **January 24, 1995** -- Meeting presenting CANDA demonstration.
- **February 23, 1995** -- Meeting for discussion of criteria used to define adverse event laboratory values.
- **August 10, 1995** -- Pre-NDA meeting occurred.
- **September 3, 1996** -- NDA 50,739 submitted for capsule formulation.
- **December 30, 1996** -- NDA 50,749 submitted for suspension formulation.

Chemistry/Manufacturing Controls

Dr. Shrikant Pagay of DAIDP's Chemistry team reviewed the Applicant's chemistry submission for NDA 50-739. See this document for a complete chemistry review.

Cefdinir is a semisynthetic cephalosporin containing aminothiazole and oxime moieties (see diagram of chemical structure above). There are 2 chiral centers (C-6 and C-7) and cefdinir is prepared and marketed as the 6R-[6α,7β(Z)]isomer. The absolute configuration of cefdinir and the Z-configuration of the oxime moiety have been established through NMR studies. The molecule has three ionizable groups (-COOH, $-NH_2$ and =N-OH).

The solubility of cefdinir is pH dependent, and it is insoluble in water and other common organic solvents. It is slightly soluble in an acid solution with a pH 4.0 and sparingly soluble in a buffered solution with a pH of 7.4, but insoluble in a buffered solution with a pH 4.0 to 7.4. It is freely soluble in sodium bicarbonate. These findings support a J-shaped pH solubility curve with minimum solubility at pH~3-4 and maximum solubility at pH ~6-7. Maximum pH stability was observed in aqueous buffered solution to be from pH 3 to 7. This is supported by animal studies which demonstrate the greatest drug stability in the stomach and small intestine.

The capsule formulation is a 300 mg hard gelatin capsule manufactured, tested, and packaged under contract by Eli Lilly Industries in Puerto Rico with bulk drug substance supplied from [redacted]. This formulation is identical to

300 mg capsules used in the clinical pivotal trials. The *in vitro* dissolution method and specification for capsules conforms to USP requirements.

The suspension formulation is a strawberry-creme flavored powder for oral suspension containing 125 mg/5ml upon constitution with water. The suspension product will be manufactured, tested and packaged under contract by Eli Lilly Industries in Puerto Rico. This formulation differs from the drug used in the clinical trials in that the latter drug has raspberry flavoring and less sucrose (2.9 gm vs 1.5 gm per 5 ml). The Applicant will include the quantity of sucrose in the label so that diabetic patients and those treating diabetic patients will be aware. *In vivo* bioequivalence was established between the proposed formulation and the formulation used in the clinical trials.

DAIDP's chemistry review is not approvable for manufacturing and controls under section 507 of the Act. Deficiencies were found by DAIDP's chemistry reviewer under the following headings: Drug Substance [Description and Characteristics, Specifications and Analytical Methods, Stability]; Drug Product [Components/Composition, Specifications and Methods for Drug Product components, Manufacturer, Specifications and Methods for Drug Product, Container/Closure System, Stability]; Investigational Formulations and Labeling. See Chemistry Review completed by reviewer on April 24, 1997.

Animal Pharmacology/Toxicology:

Dr. Oluwadare Adeyemo of DAIDP's Pharmacotoxicology team reviewed the Applicant's pharmacotoxicology submission and concluded that there are no outstanding issues with respect to this part of the application. The following reflects the summary of Dr. Adeyemo's review. **Doses as high as 1000 mg/kg were tested as follows with no observable effects:**

Central Nervous System

- general behavior in rats
- locomotor activities in the tract test in mice
- sleeping time induced by hexobarbital in mice
- the analgesic test in mice
- the conditioned avoidance response in rates
- the spinal reflex in rabbits

Autonomic Nervous System

- epinephrine-induced hypertensive response in rats
- the contractile response of isolated guinea pig ileum to acetylcholine or histamine
- the contractile response of isolated rat vas deferens to norepinephrine
- sympathetic transmission in dogs
- salivary secretion in dogs

Respiratory and Cardiovascular System

- blood pressure in conscious or anesthetized dogs or conscious rats
- heart rate in conscious or anesthetized dogs
- ECG in conscious dogs
- blood flow in the common carotid artery and femoral artery in dogs

Gastrointestinal Tract

- gastric secretion in rats
- restraint stress ulcer in rats
- intestinal charcoal meal transit in rats

Hematological system

- bleeding time in mice
- coagulation time in rats
- no hemolysis in rabbit blood at 20% concentration

Urinary System and Others

- the spontaneous contraction of isolated nonpregnant and pregnant rat uterus.

The above items summarize those evaluations performed for assessment of safety pharmacology which found no effect at the dose of 1000 mg/kg. Findings that did emerge are as follows: (1) cefdinir did produce a dose-dependent inhibition of ADP- and collagen-induced aggregation of human platelets, with $IC_{50's}$ of 3.9×10^{-3} g/ml and 4.3×10^{-3} g/ml, respectively; and (2) it also increased urine volume and excretion of Na^+ and K^+ in rats at 1000 mg/kg, po.

Pharmacokinetic and ADME studies on Cefdinir

- cefdinir distribution is rapid following iv administration
- V_d approximates extracelluar fluid volume
- $T_{1/2}$ is longer following po than iv administration suggesting absorption rate is slower than elimination rate
- 76.1% of the iv dose is eliminated unchanged in the urine (renal excretion)
- plasma cefdinir concentrations in juvenile rats were higher and in juvenile dogs were lower than adult rats and adult dogs, respectively, probably due to effects of age on tubular secretion and volume of distribution, respectively

Toxicokinetic studies on Cefdinir

- cefdinir distributed rapidly and widely throughout body with V_d equal to the extracelluar fluid volume
- after po dosing in rats, [^{14}C]cefdinir distributed to most tissues in the body, excluding brain, bone marrow, and thyroid

- [^{14}C]cefdinir reached highest radioequivalents in the gastrointestinal tract, urinary bladder and kidney, with higher and more persistent levels in the bladder and kidney consistent with renal excretion as the primary route of elimination
- after iv dosing, radioactivity distribution and elimination were similar to that observed following an oral dose

Toxicology studies on Cefdinir

- 26 week oral toxicity study of cefdinir in rats treated at 5 doses up to 1000 mg/kg demonstrated a NOEL level 100 mg/kg po and resulted in no deaths and no ophthalmic findings, but higher doses showed persistent dark red feces and cecal involvement at autopsy with absolute and relative kidney weights increased 12 and 18% in male rats
- 26 week oral toxicity study of cefdinir in dogs treated at 4 doses up to 800 mg/kg demonstrated no histopathologic changes on autopsy, dark red stools were observed and attributed to the presence of iron complexed with cefdinir in the gastrointestinal tract
- nephrotoxicity study of cefdinir in rats treated orally at 4 doses up to 560 mg/kg for 14 days with or without furosemide did not demonstrate nephrotoxicity or exacerbate the effects of furosemide
- eye mucosa and primary skin irritation studies in rabbits demonstrated that cefdinir is an ocular nonirritant and has low dermal irritation potential
- cefdinir was not teratogenic in rats or rabbits and it exhibited no adverse effects on fertility, general reproduction and did not affect offspring survival, development, behavior or reproduction

The divisional pharmacology review found cefdinir to be relatively non-toxic and tolerated at high doses *in vivo* animal studies. The only labeling suggestion was that the relevant animal studies be expressed in terms of total body surface area in mg/m^2 unless AUC ratios can be calculated from animal and human values.

Microbiology

The information in this section was synopsized from Applicant's submission. When relevant, the recommendations and findings of Dr. Sousan Altaie's review (DAIDP's microbiology review team) are incorporated in the Medical officer's notes. Like other cephalosporins, cefdinir exerts its antibacterial activity by inhibiting bacterial cell wall synthesis by inhibiting the transpeptidase enzyme responsible for cross-linking nascent peptidoglycan.

The Applicant reports mean peak plasma concentration (Cmax) of 2.87 μg/mL was obtained from subjects given a single 600-mg oral dose of cefdinir; a 300-mg dose resulted in a mean Cmax of 1.6 μg/mL and suggests that these achievable plasma concentrations support the following MIC interpretive breakpoints: Susceptible, MIC $\leq$1 μg/mL; Intermediate, MIC = 2 μg/mL; and Resistant, MIC $\geq$4 μg/mL.

Cefdinir is active *in vitro* against a wide range of gram-positive and gram-negative

bacteria. Since cefdinir is highly stable in the presence of many common β-lactamase enzymes, it is active *in vitro* against some β-lactamase producing organisms. A summary of cefdinir for MICs for target organisms as determined in preclinical studies and clinical trials is shown in Table 1 which has been reproduced from the Applicant's submission. The Applicant states that cefdinir is active against most strains of the following microorganisms at concentrations of 1 μg/mL or less *in vitro*, and in clinical infections:

Gram-Positive Aerobes: *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus pyogenes* (Group A, β-hemolytic streptococci), *Streptococcus agalactiae* (Group B), and *Streptococcus pneumoniae* (penicillin-susceptible strains).

Gram-Negative Aerobes: *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Moraxella catarrhalis* (including β-lactamase producing strains), *Escherichia coli*, and *Klebsiella pneumoniae*.

The applicant also claims that cefdinir exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μg/mL or less against (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefdinir in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes: *Gemella morbillorum*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Streptococcus* Group C, *Streptococcus* Group G, *Streptococcus intermedius*, *Streptococcus mitis*, and *Streptococcus sanguis*.

Gram-Negative Aerobes: *Aeromonas hydrophila*, *Citrobacter diversus*, *Enterobacter sakazakii*, *Escherichia hermanii*, *Klebsiella oxytoca*, *Pantoea (Enterobacter) agglomerans*, *Pasteurella multocida*, and *Proteus mirabilis*.

Anaerobes: *Peptostreptococcus anaerobius*, *Peptostreptococcus asaccharolyticus*, *Peptostreptococcus magnus*, and *Peptostreptococcus micros*.

Cefdinir is inactive against most strains of *Enterococcus*, methicillin-resistant *Staphylococcus*, *Pseudomonas*, and *Enterobacter* spp.

TABLE 1. Summary of Cefdinir MICs for Target Organisms

Pathogen	Preclinical Studies			Clinical Trial Results			
	N	Range	MIC_{90}	N	Range	MIC_{50}	MIC_{90}
Pathogens in Indications & Usage Labeling							
Staphylococcus aureus							
Methicillin/oxacillin unspecified	1865	≤0.002->128	0.8	1108	0.016-0.5	0.016	0.5
Methicillin/oxacillin-resistant	925	0.2->128	>64				
Methicillin/oxacillin-susceptible	1609	0.008-25	0.5				
Streptococcus agalactiae	402	≤0.008-0.5	≤0.03	109	0.16-2.0	0.06	0.12
Streptococcus pneumoniae							
Penicillin susceptibility unspecified	744	≤0.002-8.0	0.1	701	0.008-16.0	0.06	0.5
Penicillin-susceptible	858	0.008-1	0.12				
Penicillin-intermediate	319	0.015-16	4.0				
Penicillin-resistant	404	≤0.03->16	8.0				
Escherichia coli	3248	0.008-128	0.5	169	0.03-16.0	0.25	0.5
Haemophilus influenzae	2035	≤0.015-25	0.5	1139	0.008-16.0	0.5	1.0
Haemophilus parainfluenzae	62	0.03-1	0.05	661	0.008-8.0	0.25	0.5
Klebsiella pneumoniae	1591	≤0.01->128	0.40	173	0.016-16.0	0.12	0.25
Moraxella catarrhalis	1088	≤0.01-32	0.25	375	0.008-16.0	0.25	0.5
Pathogens on *In Vitro* List in Labeling							
Gemella morbillorum	10	0.05-0.4	0.4	4	0.06-4.0	ND	
Staphylococcus epidermidis							
Staphylococcus haemolyticus							
Methicillin/oxacillin unspecified	208	≤0.025->128	>64	0			
Methicillin/oxacillin-resistant	7	16->128	ND[a]	0			
Methicillin/oxacillin-susceptible	33	0.03->64	0.5	0			
Staphylococcus hominis							
Methicillin/oxacillin unspecified	17	0.03-0.4	0.1	1	0.25	ND	ND
Methicillin/oxacillin-susceptible	12	0.03-0.12	0.12	0			
Streptococcus anginosus	52	0.016-0.25	0.1	6	0.16-16.0	ND	ND
Streptococcus constellatus	25	≤0.025-0.1	0.1	0			
Streptococcus Group C	10	≤0.016-0.03	ND	3	0.016-0.25	ND	ND
Streptococcus Group G	32	0.008-0.03	0.016	14	0.016-1.0	0.03	0.03
Streptococcus intermedius	25	≤0.025-0.2	0.05	0			
Streptococcus mitis	27	0.016-6.25	0.4	3	0.016-1.0	ND	ND
Streptococcus sanguis	31	≤0.025-0.2	0.05	0			
Aeromonas hydrophila	72	≤0.03->16.0	0.5	2	0.25-0.5	ND	ND
Citrobacter diversus	141	≤0.015-64	0.25	21	0.12-0.5	0.12	0.25
Enterobacter sakazakii	13	0.06-2.0	0.25	2	0.5-0.5	ND	ND
Escherichia hermanii	0			9	0.06-1.0	ND	ND
Klebsiella oxytoca	559	≤0.008-128	0.25	54	0.03-0.25	0.125	0.25
Pantoea (Enterobacter) agglomerans	31	≤0.03->4.0	0.5	43	0.008-16.0	0.25	2.0
Pasteurella multocida	9	0.008-0.12	ND	5	0.016-1.0	ND	ND
Proteus mirabilis	1224	≤0.01-100	0.13	68	0.03-16.0	0.125	0.5
Peptostreptococcus anaerobius	28	≤0.025-12.5	0.8	1	0.06	ND	ND
Peptostreptococcus asaccharolyticus	39	≤0.025-0.4	0.2	0			
Peptostreptococcus magnus	51	≤0.025-16.0	0.4	0			
Peptostreptococcus micros	16	≤0.025-0.1	≤0.025	1	0.06	ND	ND

Resistance to β-lactam antibiotics such as cefdinir is primarily due to the production of inactivating enzymes (β-lactamases) by both gram-positive and gram-negative bacteria. The Applicant states that cefdinir is able to resist enzymatic hydrolysis by commonly found β-lactamases and functions as an inhibitor of these enzymes.

***Medical officer's note**: Dr. Altaie's review mentions that cefdinir is able to resist enzymatic hydrolysis to the most commonly found β-lactamases, but the activity of cefdinir and other cephalosporins can be decreased by coupling diminished uptake in specifically constructed porin-deficient mutants with an enhanced expression of β-lactamase production.*

The Applicant claims that such a profile allows for broad spectrum of activity against certain β-lactamase producing bacterial species such as *Staphylococcus aureus, S. epidermidis,* and many commonly encountered gram-negative species. The Applicant also claims that like other oral cephalosporins, susceptibility to other β-lactamases renders cefdinir ineffective against some gram-negative species and anaerobes, such as *Pseudomonas aeruginosa* and other *Pseudomonas* species, *Citrobacter freundii, Enterobacter aerogenes, E. cloacae, Morganella morganii, Proteus vulgaris, Serratia marcescens, Bacteroides* species and *Clostridium difficile.* In addition, alteration of PBS by mutation renders penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus* species resistant to cefdinir.

The applicant tested the development of spontaneous resistance to cefdinir by studying multiple concentrations of cefdinir and very high bacterial inocula. The development of resistance was rare at all concentrations used, and when bacteria were passed through multiple transfers using increasing concentrations of drug, resistance developed in a slow and stepwise fashion.

In the clinical trials, the Applicant found seven of 3,309 (0.02%) pathogens isolated from adult patients developed resistance following treatment with cefdinir. Four of 600 isolates of *Haemophilus influenzae* developed resistance. Other organisms that developed resistance to cefdinir included *Staphylococcus aureus, Serratia proteamaculans, Klebsiella oxytoca,* and *K. pneumoniae.* No resistance development was seen in isolates from pediatric patients.

***Medical officer's note**: Dr. Altaie's review agreed with the Applicant's assessment of cefdinir resistance.*

The Applicant proposes the following breakpoints for interpreting results in clinical microbiology laboratories:

" **Diffusion Techniques**: Reports from the laboratory providing results of the standardized single disk susceptibility test using a 5-μg cefdinir disk should be interpreted according to the following criteria when testing organisms other than *Streptococcus pneumoniae*:

Susceptible: ≥20 mm (MIC equivalent ≤1 μg/mL)
Intermediate: 17 to 19 mm (MIC equivalent = 2 μg/mL)
Resistant: ≤16 mm (MIC equivalent ≥4 μg/mL)

Isolates of *S. pneumoniae* should be tested against a 1-μg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to penicillin and can be considered susceptible to cefdinir.

Cephalosporin "class" disks should not be used to test susceptibility to cefdinir.

The 5-μg cefdinir disk should give the following zone diameters in laboratory test quality control strains:

TABLE3. Quality Control Guidelines for Disk Diffusion Susceptibility Tests

Organism	Quality Control Ranges (Zone Diameter in mm)
Staphylococcus aureus ATCC 25923	28 to 37
Escherichia coli ATCC 25922	24 to 28
Haemophilus influenzae ATCC 49766	24 to 31
Neisseria gonorrhoeae ATCC 49226	40 to 49
Streptococcus pneumoniae ATCC 49619	26 to 31

Dilution Technique: The MIC values obtained by broth, microbroth or agar dilution should be interpreted according to the following criteria when testing organisms other than *Streptococcus pneumoniae*:

Susceptible: MIC ≤1 μg/mL
Intermediate: MIC = 2 μg/mL
Resistant: MIC ≥4 μg/mL

A pneumococcal isolate that is susceptible to penicillin (MIC ≤0.06 μg/mL) can be considered susceptible to cefdinir. Testing of cefdinir against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for cefdinir against *S. pneumoniae* are not available.

Cefdinir susceptibility powder should give the following MIC values against laboratory test control organisms:

TABLE 4. Quality Control Ranges for Dilution Tests

Organism	Quality Control Ranges (μg/mL)
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Escherichia coli ATCC 25922	0.12 to 0.5
Haemophilus influenzae ATCC 49766	0.12 to 0.5
Neisseria gonorrhoeae ATCC 49226	0.008 to 0.03
Streptococcus pneumoniae ATCC 49619	0.03 to 0.25

Medical Officer's Note: Dr. Altaie's review found these breakpoints – for diffusion and dilution techniques – acceptable and did not recommend any changes. In addition, the recommendation of cefdinir susceptibility for S. pneumoniae when the isolate is susceptible to penicillin at MIC ≤0.06 μg/mL is also acceptable.

Human Pharmacokinetics/Pharmacodynamics

DAIDP's Clinical Pharmacology/Biopharmaceutics Review was written by Dr. Philip M. Colangelo and this summary reflects that review. There are no unresolved deficiencies found in the human pharmacokinetics or pharmacodynamics submission.

Bioequivalence between clinical trials capsule and suspension formulations and between market image capsules and Phase III clinical trials capsules was established. The effect of eating a high fat meal and timing of such a meal on the bioavailability of the capsules was determined to be minimal.

Medical Officer's Note: Both the bioequivalence between capsule and suspension and the effect of eating a high fat being minimal are included in the Applicant's proposed label.

The *in vitro* plasma protein binding of cefdinir was determined to be moderate (60 to 70%) and linear over clinically relevant plasma concentrations in both adult and pediatric subjects. The methods and specifications for *in vitro* dissolution testing of capsules were adequate. Currently, the proposed methods and specifications for the *in vitro* dissolution testing of the suspension's market image formulation were not provided, but the Applicant has agreed to provide the proposed dissolution methods, specifications, and data from the pilot scale batches of the market image suspension as interim data. The Applicant has also agreed to provide dissolution results for the full scale production batches of the suspension manufactured at the contract facility in[ ]Phase IV commitment.

Drug interactions that were significant with a 300 milligram dose of cefdinir include the following:

- 1000 mg probenicid coadministration -- Mean cefdinir Cmax and AUC were increased by ~1.5 and ~2.0-fold, respectively. Mean renal clearance was reduced ~65% from 192 to 67.6 ml/min, and mean cefdinir $T_{1/2}$ was increased 1.5 fold from 1.4 hours to 2.1 hours. This suggests that coadministration of probenicid with cefdinir approximately doubled systemic exposure to cefdinir, reduced creatinine clearance, and substantially increased cefdinir $T_{1/2}$. The mechanism of action appears to be due to inhibition of active renal tubular secretion of cefdinir by probenicid.

- 30 ml Maalox® TC coadministration and administration 2 hours prior to and after taking cefdinir -- Coadministration resulted substantial reductions in Cmax, Tmax, AUC and Ae% (the % of cefdinir excreted in the urine as unchanged drug). The were no observed changes in cefdinir renal clearance or $T_{1/2}$. This decrease appears to be due to a reduction in systemic availability (i.e., AUC). The Applicant recommends that, if an aluminum or magnesium containing antiacid is to be taken with cefdinir therapy, cefdinir should be given at least 2 hours before of after the antiacid.

- oral iron supplements (both ferrous sulphate with 60 mg elemental iron and multivitamins with 10 mg of elemental iron were evaluated), coadministration and administration 2 hours prior to and after taking cefdinir -- Coadministration of either ferrous sulphate or a multivitamin containing 10 mg of elemental iron reduced systemic exposure (mean Cmax, AUC, and Ae%) to cefdinir in a fashion dose-related to the amount of elemental iron ingested. Changes in renal clearance and $T_{1/2}$ were not significantly changed suggesting no effect on elimination. If the iron was taken 2 hours before or after cefdinir, the reduction in systemic exposure was no different than if the cefdinir were taken alone. The Applicant believes that iron reduces the absorption of cefdinir from the gastrointestinal tract by formation of nonabsorbable iron-cefdinir complexes in the gut. The Applicant recommends that if iron supplements are necessary during cefdinir therapy, cefdinir should be taken either 2 hours before or after the iron supplement.
- the effect of iron-fortified infant formula (~2.7 mg elemental iron) on cefdinir pharmacokinetics in healthy infants was also evaluated (15 subjects aged 6-12 mos, 2-way crossover design) -- Coadministration of a single 7 mg/kg dose of cefdinir suspension with an iron fortified infant formula to healthy infants significantly reduced mean Cmax by ~20%, but did not significantly alter Tmax, AUC, or the apparent elimination $T_{1/2}$. The Applicant concluded that iron supplementation in infant formula has little effect on the rate and extent of cefdinir absorption.

Medical officer's note: Dr. Colangelo found the Applicant's conclusion with respect to the coadministration of cefdinir with iron-fortified infant formula acceptable.

Meta-analyses were performed using data from pooled pharmacokinetic studies to evaluate predictive influence of several adults and pediatric subject/patient covariates on cefdinir

pharmacokinetics. Furthermore, a population pharmacokinetic (PPK) analysis was performed from the pharmacokinetic database that was created to determine the mean PPK parameter values for adults and children. From this, the population bioavailability estimates for the capsule and suspension were calculated to be 16 to 21% and 25%, respectively.

The following two Tables duplicated from the Applicant's submission reflect the conclusions of the PPK analysis:

Table 5 Population Mean Cefdinir Pharmacokinetic Parameter Values in Healthy Subjects Following Administration of 300- and 600-mg Oral Cefdinir Capsules

Parameter	Mean	SD	%RSD	N
Dose = 300 mg				
Cmax, μg/mL	1.84	0.756	41.1	115
AUC(0-∞), μg·hr/mL	8.49	3.84	45.3	115
Vd_{area}/F, L	123	83.7	68.2	181[a]
Vd_{area}/F, L/kg	1.68	1.21	72.2	181[a]
CL/F, mL/min	849	454	53.5	181[a]
CL/F, mL/min/kg	11.6	5.96	51.6	181[a]
Ae%	18.4	6.36	34.6	158[a]
Dose = 600 mg				
Cmax, μg/mL	2.63	0.904	34.3	39
AUC(0-∞), μg·hr/mL	10.7	3.86	36.2	39
Vd_{area}/F, L	147	55.3	37.6	39
Vd_{area}/F, L/kg	2.12	0.683	32.1	39
CL/F, mL/min	1059	372	35.1	39
CL/F, mL/min/kg	15.5	5.41	34.8	39
Ae%	11.6	4.62	40.0	39

[a] Parameter calculated using data following doses of 200 to 400 mg.

Table 6 Population Mean Cefdinir Pharmacokinetic Parameter Values in Healthy Pediatric Subjects Following Administration of 7- and 14-mg/kg Oral Doses of Cefdinir Suspension

Parameter	Mean	SD	%RSD	N
Dose = 7 mg/kg				
Cmax, μg/mL	1.70	0.753	44.3	27
AUC(0-∞), μg·hr/mL	6.77	2.54	37.5	27
Dose = 14 mg/kg				
Cmax, μg/mL	3.86	0.652	16.9	12
AUC(0-∞), μg·hr/mL	13.4	2.75	20.6	12

In addition, the following two conclusions were drawn by the Applicant:

(1) In adults, CrCl is the most relevant covariate to predict cefdinir pharmacokinetics and dosage adjustments required in patients with renal impairment; and

(2) In children, BSA was the best predictor of pharmacokinetics.

The Applicant's evaluation of pharmacokinetics in special populations consisted of the following:

- Systemic exposure to cefdinir was significantly decreased in an elderly population when compared to a young population (16 patients aged 20-27 years versus 16 patients aged 65-91 years). Significant reductions were observed in the Cmax, AUC, renal clearance, apparent oral clearance and volume of distribution. Because the Ae% remained unchanged in the two populations, the finding is believed due to reduced cefdinir elimination resulting from age related decline in renal function. The Applicant has proposed that the labeling state that elderly patients do not require dosage adjustment unless they have intrinsic renal dysfunction (<30 mg/ml CrCl).

Medical officer's note: Dr. Colangelo found this labeling appropriate because the relatively modest increases in the short $T_{1/2}$ resulted in minimal drug accumulation in elderly patients with repeated bid or qd dosing.

- Plasma concentrations of cefdinir following a single 300 mg dose in subjects with moderate or severe renal impairment were higher and persisted long when compared to subjects with normal renal function [8 subjects with normal renal function (CrCl > 60 ml/min, mean 99 ml/min) versus 4 subjects with moderate renal impairment (CrCl > 30-60 ml/min, mean 44 ml/min) versus 9 subjects with severe renal impairment (CrCl < 30 ml/min, mean 20 ml/min)]. In subjects with renal impairment, significant increases were observed in the AUC and mean cefdinir Cmax. Among the subjects with severe renal impairment, a prolonged higher Cmax occurred. The findings were due to significant reduction in cefdinir elimination with decreases in both renal and apparent oral clearances of ~70-80% in the moderately impaired group and ~85-90% in the severely impaired group. These reductions in clearance resulted in a $T_{1/2}$ increase to 11.4 hours in the severely impaired group and 3.9 hours in the moderately impaired group (normal 1.6 hours). The Applicant proposes that the label recommend that the dose of cefdinir be reduced to 300 mg once daily in patients with severe renal impairment (CrCl < 30 ml/min).

Medical officer's note: Dr. Colangelo found this labeling appropriate because although clearance was moderately reduced in subjects with moderate and severe renal impairment, $T_{1/2}$ was not significantly increased in the moderately impaired group and predicted drug

accumulation would be minimal (<10%) for these subjects at a dosing of either 12 or 24 hours. The only caveat with respect to this recommendation is that it is based on evaluating only four subjects with moderate renal impairment.

- Following administration of a single 300 mg dose of cefdinir to 8 patients on hemodialysis, systemic drug exposure while not on dialysis was substantially increased, demonstrated by increases in Cmax and AUC. Apparent elimination increased substantially, with $T_{1/2}$ estimates ranging from 13 to 24 hours (mean 15.9 hours). Hemodialysis cleared cefdinir, and the Applicant estimates that a 4 hour dialysis treatment would remove ~63% of the drug from the systemic circulation. The Applicant proposes labeling stating the the initial dosage regimen of cefdinir in hemodialysis patients be adjusted to 300 mg given every other day, with 300 mg administered at the end of each dialysis session.

Medical officer's note: *Dr. Colangelo was in agreement with the Applicant's proposal dosing cefdinir in patients undergoing hemodialysis.*

- With respect to the suspension for pediatric use, a dose of 7 mg/kg was demonstrated to be equivalent to an adult capsule dose of 300 mg, and a dose of 14 mg/kg was demonstrated to be equivalent to an adult capsule dose of 600 mg. See Tables 19 and 21 reproduced from Applicant's submission above.

- Penetration into multiple tissue and fluid sites of interest were evaluated by the Applicant, see Table on the following page duplicated from the Applicant's submission.

TABLE 7. Mean (Range) Plasma and Fluid/Tissue Cefdinir Concentrations and Fluid/Tissue to Plasma Ratios Following Administration of Single Cefdinir Doses

Fluid/Tissue	Dose (mg)	N	Time of Sample Collection (hr postdose)	Plasma Concentration (μg/mL)	Fluid/Tissue Concentration (μg/mL)	Fluid/Tissue-to-Plasma Ratio
Tonsil	300	6	4	1.13 (0.6-2.0)	0.28 (0.22-0.46)	0.27 (0.16-0.43)
	600	6	4	2.17 (1.1-3.4)	0.44 (0.22-0.80)	0.21 (0.14-0.29)
Sinus	300	6	4	0.97 (0.7-1.4)	0.12 (0.0-0.46)[a]	0.12 (0.0-0.42)[a]
	600	6	4	2.27 (0.8-3.5)	0.46 (0.0-2.0)[b]	0.20 (0.0-0.57)[b]
Bronchial Mucosa	300	8	4	2.79 (1.40-8.00)	0.77 (0-1.33)	0.37 (0 - 0.67)
	600	8	4	4.46 (3.05-6.40)	1.08 (0-1.92)	0.25 (0-0.35)
Epithelial Lining Fluid	300	8	4	2.79 (1.40-8.00)	0.97 (0-4.73)	0.65 (0 - 3.26)
	600	8	4	4.46 (3.05-6.40)	0.38 (0-0.59)	0.09 (0-0.14)
Middle Ear Effusion	7 mg/kg	6	3	1.96 (0.80-3.22)	0.23 (0.0-0.94)	0.10 (0.0-0.40)
	14 mg/kg	8	3	3.37 (0.89-5.54)	0.63 (0.0-1.42)	0.20 (0.0-0.35)

[a] 11 samples from 6 subjects
[b] 10 samples from 6 subjects

Cefdinir tissue penetration was evaluated by relating drug concentrations measured in blister, tonsil, lung, sinus and middle ear fluids/tissues of infection following clinical doses of either 300 or 600 mg of the capsules or 7 and 14 mg/kg of the suspension with the MIC_{90} values for the causative organisms. The following chart which submitted by the Applicant summarizes the findings of these studies:

TABLE 8. Tissue/Fluid Cefdinir Concentrations Following Administration of Single 300-mg (7 mg/kg) and 600-mg (14 mg/kg) Doses Compared with MIC_{90} Values for Causative Pathogens

Tissue/Fluid		Blister Fluid		Tonsil Tissue		Sinus Tissue		Bronchial Mucosa		Epithelial Lining Fluid		Middle Ear Effusion Fluid	
Dose		300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	300 mg	600 mg	7 mg/kg	14 mg/kg
Concentration, µg/mL		0.674	1.091	0.28	0.44	0.12	0.46	0.77	1.08	0.97	0.38	0.23	0.63
Pathogen	MIC_{90}												
Gram Positive													
S.aureus[a]	0.5	A	A	–	–	B	A	A	A	A	B	B	A
S.pneumoniae[b]	0.125	–	–	–	–	A	A	A	A	A	A	A	A
S.pyogenes (Group A)	0.03	A	A	A	A	A	A	A	A	A	A	A	A
S.agalactiae (Group B)	≤0.03	A	A	–	–	–	–	–	–	–	–	–	–
Gram Negative													
H. influenzae	0.5	–	–	–	–	B	A	A	A	A	B	B	A
H.parainfluenzae	0.05	–	–	–	–	A	A	A	A	A	A	–	–
M.catarrhalis	0.25	–	–	–	–	B	A	A	A	A	A	B	A
E.coli	0.5	–	–	–	–	B	A	A	A	A	B	–	–
K.pneumoniae	0.39	A	A	–	–	B	A	A	A	A	A	–	–

A= Adequate tissue/fluid concentrations; B= Inadequate tissue/fluid concentrations; – = Pathogen not associated with infections related to tissue/fluid.

[a] Methicillin/oxacillin-susceptible

[b] Penicillin-susceptible

- Cefdinir concentrations in middle ear fluid and plasma were measured in pediatric patients with acute otitis media after administration of 7 mg/kg bid or 14 mg/kg qd (8 children receiving 7 mg/kg and 6 children receiving 14 mg/kg). There appeared to be no relationship between concentration of cefdinir in middle ear fluid and in plasma, and the ratios also appeared to be independent of plasma drug concentrations over the range of doses studied. At 14 mg/kg, the mean middle ear fluid concentration of 0.63 mcg/ml was above the MIC_{90} for the 5 common pathogens associated with acute otitis media. At 7 mg/kg, the mean middle ear fluid concentration of 0.23 mcg/ml was above the MIC_{90} for the *S. pneumoniae* and *S. pyogenes*, but below those for *S. aureus*, *H. influenzae* and *M. catarrhalis*.

Medical officer's note: *These findings are worrisome, and discussion with Dr. Colangelo and reivew of the raw data suggests that the data is scant and inconsistent. See two Tables on the following pages duplicated from the Applicant's submission (Study 983-48, vol 1.33, page1).*

Table 9 Plasma and Middle Ear Effusion Cefdinir Concentrations (ug/mL) Approximately 3 Hours After a 7-mg/kg Oral Dose of Cefdinir

Patient	Plasma Cefdinir Concentration	Effusion Sample Weight (mg)	Middle Ear Effusion Fluid Cefdinir Concentration	Cefdinir Effusion Fluid-to-Plasma Ratio
1	1.67	100	0.207	0.124
4	0.802	60.1	0	0
7	1.11	4.9	0	0
8	2.6	27.7	0	0
10	2.34	50.3	0.944	0.402
12	3.22	39.2	0.24	0.075
N	6		6	6
Mean	1.96(0.8-3.2)		0.232(0-0.94)	0.10(0-0.40)
SD	0.93		0.37	0.16
%RSD	47.3		158	156

Limit of Quantitation = 0.016 ug/mL.

a Weight of middle ear effusion fluid sample was estimated due to a possible error in vial weighing during sample processing.

Three patients with levels of "0" at the lower dose may reflect inadequate sample size for assay. Unfortunately, there is no additional supporting data for pharmacokinetics on middle ear fluid levels and the data submitted does not allow extrapolation from fluid levels. A discussion of pharmacokinetics and pharmacodynamics of antibiotics and efficacy in otitis media is attached.[1] This publication proposes that the measurement of middle ear fluid levels is often unreliable, and that the time serum concentrations are above MIC is as useful as middle ear fluid levels in predicting antibiotic efficacy in otitis media.

[1] Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 1996;15:255-259.

Table 10. Plasma and Middle Ear Effusion Cefdinir Concentrations (ug/mL) Approximately 3 Hours After a 14-mg/kg Oral Dose of Cefdinir

Patient	Plasma Cefdinir Concentration	Effusion Sample Weight (mg)	Middle Ear Effusion Fluid Cefdinir Concentration	Cefdinir Effusion Fluid-to-Plasma Ratio
2	2.98	11.3	0.718	0.241
3	5.54	41.2	0.137	0.025
5	4.52	78.3	0.843	0.187
6	4.02	59.8	1.42	0.353
9	4.14	43.7	1.17	0.283
11	0.894	117.3	0.308	0.345
13	2.48	1.6	0	0
14	2.36	38.8	0.434	0.184
N	8	8	8	8
Mean	3.37(0.9-5.5)	0.629(0-1.4)	0.629(0-1.4)	0.202(0-0.35)
SD	1.5	0.5	0.5	0.13
%RSD	43.7	79.5	79.5	65.8

Limit of Quantitation = 0.016 ug/mL.

See figure 2 on the following page for time curve of serum concentrations of suspension in children.

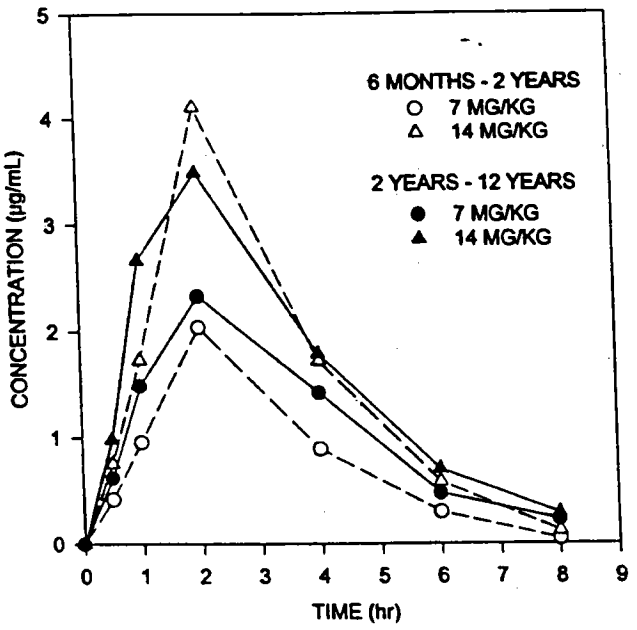


FIGURE 1. Study 983-23: Mean Plasma Cefdinir Concentration-Time Profiles After Administration of Single Suspension Doses of 7 or 14 mg/kg Cefdinir to Subjects Aged 2 to 12 Years and 6 Months to 2 Years

The pharmacokinetic support for the indication of otitis media must be scrutinized carefully if the clinical data submitted is not strongly supportive. The drug's half life is short (1.6 hours) and the time above the MIC for several of the critical pathogens is a small portion of the dosing interval (<30%) when dosed on a 24 hour schedule.

Human Clinical Experience

Foreign Experience:

The drug was originally developed in and is currently being licensed by the A 200 milligram capsule formulation was approved in Japan in 1991 and a pediatric sachet formulation was approved in 1993 and both are currently available in Japan. Recently the drug was approved in the United Kingdom; labeling negotiations are ongoing. The Applicant also plans to submit applications in Canada,

Europe, Australia and South Africa. The studies used to support this submission supported the United Kingdom application.

Post-Marketing Experience:

The Applicant reports that extensive post-marketing experience is available from Japan. estimates that as of December 31, 1995, courses of capsules have been dispensed, as well as courses of the pediatric granule formulation for a total of exposures. Surveillance of postmarketing adverse events has been ongoing during this period. Serious adverse events, rarely fatal, have been reported in association with cefdinir use. These events are the same events reported other β-lactam agents and include anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pseudomembranous colitis, hemorrhagic colitis, hepatic dysfunction and failure, interstitial pneumonitis, granulocytopenia, and thrombocytopenia. The Applicant does not anticipate significant future safety information in view of the large numbers of exposures already recorded.

Clinical Studies

Introduction

The clinical effectiveness and safety of cefdinir are described for treating mild to moderate bacterial infections of

- Community-acquired pneumonia (pneumonia) in adults,
- Acute exacerbations of chronic bronchitis (AECB) in adults,
- Secondary bacterial infections of acute bronchitis (acute bronchitis) in adults,
- Acute suppurative otitis media (otitis media) in children,
- Acute maxillary sinusitis (sinusitis) in adults,
- Pharyngitis/tonsillitis (pharyngitis) in adults and children, and
- Uncomplicated skin and skin structure infections (SSSI or skin infection) in adults and children.

Two cefdinir formulations were evaluated, cefdinir capsules for adults and adolescents aged 13 years and older and cefdinir suspension for children aged 6 months to 12 years. Both

formulations were studied under IND Separate capsule and suspension data are presented here from all studies.

Data from 16 Parke-Davis Pharmaceutical Research-sponsored pivotal and supporting clinical studies, 10 in adults and adolescents and 6 in children, demonstrate the efficacy of cefdinir. In these studies, 4622 adults and adolescents were randomized to receive cefdinir 600 mg QD or 300 mg BID, and 2138 children were randomized to receive cefdinir 14 mg/kg QD or 7 mg/kg BID. Efficacy data are presented by indication and study.

Safety data from the 4607 adults and 2133 children who actually received cefdinir in these studies are integrated and discussed. Safety data from 2 small pediatric studies are also included, adding 6 patients from a terminated pharyngitis study and 14 from an otitis media study that measured cefdinir tissue penetration; all received cefdinir 14 mg/kg QD or 7 mg/kg BID. The integrated safety database, then, includes 4607 adults and adolescents and 2153 children. Capsule (adult) and suspension (pediatric) data are presented separately.

Safety data from 3 other clinical studies in adults are described separately. These data are from 2 studies (983-2 and 983-3) in uncomplicated urinary tract infections (UTIs) and one (983-16) in lower respiratory infections (LRTIs). All patients in the UTI studies and some in the LRTI study received cefdinir regimens other than 600 mg/day. Data from patients in Study 983-16, who received cefdinir 600 mg/day and who had pneumonia, AECB, or acute bronchitis, were included in the integrated database described in the previous paragraph.

Safety information from other sources (ie, other than the NDA studies) are also reported. Deaths and adverse event information from ongoing studies reported through June 30, 1996 and from studies conducted for local registration purposes in Italy and France are presented.

Medical officer's note: The above information was duplicated from the Applicant's submission; the charts beginning on the following page detail the submitted studies.

Medical officer's note: Most of the following text has been duplicated from the Applicant's submission as the CANDA allows for copying pieces of the submission. The medical officer's comments appear in the notes.

Indication: Community Acquired Pneumonia

The portions of the proposed package insert relevant to the indication of community acquired pneumonia submitted by the Applicant are as follows:

Lower Respiratory Tract Infections

Community-Acquired Pneumonia caused by susceptible strains of
Haemophilus influenzae (including β-lactamase producing strains),
Haemophilus parainfluenzae (including β-lactamase producing strains),
Streptococcus pneumoniae (penicillin-susceptible strains),
Staphylococcus aureus (including β-lactamase producing strains),
Moraxella catarrhalis (including β-lactamase producing strains),
Escherichia coli, and *Klebsiella pneumoniae.*

Dosage and Administration

Adults and Adolescents (Age 13 years and Older)

Type of Infection	Dosage	Duration
Community-Acquired Pneumonia	300 mg q12h	10 days

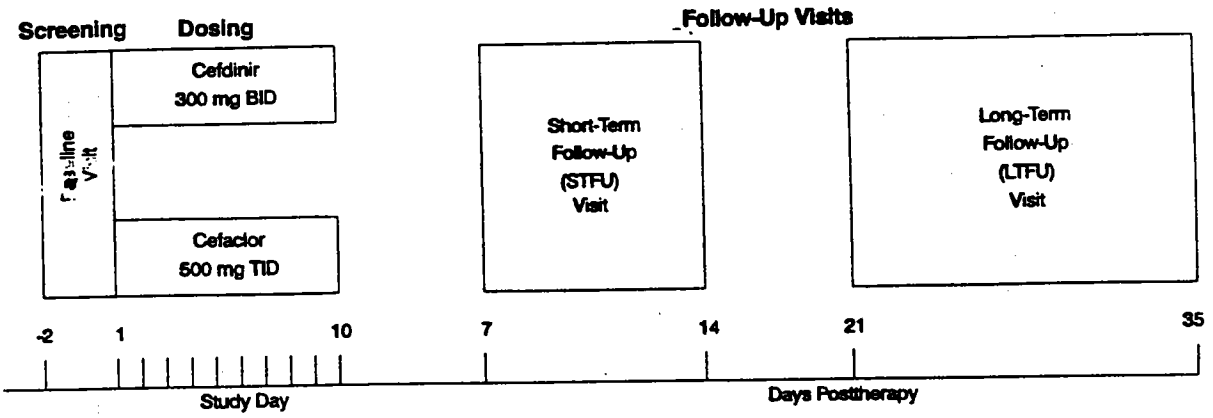
Title and Study Number: A Phase 3, 10-day, double-blind, randomized, comparative, multi center study of cefdinir (CI-983) versus cefaclor in the treatment of adult patients with community-acquired pneumonia (Protocol 983-4)

Objective: The objective of this study was to evaluate the efficacy and safety of cefdinir 300 mg BID and cefaclor 500 mg TID in the treatment of community-acquired pneumonia in adult patients.

Medical officer's note: A 600 mg qd cefdinir treatment group in the original study was discontinued due to theoretical concerns that qd dosing might not be adequate for treating serious, potentially life-threatening pneumonia (Applicant's Amendment 2). Thus, this was dropped from the original Objective and Study Design.

Study Design: Protocol 983-4 is a double-blind, randomized, comparative, multi center study with 2 parallel-treatment groups. Duration of therapy was ten days. Forty-eight centers in the

United States enrolled patients. Treatment was followed by short-term (test-of-cure at 6-14 days posttherapy) and long-term (follow up at 21-35 days posttherapy) follow-up visits. A chart detailing study design which was duplicated from the Applicant's submission is presented below.



BEACHJ/CLC/081495/DSGN13
983/13/RR

Figure 2. Protocol 983-4 Study Design

Medical officer's note: Deviations from the Applicant's original protocol are as follows:
(1) The original randomization schedule involved three treatment arms and was 1:1:1. After the qd dosing arm was dropped, the numbers assigned to that arm were unblinded and not used in the randomization. The randomization schedule assigned to the other two arms (cefdinir BID and cefaclor TID) was adhered to and resulted in a 1:1 randomization.
(2) Changing the test-of-cure visit from 3 to 7 days posttherapy to 7 to 14 days posttherapy (days 17 through 24 for patients completing treatment on day 10) was another deviation from the original protocol (Applicant's Amendment 2). For many patients, the TOC visit beginning on Day 17 was actually 6 days posttherapy since patients who started BID or TID treatment midday on Day 1 ended treatment on Day 11. For analysis purposes, the TOC window was widened to 6 to 14 days posttherapy to include this patient data.

Protocol Overview

Population and Inclusion/Exclusion Criteria (as duplicated from the Applicant's submission)

Population: Eligible patients were males and nonpregnant, nonlactating females ≥13 years of age who had community-acquired pneumonia confirmed by chest x-ray. Females were to be either adolescent and not sexually active, using an effective means of contraception and have a

negative pregnancy test at baseline, postmenopausal, or surgically sterilized.

Inclusion Criteria: Patients were required to have cough and sputum production and could have chest pain, chest sounds (rales, rhonchi), shortness of breath, or fever for study entry. The investigator performed an evaluation of these clinical signs and symptoms and classified all of them (except chest sounds and fever) as absent, mild, moderate, or severe at each visit. Chest sounds were classified as present or absent. Body temperature was recorded by the investigator and fever severity was determined by the sponsor using an objective temperature guideline.

Medical Officer's Note: Although this protocol was designed and initiated before the availability of the Guidelines for the Evaluation of Anti-Infective Drug Products[1], because the fact the population was selected based on chest x-ray, and the inclusion criteria required the presence of cough and sputum and possible other findings such as fever, chest pain, chest sounds and shortness of breath, the Guidelines are met and consistent with current DAIDP requirements for study of community acquired pneumonia. No procedures were planned for the Protocol.

Exclusion Criteria: Patients were excluded from entering the study for any of the following reasons:

- A disease or condition that would preclude evaluation of the therapeutic response, including cystic fibrosis or significant pulmonary structural defects;
- Hepatic disease, obstruction of the biliary tract, baseline bilirubin or hepatic enzyme levels (AST, ALT) >2 times the upper limit of normal;
- Baseline serum creatinine >1.5 times the upper limit of normal or known creatinine clearance <30 mL/min;
- Use of another systemic antibacterial within 7 days of the start of study medication; or if the interval between the last dose of the prior systemic antibacterial and the first dose of study medication is <5 half-lives of the prior antibacterial;
- Hypersensitivity to β-lactams;
- Baseline pathogen(s) known to be resistant to either study medication prior to randomization;

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[1] Chow AW, Hall CB, Klein JO, Kammer RB, Meyere RD, Remington JS. Evaluation of New Anti-Infective Drugs for the Treatment of Respiratory Tract Infections CID 1992;15(Suppl 1):S62-S88.

- Concomitant infection(s) requiring systemic antibacterial therapy;
- Prior participation in this or any other cefdinir study; or
- Receipt of any other investigational compound within 4 weeks of study entry.

Medical Officer's Note: These exclusion criteria are not inconsistent with the Guidelines. They are fair, and the medical officer commends the protocol and study design and is in agreement with inclusion and exclusion criteria.

Patients requiring concurrent treatment with other systemic antibacterial medications, probenecid, dietary iron containing supplement or multivitamins were to be excluded. Patients requiring aluminum- or magnesium-containing antacids were to withhold antacid therapy for 2 hours before and after study medication dosing.

Medical officer's note: See Section 6. Human Pharmacokinetics/Pharmacodynamics, page 23, in this review for Applicant's studies which support these prohibitions and limitations. These prohibitions and limitations are also included in the Applicant's label.

Evaluability Criteria: Patients could be withdrawn from the study because of insufficient efficacy; an adverse event; a clinical laboratory abnormality; lack of patient cooperation; patient or guardian request; failure to isolate a baseline pathogen; or isolation of a baseline pathogen resistant to either cefdinir or cefaclor. Reasons for withdrawal were reported on the appropriate CRF.

Confirmation of bacteriological etiology and *in vitro* susceptibility (or intermediate susceptibility) to both study medications were required for a patient to be evaluable for efficacy analyses. If these conditions were not met, a patient could be discontinued from study medication and given appropriate therapy. The investigator could continue to treat patients who had a baseline pathogen that was resistant to one study medication and susceptible to the other if, in his or her judgement, they were exhibiting satisfactory clinical improvement.

When patients discontinued treatment early, the following were to be completed: sputum culture and susceptibility testing, a clinical assessment (i.e., assessment of signs and symptoms as well as an overall assessment of clinical efficacy), a physical examination, clinical laboratory

tests, as well as records of adverse events and concurrent medications. If additional antibiotics were not required at the time study medication was discontinued and the patient had received at least three days of study medication, both follow-up visits were scheduled to be completed. If additional antibiotics were required or if the patient had no baseline pathogen, follow-up visits were not scheduled.

Assessments of microbiologic and clinical response at the TOC visit, 6 to 14 days posttherapy, were used to evaluate the efficacy of cefdinir. The LTFU visit, 21 to 35 days posttherapy, provided information on recurrence of infection.

Three primary efficacy measures were used in this study: Microbiologic eradication rate by pathogen, microbiologic eradication rate by patient, and clinical cure rate by patient. The appearance of new pathogens was examined as a secondary efficacy parameter.

Medical officer's note: *The medical officer agrees with the above evaluability criteria; most patients are carried forward as failures in the intent-to-treat analysis. In addition most patients are carried forward in the modified-intent-to-treat. When assigning outcome, the Applicant consistently selected the outcome least apt to favor therapy in a blinded fashion.*

Endpoints Defined (Clinical and Microbiological)

The following table, duplicated from the Applicant's submission, described what data was collected and at what visits.

Table 11. Schedule of Clinical Observations and Laboratory Measurements

Procedure/Observation	Baseline[a]	Day 1	Days 3-5	Day 10	Posttherapy Visits: 7 to 14 Days	Posttherapy Visits: 21 to 35 Days
Medical History	X					
Physical Examination (including x-ray)[b]	X				X	X
Clinical Assessment of Signs and Symptoms[b]	X		X		X	X
Gram Stain, Sputum Culture, and Susceptibility Testing[b]	X		X		X	X
Clinical Laboratory Testing[b]	X				X	X[c]
Assessment of Clinical Efficacy[b]					X	X
Adverse Events		X—	——	——	X—	—X
Dosing		X—	——	—X		

[a] Prior to treatment (within 48 hours)
[b] Also performed whenever a patient was withdrawn
[c] Performed only if abnormalities were detected at the previous visit

Microbiological endpoints: Specimens were collected for culture at the baseline, TOC, and LTFU visits. At the TOC and LTFU visits, the microbiologic response of each baseline pathogen was classified as:

- Eradication - Baseline pathogen not present in follow-up culture or no material available to culture at follow-up (presumed eradication);
- Persistence - Baseline pathogen present in follow-up culture; or
- Not Assessable - No follow-up data.

Microbiologic eradication rate by pathogen was the percentage of baseline pathogens that were absent from specimens obtained at the TOC or LTFU visits. Patients with multiple baseline pathogens provided multiple observations in the analyses of microbiological efficacy on a per pathogen basis. The eradication rate by pathogen was calculated separately for each of the follow-up visits. Qualified patients who had persistent pathogens at TOC were automatically considered to have persistent pathogens at the LTFU visit. Patients without baseline pathogens could develop a superinfection.

Microbiologic Response by Patient: At the TOC visit, patients were classified by their microbiologic response based on the baseline and 6- to 14-day posttherapy culture results as:

- Patients With Eradication - All baseline pathogens eliminated at TOC or no material available to culture at TOC (i.e., presumed eradication);
- Patients With Persistence - Presence of at least one baseline pathogen in the TOC culture; or
- Not Assessable - No proven baseline pathogen or no follow-up data.

At the LTFU visit, patients were classified by their microbiologic response based on the baseline, 6- to 14-day posttherapy, and 21- to 35-day posttherapy culture results as:

- No Relapse - Patients with eradication at TOC and either continued eradication of all baseline pathogens at LTFU or no material available to culture at LTFU;
- Relapse - Patients with eradication at TOC and reappearance of at least one baseline pathogen at LTFU;
- Patients With Persistence - All patients with persistence at TOC; or
- Not Assessable - No proven baseline pathogen or no follow-up data.

The microbiologic eradication rate by patient was the percentage of patients who had all baseline pathogens eliminated. Each patient provided one observation. The microbiologic eradication rate by patient was calculated separately for each follow-up visit.

The appearance of a new pathogen during or after treatment was classified as:

- Superinfection - The appearance of a nonbaseline pathogen at any time during treatment through the TOC visit and <50% decrease in clinical score at the corresponding clinical evaluation of signs and symptoms relative to baseline;
- Reinfection - The appearance of a new pathogen (i.e., not present at any prior visit) at the LTFU visit, and the clinical assessment of Recurrence at LTFU; or
- Not Assessable - No follow-up data.

The appearance of a new pathogen together with a clinical worsening or failure at the corresponding clinical assessment also constituted a superinfection or a reinfection. If a patient had a new organism(s) isolated in any postbaseline culture, but had no corresponding clinical assessment of signs or symptoms, the determination of pathogenicity was made by the sponsor.

Medical officer's note: The medical officer agrees with these endpoint classifications. The Guidelines were not available at the time the study was designed and initiated. Although these endpoints are not identical to those recommended in the Guidelines, they reflect adequate consideration of the recommended microbiologic endpoints to be valid.

Clinical Response by Patient:

All clinical signs and symptoms were assessed by the investigator at the baseline, TOC, and LTFU visits. The recorded clinical signs and symptoms provided the basis for all assessments of patient clinical response. The investigator's impression of patient clinical response used the following protocol-specified definitions.

Investigator's Assessment of Clinical Response at TOC:

- Cure - Absence or satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- Improvement - Satisfactory remission but not complete disappearance of baseline clinical signs and symptoms;
- Failure - No significant remission of baseline signs and symptoms; further antibacterial therapy required; or
- Not Assessable - Unable to assess patient; no data.

Investigator's Assessment of Clinical Response at LTFU:

- Cure - Absence or satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- Improvement - Satisfactory remission but not complete disappearance of baseline clinical signs and symptoms;
- Failure/Recurrence - Worsening or no significant remission of baseline signs and symptoms since the previous visit; further antibacterial therapy required; or
- Not Assessable - Unable to assess patient; no data.

Medical officer's note: *The medical officer agrees with these endpoint classifications.*

The protocol specified that both investigator and sponsor assessments of patient clinical response would be made. Based on the investigator's follow-up assessments of clinical signs and symptoms (but before unblinding), the sponsor used a scoring algorithm to calculate an assessment of clinical efficacy. This scoring system is described in detail in Applicant's Appendix A.4.

Medical officer's note: *Review of Appendix A.4 demonstrates the clinical scoring system developed and used consistently by the Applicant. Clinical signs and symptoms (cough, sputum production, shortness of breath, chest pain, chest sounds and fever) were assigned a score by the investigators based on severity (0, 1, 2, or 3 respectively correlates with absent, mild, moderate or severe). A composite clinical score based on the weighted value was derived. This score could vary from 4 to 28 at baseline and from 0 to 28 at TOC and LTFU.*

The Applicant's clinical assessments, based on a quantitative evaluation of the total clinical

score, were defined as follows:

Sponsor's Assessment of Clinical Response at TOC utilizing clinical scoring system:

- Cure - ≥50% decrease in clinical score at TOC relative to baseline;
- Failure - <50% decrease in clinical score at TOC relative to baseline; or
- Not Assessable - No baseline signs or symptoms or no follow-up data.

Sponsor's Assessment of Clinical Response at LTFU utilizing clinical scoring system:

- Cure - Cure at TOC and <2-point increase in clinical score at LTFU relative to TOC and ≥50% decrease in clinical score at LTFU relative to baseline;
- Recurrence - Cure at TOC and either ≥2-point increase in clinical score at LTFU relative to TOC or <50% decrease in clinical score at LTFU relative to baseline;
- Failure - Failure at TOC; or
- Not Assessable - No baseline signs or symptoms or no follow-up data.

The sponsor's assessment of clinical response was computerized. Symptoms that were not assessed at baseline or at a follow-up visit were not used in calculating percentage changes from baseline for that visit. If a patient fulfilled the criteria for a particular response, but had important or extenuating circumstances during the study (e.g., very low scores at baseline), the computerized determination of clinical effectiveness could be changed by the sponsor prior to randomization code release.

Medical officer's note: The medical officer believes this to be an unbiased and simple method with which to assign patient endpoints providing that it is consistently adhered to. The medical officer also believes that such clearly defined outcome assignments are more valid than a gestalt assignment after review of the CRF.

A combination of investigator and sponsor assessments, referred to as the combined investigator/sponsor clinical assessment in this report, was used as the primary measure of patient clinical response in the efficacy analyses. If the investigator assessment at TOC was Improvement or Not Assessable and clinical signs and symptoms data had been collected, the patient was reclassified according to the sponsor assessment. Investigator assessments of Cure and Failure were retained regardless of the sponsor assessment.

The combined investigator/sponsor clinical assessment at the LTFU visit depended not only on the investigator assessments at LTFU, but also on the combined investigator/sponsor clinical assessment at TOC. For patients with a combined assessment of Cure at TOC, the rules for the combined assessment at LTFU were analogous to those at TOC: Investigator assessments of Cure and Recurrence took precedence over the sponsor assessment (i.e., were used) while investigator assessments of Improvement and Not Assessable were reclassified according to the sponsor assessment. In contrast, patients with a combined investigator/sponsor assessment of

Failure at TOC were considered failures using the combined investigator/sponsor clinical assessment at LTFU, regardless of investigator determination. (Patients assessed as failures by the sponsor at the TOC visit were automatically considered sponsor failures at LTFU.)

Table 12. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU[a,b]

Sponsor Assessment at TOC	Investigator Assessment at TOC			
	Cure	Improvement	Failure	Not Assessable
Cure	**Cure**	**Cure**	**Failure**	**Cure**
Failure	**Cure**	**Failure**	**Failure**	**Failure**
Not Assessable	**Cure**	**Not Assessable**	**Failure**	**Not Assessable**
	Investigator Assessment at LTFU			
Sponsor Assessment at LTFU	Cure	Improvement	Recurrence	Not Assessable
Cure	**Cure**	**Cure**	**Recurrence**	**Cure**
Failure	**Cure**	**Failure**	**Recurrence**	**Failure**
Recurrence	**Cure**	**Recurrence**	**Recurrence**	**Recurrence**
Not Assessable	**Cure**	**Not Assessable**	**Recurrence**	**Not Assessable**

[a] The combined assessments are shown in bold typeface.
[b] Note: If a patient had a combined clinical assessment of Failure at the TOC visit, the patient was automatically a Failure on the combined assessment scale at LTFU.

The clinical cure rate was the percentage of patients rated as Cure on the combined assessment scale.

Medical officer's note: The medical officer believes that as long as this outcome assignment is adhered to consistently, it is acceptable.

Statistical Considerations

Sample Size: This double-blind, comparative study of cefdinir versus cefaclor was designed with a sample size of 190 evaluable patients per randomized treatment group.

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

At TOC, the primary endpoint, the microbiologic eradication rates by pathogen and by patient, were calculated for each treatment group in the evaluable, MITT, and ITT patient populations. Clinical cure rates and mean clinical signs/symptoms scores were calculated for each treatment group in the evaluable, clinically evaluable, and the ITT patient populations.

At LTFU, the secondary endpoint, the microbiologic eradication rates by pathogen and by patient (i.e., the "no relapse" rates) were calculated for each treatment group in the qualified and ITT patient populations. Clinical cure rates (i.e., the "no recurrence" rates) and mean clinical scores were calculated for each treatment group in the qualified and ITT patient populations.

Two methods of investigating treatment equivalence at TOC were used. One method was based on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient (or each pathogen, for the by-pathogen case) in the analysis, and were calculated as the total number of cures or eradications in the study population, divided by the total number of cases.

The second method used a categorical modeling procedure to obtain center-adjusted estimates of the response rates and their standard errors. The model contained terms for study center, treatment group, and treatment-by-center interaction. The resulting parameter estimates were used to construct estimates of the treatment group response rates and standard errors in which each center was given equal weight.

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

Table 13. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Treatments Are Equivalent If 95% Confidence Interval For Treatment Difference Is Within Bounds
90% or greater	-10%, +10%
80%-89%	-15%, +15%
60%-79%	-20%, +20%

Results under the two methods were compared for consistency. When the two methods agreed, the pooled analysis was presented as the final analysis. If results from the two methods disagreed, the differences were addressed and results from both methods were presented.

Study Results

Investigators and Numbers Enrolled

Table 14. List of Investigators

Center	Investigator	Number of Patients		
		Randomized to Treatment(N)	Completed Treatment(% of N)	Evaluable (% of N)
1	A. Rosenthal	8	4(50)	1(12.5)
2	J. Applegate	16	11(68.8)	10(62.5)
3	R. Chiulli	9	6(66.7)	5(55.6)
4	P. Finch	4	4(100)	3(75)
5	R. Greenberg	47	31(66.0)	19(40.4)
7	K. Guntupalli	16	11(68.8)	11(68.8)
10	M. Kutner	1	1(100)	1(100)
11	A. Puopolo	28	21(75)	16(57.1)
12	J. Scott	11	9(81.8)	10(90.9)
13	A. Robbins	15	11(73.3)	7(46.7)
14	R. Snow	18	12(66.7)	9(50)
15	M. Sperling	17	12(70.6)	9(52.9)

16	T. Littlejohn	28	23(82.1)	20(71.4)
18	H. Collins	5	3(60)	3(60)
20	D. Stryker	9	8(88.9)	6(66.7)
21	A. Sands	1	1(100)	0(0)
25	D. Dark	6	5(83.3)	3(50)
26	J. Salisbury	113	92(81.4)	47(41.6)
27	M. Drehobl	52	33(63.5)	31(59.6)
28	L. Cosmo	1	0(0)	1(100)
29	J. Frey	3	0(0)	2(66.7)
30	G. Mayer	1	1(100)	1(100)
31	R. Kearley	5	2(40)	0(0)
33	S. Pingleton	2	2(100)	2(100)
36	C. Khurana	4	3(75)	2(50)
37	T. Chestnut	2	1(50)	1(50)
38	D. Williams	7	5(71.4)	4(57.1)
40	J. Zaremba	51	35(68.6)	24(47.1)
41	A. Russakoff	5	4(80)	3(60)
50	R. Connor	3	2(66.7)	1(33.3)
53	J. Westerman	4	1(25)	2(50)
56	A. Iravani*	7	4(57.1)	2(28.6)
58	G. Heinz, III	16	16(100)	9(56.2)
59	B. Sherman	4	1(25)	0(0)
61	R. Wainz	1	1(100)	1(100)
62	S. Hirsch	3	3(100)	1(33.3)
63	R. Bianchi	92	64(69.6)	63(98.4)
64	J. Schoenberger	9	7(77.8)	3(33.3)
66	R. Schwartz	1	1(100)	0(0)
69	D. Cernea	10	8(80)	1(10)
70	J. McCarty	3	2(66.7)	1(33.3)
71	B.-Cochran	2	2(100)	2(100)
72	D. Henry	19	17(89.5)	15(78.9)
73	R. Knight	12	7(58.3)	6(50)
74	B. Diener	5	3(60)	2(40)
75	B. Harrison	14	14(50)	7(50)
76	J. Hedrick	7	6(85.7)	6(85.7)
77	W. Ziering	7	7(100)	3(42.9)
	Total	704	517(73.4)	376(53.4)

* Dr. Iravani was eliminated from other studies in this application. See ***Medical officer's note*** below for why reanalysis was not performed excluding these two patients.

Medical officer's note: *Inspection by DSI personnel raised questions concerning the validity of data obtained by Dr. Iravani at center 56. As the table above demonstrates, he enrolled only seven patients; three to the cefdinir treatment arm and four to the cefaclor treatment arm. Among these seven enrollees, only two were evaluable and both were in the cefaclor treatment arm. The contribution of two evaluable patients to 337 evaluable can have no impact on study results, either with respect to efficacy or safety. Thus, no effort was made to eliminate his data as was done in other indications of this NDA review.*

Number of Patients Enrolled per Site, and those Evaluable by Site

See Appendix 1 annexed to the end of this study review for a detailed chart of total number of patients enrolled by each site, and number of patients clinically evaluable and microbiologically/clinically evaluable by site.

Medical officer's note: *Review of this Appendix and Table 4 above demonstrates that number of patients enrolled at the 77 centers varied from 0 to 111. Five centers enrolled more than 40 patients (47, 111, 52, 51 and 92). This totals 353 or 50.1% of the 704 patients enrolled. Those evaluable among these sites vary from 19 to 63, with a total of contribution of 184 of 376 evaluables or 48.9%. Another two centers enrolled between 20 and 40 patients (28 patients each) contributing 8.0% of those patients enrolled 36 or 9.6% of those evaluable. The remaining 70 centers enrolled 41.9% of the study population which constitutes 41.5% of those evaluable. Thus, although a few centers enrolled half of all patients, the percent evaluable rate is fairly stable regardless of number enrolled. Randomization appears to have been grossly effective as approximately one-half the patients at each study site are assigned to each treatment arm. No inappropriate biases are suggested by this information.*

Demographics, Evaluability

The baseline characteristics of all patients randomized to treatment (N = 704; Table 5) were similar to those of the evaluable patient population (N = 376; Table 16) and the clinically evaluable patient population (N = 453). For all patients randomized to treatment, there were slightly more males (56%) than females (44%); 85% of patients were white; and most patients (75%) were 18 to ≤65 years of age.

Patients were similarly distributed by sex, race, and age across the three treatment groups in each patient population.

Table 15. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 14	Cefdinir BID N = 347	Cefaclor N = 343	Total N = 704
Sex				
Male	7 (50.0)	193 (55.6)	192 (56.0)	392 (55.7)
Female	7 (50.0)	154 (44.4)	151 (44.0)	312 (44.3)
Race				
White	12 (85.7)	298 (85.9)	288 (84.0)	598 (84.9)
Black	2 (14.3)	32 (9.2)	44 (12.8)	78 (11.1)
Asian	0 (0.0)	3 (0.9)	1 (0.3)	4 (0.6)
Other[a]	0 (0.0)	14 (4.0)	10 (2.9)	24 (3.4)
Age, year				
Median	46.0	44.0	44.0	44.0
Range	22.0 - 79.0	13.0 - 89.0	13.0 - 93.0	13.0 - 93.0
Distribution				
13 to <18	0 (0.0)	10 (2.9)	8 (2.3)	18 (2.6)
18 to <65	10 (71.4)	255 (73.5)	263 (76.7)	528 (75.0)
≤65	4 (28.6)	82 (23.6)	72 (21.0)	158 (22.4)

[a] Other = Hispanic, Filipino, American Indian, and Brazilian.

Table 16. Patient Characteristics - Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 3	Cefdinir BID N = 187	Cefaclor N = 186	Total N = 376
Sex				
Male	1 (33.3)	105 (56.1)	102 (54.8)	208 (55.3)
Female	2 (66.7)	82 (43.9)	84 (45.2)	168 (44.7)
Race				
White	3 (100.0)	161 (86.1)	157 (84.4)	321 (85.4)
Black	0 (0.0)	16 (8.6)	24 (12.9)	40 (10.6)
Asian	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.5)
Other[a]	0 (0.0)	8 (4.3)	5 (2.7)	13 (3.5)
Age, year				
Median	46.0	44.0	45.5	45.0
Range	44.0 - 46.0	13.0 - 87.0	13.0 - 93.0	13.0 - 93.0
Distribution				
13 to <18	0 (0.0)	7 (3.7)	5 (2.7)	12 (3.2)
18 to <65	3 (100.0)	133 (71.1)	140 (75.3)	276 (73.4)
≥65	0 (0.0)	47 (25.1)	41 (22.0)	88 (23.4)

[a] Other = Hispanic, American Indian, and Brazilian.

Medical officer's note: *There appears to be random and even distribution of sex, age and race by treatment arm among the cefdinir BID and cefaclor arms among those enrolled and those evaluable. Because the cefdinir qd dosing is not submitted for approval, the findings related to*

the seven enrolled and the three evaluable patients in this arm are inconsequential with respect to efficacy.

Smoking and Past Medical History: No smoking or tobacco use history was obtained in this study. History of existing or prior pulmonary disease was in an open ended inquiry regarding "Past Medical History" which appeared in the questionaire. That question provided the follow results for clinically evaluable patients:

Table 17: Prior Pulmonary Diagnoses & Conditions Predisposing to Community Acquired Pneumonia for All Clinically Evaluable Patients

Pulmonary Diagnosis	cefdinir 300 mg	cefaclor
COPD	56	51
Asthma	30	31
Pneumonia	11	12
Bronchitis	15	15
Lung cancer	2	2
Bronchiectasis	1	1
Pulmonary Fibrosis	0	1
Cor pulmonale	0	1
Pneumonia	0	1
Total	115	115

<u>Medical officer's note</u>: Although not requested by DAIDP in orignal review, we have requested the Applicant provide us with any information obtained in study 983-4 with respect to distribution of patients' smoking, tobacco use and past medical history with respect to pulmonary disease to the best of the Applicant's ability. As stated above, no information was obtained with respect to smoking or tobacco use. This remains a potential confounder and the assumption must be made that patient randomization will control for assignment of this variable between the treatment arm. However, it can never be tested or proved because no information is available. Information regarding prior pulmonary diagnoses and conditions predisposing to community acquired pneumonia was obtained via open-ended question. Therefore, the data

cannot be expected to be complete, and there is no way to determine how thoroughly this patient history was elicited. However, scrutiny of the above table provides the observation that equal numbers of diagnoses such as COPD, asthma, prior pneumonia and bronchitis and lung cancer are evenly distributed by treatment is reassuring that randomization effectively controlled for this potential confounder.

Severity of Illness/Clinical Score upon Enrollment: Among those enrolled, the following rates of signs and symptoms occurred among enrollees: cough, 100%; sputum production; 100%; chest sounds, 95%; shortness of breath, 83%; chest pain, 71%; and fever, 19%. The clinical scoring system allowed for a maximum score of 28. The mean baseline scores at enrollment were 14.2 for the cefdinir, 300 mg bid arm and 14.3 for the cefaclor treatment arm. Among clinically evaluable patients, those receiving cefdinir, 300 mg bid had a mean baseline score of 14.1 and those receiving cefaclor had a mean baseline score of 14.6. Among the evaluable population, those receiving cefdinir bid had a mean baseline score of 14.3 and those receiving cefaclor had a mean baseline score of 14.8.

Medical officer's note: *There does not appear to be differences of note with respect to baseline clinical scores, and clinical scores among evaluable and clinically evaluable patients by treatment arm. Overall, the patients were not severely ill, and fever was fairly uncommon.*

Compliance with study medication

Table 18. Patient Exposure to Study Medication - All Patients

Days on Study Medication	Cefdinir QD N = 14	Cefdinir BID N = 347	Cefaclor N = 343
1	0	5	2
2	0	2	5
3	0	8	5
4	0	7	16
5	0	11	16
6	0	10	9
7	0	10	13
8	1	13	4
9	0	9	2
10	7	114	112
11	6	146	134
12	0	2	0
13	0	0	2
14	0	1	0
16	0	1	0
21	0	0	1
Median	10.0	10.0	10.0
Unknown[a]	0	8	22

[a] Three cefdinir BID-treated and three cefaclor-treated patients were randomized but received no study medication.

Medical officer's note: *The protocol was designed to provide a ten day exposure to either study or comparator drug. The great number of subjects enrolled completed therapy and this validates the equivalence and adequacy of exposure to drug in each study arm,*

Efficacy

The numbers of patients randomized to treatment (i.e., the ITT population) are compared to other patient populations in the following table.

Table 19. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	N		Cefdinir QD		Cefdinir BID		Cefaclor	
ITT	704	(100.0)	14	(100.0)	347	(100.0)	343	(100.0)
MITT	509	(72.3)	13	(92.9)	256	(73.8)	240	(70.0)
Clinically Evaluable	453	(89.0)	4	(28.6)	222	(64.0)	227	(66.2)
Evaluable	376	(83.0)	3	(21.4)	187	(53.9)	186	(54.2)
Qualified[a]	278	(73.9)	2	(66.7)	137	(73.3)	139	(74.7)

[a] As a percentage of the Evaluable patient population

Medical officer's note: *Definitions of these populations appear in footnote below.*[2]

[2] Analysis populations for efficacy examined in this report include the evaluable, the clinically evaluable, the modified intent-to-treat (MITT), and the intent-to-treat (ITT).

Evaluable patients had no known protocol violations that might have affected efficacy assessments at TOC using the specific, predefined criteria detailed above. Patients who had microbiologic and/or clinical assessments done early (i.e., before the follow-up visit window) or who took a concurrent antibacterial because they were early treatment failures were not removed from the evaluable patient population for these reasons.

A subset of evaluable patients identified as "qualified patients" was examined at LTFU. **Qualified patients** were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits (e.g., qualified patients did not take concurrent systemic or topical antibacterial agents).

Patients in the **clinically evaluable population** had the correct indication documented by a baseline chest x-ray; at least one clinical sign and symptom at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy; and had their clinical assessments performed within the range of days specified in the protocol. Patients were not excluded from this data set if they had no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

Patients in the **MITT** population had the correct indication, had at least one baseline pathogen, and had a follow-up culture. The MITT population was the same at TOC and LTFU.

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

Table 20. Patient Disposition - All Patients
[Number (%) of Patients]

Patient Disposition	Cefdinir QD		Cefdinir BID		Cefaclor		Total	
Randomized to Treatment	14		347		343		704	
Withdrawn Prior to End of Treatment								
Lack of Compliance[a]	0	(0.0)	14	(4.0)	19	(5.5)	33	(4.7)
No Baseline Pathogen	0	(0.0)	29	(8.4)	34	(9.9)	63	(8.9)
Adverse Event[b]	0	(0.0)	21	(6.1)	16	(4.7)	37	(5.3)
Lack of Efficacy	0	(0.0)	7	(2.0)	6	(1.7)	13	(1.8)
Resistant Baseline Pathogen	1	(1.7)	6	(1.7)	10	(2.9)	17	(2.4)
Other/Administrative[c,d]	0	(0.0)	13	(3.7)	11	(3.2)	24	(3.4)
Completed Treatment	13	(92.9)	257	(74.1)	247	(72.0)	517	(73.4)
Completed Follow-Up Visits								
STFU (TOC)	13	(92.9)	266	(76.7)	243	(70.8)	522	(74.1)
LTFU	11	(78.6)	216	(62.2)	197	(57.4)	424	(60.2)

[a] Patient 8, Center 31 (cefdinir BID) and Patient 8, Center 1 (cefaclor) were randomized but received no study medication.

[b] Patient 4, Center 59 (cefdinir BID) and Patient 7, Center 13 (cefaclor) were randomized but received no study medication.

[c] Patient 3, Center 59 (cefdinir BID) and Patient 124, Center 26 (cefaclor) were randomized but received no study medication.

[d] Reason includes lost to follow-up.

Medical officer's note: *The reasons for disqualification or dropout are justifiable and distributed evenly across the two evaluated treatment arms.*

Medical officer's note: *The medical officer reviewed case report forms for all patients considered to be nonevaluable or failures and 15% of patients considered to be cures. All data reviewed was consistent with data presented in summary in CANDA. The medical officer also found the patients to be fairly assigned outcomes as per protocol. Reassignment of outcome would have occurred in <5% of cases and presented no bias with respect to treatment arm (blind was maintained). To check that such random sampling was adequate to confirm the Applicant's findings, finite population bootstrapping to estimate the variance of the predicted lower bound of the confidence interval for the difference in response rates was employed. This technique supported that such a small discrepancy, with nondifferential reassignment, would not significantly effect either the confidence intervals or the corresponding conclusions about equivalence. Thus, the medical reviewer has accepted the Applicant's numbers, outcome assignments and cure rates.*

Clinical Efficacy

Test of Cure, Clinical Cure

Table 21. Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the Test-of-Cure Visit – Evaluable Patients

Investigator Determination	Combined Investigator/Sponsor Determination			
	Cefdinir BID N = 187		Cefaclor N = 186	
	Cure	Failure	Cure	Failure
Cure	80	0	91	0
Improvement	70	16	56	13
Failure	0	21	0	23
Not Assessable	0	0	0	3
Same Clinical Response for both Applicant & Investigator	101/187(54%)		114/186(61%)	
Investigator called improved, <50% improved by Applicant's score (Clinical Failure by score)	16/86(19%)		13/69(19%)	

Table 22: Clinical Patient Outcomes Investigator vs. Applicant at TOC

Patient Outcome	Investigator	Applicant
Cefdinir	n=187	n=187
Success[a]	166	150
Failure	21	37
Not Assessable	0	0
Cefaclor	n=186	n=186
Success[a]	160	147
Failure	23	39
Not Assessable	3	0

[a] For investigator, "success"= cure + improvement. For Applicant, success is based on the clinical scoring system described above.

***Medical and statistical officer's note**: Unless otherwise noted, all confidence intervals presented in the following review will be double-sided, 95% confidence intervals about the difference between test and comparator drug with continuity correction and no correction for center effect.*

95% CI for Investigator Determination of Clinical Outcome at TOC is (-4.52, 10.02).

95% CI for Applicant Determination of Clinical Outcome at TOC is (-7.53, 9.89).

***Medical and statistical reviewer's note**: The clinical outcome at test-of-cure, which is a primary endpoint, met DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.*

Long-Term Follow Up, Clinical Cure

Table 23. Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the Long-Term Follow-Up Visit - Qualified Patients

Investigator Determination	Cefdinir BID N = 137		Cefaclor N = 139	
	Cure	Failure/Recurrence	Cure	Failure/Recurrence
Cure	109	10	117	3
Improvement	9	3	5	8
Failure/Recurrence	0	6	0	5
Not Assessable	0	0	0	1
Same Clinical Response for both Investigator & Applicant	115/137 (84%)		122/139 (88%)	
Investigator called improved, <50% improved by Applicant's score (Clinical Failure)	3/13 (23%)		8/13 (35%)	
Failure carried forward as Failure Assigned at TOC	12		7	

Table 24: Clinical Patient Outcomes Investigator vs. Applicant at LTFU

Patient Outcome	Investigator	Applicant
Cefdinir	n=137	n=137
Success[a]	131	118
Failure	6	19
Not Assessable	0	0
Cefaclor	n=139	n=139
Success[a]	133	122
Failure	5	17
Not Assessable	1	0

[a] For investigator, "success"= cure +improvement. For Applicant, success is based on the clinical scoring system described above.

95% CI for Investigator Determination of Clinical Outcome at LTFU is (-5.60, 5.47).

95% CI for Applicant Determination for Clinical Outcome at LTFU is (-1.03, 7.03).

Medical officer's and statistical reviewer's note: The clinical outcome at long-term follow up, although not a primary endpoint, met DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.

Medical officer's note: The rates of agreement between Applicant and Investigator clinical outcome assignment based on the clinical score system differed somewhat between TOC and Long-Term Follow Up (54% and 84% agreement on cefdinir, and 61% and 88% agreement on cefaclor, respectively). Those assigned failure by Applicant's clinical score that were improved by Investigator's assessment was more similar (19% and 23% on cefdinir, and 19% and 35% on cefaclor, respectively). As the singular major outcome of interest is TOC, the differences matter little. In addition, most of the reassignment involved increasing clinical failures in a manner unbiased to treatment arm.

Test of Cure and Long-Term Follow Up Visits, ITT and MITT Analysis

Table 25. Clinical Efficacy at TOC and LTFU – ITT and MITT Populations by Clinical Cure, Microbiologic Eradication by Patient and Clinical Cure Among Clinically Evaluable Patients

Parameter	Cefdinir BID		Cefaclor	
	n/N	%	n/N	%
TOC/ITT: Microbiologic Eradication by Patient[a]	234/347	67.4	221/343	64.4
TOC/ITT: Clinical Cure[b]	265/347	76.4	237/343	69.1
TOC/MITT: Microbiologic Eradication by Patient[c]	228/256	89.1	215/240	89.6
LTFU/ITT: Microbiologic Eradication by Patient[d]	177/347	51.0	166/343	48.4
LTFU/ITT: Clinical Cure[e]	187/347	53.9	170/343	49.6
Clinical Cure Rate[f] Among Clinically Evaluable Patients	164/222	73.8	163/227	71.8

[a] n/N = Number of patients with eradication/total number of patients.
[b] n/N = Number of patients with combined determination of cure/total number of patients.
[c] n/N = Number of patients with eradication/total number of patients.
[d] n/N = Number of patients with continued microbiologic eradication (ie, no relapse)/total number of patients.
[e] n/N = Number of patients with combined determination of cure/total number of patients.
[f] n/N= Number of patients with clinical cures divided by all clinically evaluable patients (microbiologic status irrelevant). See footnote 2 on page 54 for more detailed description.

95% CI for TOC/ITT, microbiologic eradication rate by patient is (-4.36, 10.36).

95% CI for TOC/ITT, clinical cure rate is (-0.36, 14.19).

95% CI for TOC/MITT, microbiologic eradication rate by patient is (-6.36, +5.32).

95% CI for LTFU/ITT, microbiologic eradication rate by patient is (-5.14, 10.36).

95% CI for LTFU/ITT, clinical cure rate, is (-3.41, 12.07).

95% CI for clinical cure rate among clinically evaluable patients is (-6.60, +10.74).

Medical officer's note: The clinical outcomes above, which are not primary endpoints but evaluate several clinical populations (intent-to-treat and modified-intent-to-treat for clinical

cure and microbiologic eradication by patient at both test of cure and long-term follow up) , all meet DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.

Test-of-Cure, Clinical Cure Rate by Patient according to Baseline Pathogens

Table 26. Clinical Cure Rate[a] by Patient (According to Their Baseline Pathogens) at the TOC Visit - Evaluable Patients

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir BID		Cefaclor		Cefdinir BID		Cefaclor	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	5/7	71.4	0/1	0	6/7	85.7	12/14	85.7
Streptococcus pneumoniae	9/9	100.0	13/16	81.3	20/23	87.0	17/19	89.4
Haemophilus influenzae	35/42	83.3	31/44	70.5	25/29	86.2	21/27	77.8
Haemophilus parainfluenzae	40/53	75.5	40/46	87.0	24/31	77.4	29/39	74.4
Escherichia coli	1/1	100.0	3/4	75.0	5/8	62.5	6/7	85.7
Klebsiella pneumoniae	1/2	50.0	1/1	100.0	5/7	71.4	11/13	84.6
Moraxella catarrhalis	4/4	100.0	3/3	100.0	5/6	83.3	5/8	62.5
Total	95/118	80.5	91/115	79.1	87/108	80.6	101/127	79.5
Total, single & multiple isolates	182/226	80.5	192/242	79.3				

n/N = Number of patients who were cured/total number of patients.
[a] Based on combined investigator/sponsor clinical assessments.

95% CI for Clinical Cure Rate at TOC by Patient according to baseline pathogens (single isolates) is (-9.79, +12.54).

Medical officer's note: The clinical cure rate at test of cure by patient according to baseline pathogens meets DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia. The applicant has by this data demonstrated provided enough clinical outcome and microbiologic information to be granted approval for the following pathogens: Streptococcus pneumoniae, Haemophilus influenzae and Haemophilus parainfluenzae.

Long-Term Follow Up, Clinical Cure by Patient according to Baseline Pathogens

Table 27. Clinical Cure Rate by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients (Classified as Cures at TOC)

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir BID		Cefaclor		Cefdinir BID		Cefaclor	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	3/3	100.0	0/0	--	4/4	100.0	11/12	91.7
Streptococcus pneumoniae	6/6	100.0	11/13	84.6	14/15	93.3	12/13	92.3
Escherichia coli	0/0	--	3/3	100.0	4/4	100.0	5/5	100.0
Haemophilus influenzae	29/32	90.6	28/29	96.6	13/14	92.9	20/21	95.2
Haemophilus parainfluenzae	35/36	97.2	30/34	88.2	23/23	100.0	22/22	100.0
Klebsiella pneumoniae	1/1	100.0	1/1	100.0	3/3	100.0	7/8	87.5
Moraxella catarrhalis	4/4	100.0	3/3	100.0	4/4	100.0	5/5	100.0
Total	112/118	94.9	119/129	92.2	65/67	97.0	83/87	95.4
Total, single & multiple isolates	177/185	95.7	202/216	93.5				

n/N = Number of patients who were cured/total number of patients.
[a] Based on combined investigator/sponsor clinical assessments

95% CI for Clinical Cure Rate at LTFU by Patient (single isolate) is (-4.23, 9.56).

Medical officer's note: The clinical cure rate at long-term follow up by patient according to baseline pathogens meets DAIDP's equivalence requirement against an approved comparator for the indication of community acquired pneumonia.

Microbiologic Efficacy

Test-Of-Cure, Microbiologic Eradication by Pathogen

Table 28. Microbiologic Eradication Rate by Baseline Pathogen at the TOC Visit - Pathogens From Evaluable Patients

Baseline Pathogen	Cefdinir BID		Cefaclor	
	n/N	%	n/N	%
Staphylococcus aureus	16/17	94.1	14/15	93.3
Streptococcus pneumoniae	31/31	100.0	35/35	100.0
Escherichia coli	7/9	77.8	9/10	90.0
Haemophilus influenzae, β-lactamase +	11/14	78.6	12/15	80.0
Haemophilus influenzae, β-lactamase -	44/51	86.3	48/57	84.2
Haemophilus parainfluenzae, β-lactamase +	7/8	87.5	4/5	80.0
Haemophilus parainfluenzae, β-lactamase -	74/81	91.4	74/77	96.1
Klebsiella pneumoniae	8/9	88.9	11/11	100.0
Moraxella catarrhalis, β-lactamase +	10/10	100.0	10/10	100.0
Moraxella catarrhalis, β-lactamase -	0/0	--	1/1	100.0
Total	208/230	90.4	218/236	92.3

n/N = Number of pathogens eradicated/total number of pathogens.

95% CI test of cure the microbiologic eradication rate by pathogen is (-7.46, +3.58).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by pathogen at the test-of-cure visit (6 to 14 days posttherapy).

Long Term Follow Up Visit, Microbiologic Eradication by Pathogen

Qualified patients who had persistent pathogens at the TOC were automatically considered to have persistent pathogens at LTFU.

Table 29. Microbiologic Eradication Rate by Baseline Pathogen at the LTFU Visit - Pathogens From Qualified Patients (Classified as Patients With Eradication at TOC)

Baseline Pathogen	Cefdinir BID		Cefaclor	
	n/N	%	n/N	%
Staphylococcus aureus	7/7	100.0	12/12	100.0
Streptococcus pneumoniae	20/20	100.0	27/27	100.0
Escherichia coli	4/4	100.0	7/7	100.0
Haemophilus influenzae, β-lactamase +	11/11	100.0	11/11	100.0
Haemophilus influenzae, β-lactamase -	34/34	100.0	40/40	100.0
Haemophilus parainfluenzae, β-lactamase+	6/6	100.0	4/4	100.0
Haemophilus parainfluenzae, β-lactamase-	50/51	98.0	51/51	100.0
Klebsiella pneumoniae	3/3	100.0	9/9	100.0
Moraxella catarrhalis, β-lactamase +	8/8	100.0	7/7	100.0
Moraxella catarrhalis, β-lactamase -	0/0	--	1/1	100.0
Total	143/144	99.3	169/169	100.0

n/N = Number of pathogens eradicated/total number of pathogens.

95% CI for the Microbiologic Eradication Rate by Pathogen at LTFU is (7.93, +20.26).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by pathogen at long-term follow-up.

Test-Of-Cure, Microbiologic Eradication by Patient

Table 30. Microbiologic Eradication Rate by Patient (According to Their Baseline Pathogens at the TOC Visit - Evaluable Patients

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir BID		Cefaclor		Cefdinir BID		Cefaclor	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	7/7	100.0	1/1	100.0	8/10	80.0	13/14	92.9
Streptococcus pneumoniae	9/9	100.0	16/16	100.0	20/22	90.9	19/19	100.0
Escherichia coli	1/1	100.0	3/4	75.0	6/8	75.0	5/5	100.0
Haemophilus influenzae	36/42	85.7	35/44	79.5	20/21	95.2	24/27	88.9
Haemophilus parainfluenzae	46/53	86.8	43/46	93.5	34/36	94.4	34/36	94.4
Klebsiella pneumoniae	2/2	100.0	1/1	100.0	4/7	57.1	9/10	90.0
Moraxella catarrhalis	4/4	100.0	3/3	100.0	6/6	100.0	8/8	100.0
Total	159/179	88.8	162/180	90.0	98/112	87.5	112/119	94.1
Total, single & multiple isolates	257/291	88.3	274/299	91.6				

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

95% CI for the Microbiologic Eradication Rate by Patient (single isolate) at TOC is (-8.09, +5.75).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by patient at the test-of-cure visit (6 to 14 days posttherapy).

At the TOC visit, 20 evaluable cefdinir BID-treated patients had 22 persistent pathogens and 19 evaluable cefaclor-treated patients had 19 persistent pathogens. All persistent pathogens were susceptible to study medication at baseline and most (39/41) remained susceptible at TOC. Two isolates of *H. influenzae* that were susceptible at baseline were intermediately susceptible at TOC; one came from a cefdinir BID-treated patient and the other from a cefaclor-treated patient.

Long Term Follow Up Visit, Microbiologic Eradication by Patient

Table 31. Microbiologic Eradication by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients (Classified as Patients With Eradication at TOC)

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir BID		Cefaclor		Cefdinir BID		Cefaclor	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	4/4	100.0	0/0	–	3/3	100.0	12/12	100.0
Streptococcus pneumoniae	6/6	100.0	13/13	100.0	14/14	100.0	15/15	100.0
Escherichia coli	0/0	–	2/2	100.0	13/13	100.0	19/19	100.0
Haemophilus influenzae	33/33	100.0	29/29	100.0	20/20	100.0	22/22	100.0
Haemophilus parainfluenzae	35/36	97.2	31/31	100.0	4/4	100.0	3/3	100.0
Klebsiella pneumoniae	1/1	100.0	1/1	100.0	2/2	100.0	6/6	100.0
Moraxella catarrhalis	4/4	100.0	3/3	100.0	4/4	100.0	4/4	100.0
Total	116/117	99.1	126/126	100.0	60/60	100.0	89/89	100.0
Total, single & multiple isolates	176/177	99.4	215/215	100.0				

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

95% CI for Microbiologic Eradication Rate by Patient (single isolate) at LTFU is (-3.35, +1.64).

Medical officer's note: Thus, criteria to demonstrate equivalence is met by microbiologic eradication rate by patient at the long-term follow up.

Test of Cure and Long-Term Follow Up Visit, Modified Intent-to-Treat Analysis

Table 32. Microbiologic Efficacy at TOC and LTFU -- MITT and ITT Populations

Parameter	Cefdinir BID		Cefaclor	
	n/N[a]	%	n/N	%
TOC/MITT: Microbiologic Eradication by Pathogen[a]	339/369	91.9	313/338	92.6
TOC/ITT: Microbiologic Eradication by Pathogen[a]	347/387	89.7	323/385	83.9
LTFU/ITT Microbiologic Eradication by Pathogen[a]	263/387	68.0	252/385	65.5

[a] n/N = Number of pathogens eradicated/total number of pathogens.

95% CI for microbiologic eradication rate by pathogen at TOC/MITT is (-4.96, +3.49).

95% CI for microbiologic eradication rate by pathogen at TOC/ITT is (-0.75, +10.79).

95% CI for microbiologic eradication rate by pathogen at LTFU/ITT is (-4.40, 9.41).

Medical officer's note: Equivalence is demonstrated for microbiologic eradication rates by pathogen for modified intent to treat at test of cure and for intent to treat at test of cure and long term follow up.

Test of Cure, Microbiologic versus Clinical Response Rates

Table 33. Microbiologic Versus Clinical Response at the Test-of-Cure Visit - Evaluable Patients (%)

Microbiologic Response	Clinical Response	
	Cure[a]	Failure
Cefdinir BID, N = 187		
Patients With Eradication	142 (75.9)	25 (13.4)
Patients With Persistence	8 (4.3)	12 (6.4)
Cefaclor, N = 186		
Patients With Eradication	140 (75.2)	27 (14.5)
Patients With Persistence	7 (3.8)	12 (6.4)

[a] Combined investigator/sponsor clinical determination

Medical officer's note: The rates of microbial persistence despite clinical cure, clinical failure with microbial eradication, clinical cure with microbial eradication, and clinical failure with microbial persistence are similar across both treatment arms.

At baseline, eight cefdinir BID- and six cefaclor-treated patients had *S. pneumoniae* isolates that were resistant (or intermediately susceptible) to penicillin (MIC ≥0.1 μg/mL). Despite this fact, all of the cefdinir BID- and cefaclor-treated patients had *S. pneumoniae* eradicated, and most (6/8) cefdinir BID- and all cefaclor-treated patients were assessed as clinical cures at TOC.

Medical officer's note: The numbers of resistant or intermediately resistant S. pneumoniae are very small and conclusions cannot be drawn. However, the applicant is not seeking labeling for resistant or intermediately resistant S. pneumoniae and the issue requires no further consideration here.

Superinfections. In this study, 3% (12) of cefdinir BID-treated and 6% (20) of cefaclor-treated patients had one or more superinfecting pathogens at the TOC visit. Most superinfecting pathogens were susceptible or intermediately susceptible to cefdinir (12 of 14 isolates) and cefaclor (23 of 29). Those isolates that were resistant to cefdinir included *Enterobacter cloacae* and *Pseudomonas aeruginosa*, while those resistant to cefaclor included *Acinetobacter calcoaceticus* var *anitratus*, *Enterobacter agglomerans*, *E. cloacae*, *P. aeruginosa*, *Pseudomonas fluorescens*, and *Pseudomonas putida*.

Table 34. Patients With Superinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir BID N = 347	Cefaclor N = 343
Gram-Positive[a]		
Streptococcus pneumoniae	0	1
Gram-Negative[a]		
Acinetobacter calcoaceticus var *lwoffi*	1	0
Haemophilus haemolyticus	0	1
Haemophilus influenzae	1	1
Haemophilus parainfluenzae	6	7
Klebsiella pneumoniae	0	1
Pseudomonas aeruginosa	1	0
Pseudomonas fluorescens	0	1
Proteus mirabilis	1	0
Multiple[b]	2	8
Total	12 (3.5%)	20 (5.8%)

[a] Pathogens appearing as sole superinfecting pathogens
[b] Applicant's Appendix C.73 has complete summary of patients with multiple pathogens.

Medical officer's note: Development of superinfection was not a common event and similar across both arms.

Reinfections. Two patients in the cefdinir BID treatment group and one patient in the cefaclor treatment group had reinfections. For the cefdinir BID group, reinfecting pathogens included *M. catarrhalis* and *S. pneumoniae* plus *H. parainfluenzae*; for cefaclor they included *S. agalactiae* plus *M. catarrhalis*.

Medical officer's note: Development of reinfection was uncommon event and similar across both arms.

Safety

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

Adverse Events. Any symptom (except those related to community-acquired pneumonia) or clinically significant concurrent illness not present at baseline which was reported by the patient/guardian or noted by the investigator was recorded as an adverse event. Worsening of pneumonia was also considered an adverse event if hospitalization was required, and abnormal clinical laboratory values could be designated as adverse events at the discretion of the

investigator.

Each adverse event reported by a patient or noted by an investigator was recorded on a CRF. Adverse events were evaluated by the investigator for relationship to drug (definitely, probably, possibly, unlikely, definitely not, or insufficient information); intensity (mild, moderate, or severe); duration; frequency; management of study medication; patient outcome (at last visit); and presence, frequency, and intensity relative to baseline. Drug-associated adverse events were those considered definitely, probably, or possibly related to study medication by the investigator.

Adverse events were considered serious if they were fatal, immediately life-threatening, severely or permanently disabling, required or prolonged hospitalization, or were an intentional or accidental overdose, a congenital anomaly, or cancer. Unexpected or serious adverse events were reported to the study manager throughout the study. During the medical review, other events could be identified as serious even if they did not meet the above definition. These other events could include:

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

Beginning December 1, 1992 (approximately 11 months after the study started), patients who discontinued treatment due to diarrhea were to be tested for *Clostridium difficile.*

Medical officer's note: The above description of safety evaluation is acceptable and should be capable of capturing ADRs of interest, particularly those associated with other cephalosporins which would also be expected with cefdinir.

Safety data were summarized for all patients who received study medication. For the cefdinir BID and cefaclor treatment groups, a CMH analysis, adjusting for center, was used to compare the rates (i.e., incidence) of all adverse events, drug-associated adverse events, diarrhea, and treatment discontinuations due to adverse events. Results of the Breslow-Day test were reviewed

in evaluating the consistency of the relationship between adverse events and treatment among centers.

The most frequently reported adverse events for patients treated with cefdinir BID included diarrhea (15%), headache (8%), nausea (3%), and rash (3%); and with cefaclor, diarrhea (6%), headache (5%), and rash (3%). When the incidence of diarrhea was not included in the analyses, there was no statistical difference between the two treatment groups in the numbers of patients experiencing adverse events ($p = 0.129$) or drug-associated adverse events ($p = 0.598$).

Twenty (6%) patients treated with cefdinir BID and 15 (4%) treated with cefaclor discontinued treatment due to an adverse event. After completing treatment, an additional four cefdinir BID- and four cefaclor-treated patients withdrew due to an adverse event. There was no statistical difference in the rates of treatment discontinuation between the two treatment groups ($p = 0.334$).

Seventeen (5%) cefdinir BID-treated patients and 15 (4%) cefaclor-treated patients experienced a serious adverse event. An additional patient in each of these treatment groups experienced a serious adverse event without ever receiving study medication; these two patients experienced worsening pneumonia that required hospitalization, a serious adverse event in this study. Six deaths occurred, three each in the cefdinir BID and cefaclor treatment groups.

Clinical laboratory abnormalities were transient and sporadic, and many of the markedly abnormal laboratory values were those commonly seen in patients treated with other β-lactam antibacterials. There were more cefdinir BID-treated patients who had markedly abnormal laboratory values than cefaclor-treated patients, but the overall rate at which markedly abnormal laboratory values occurred was similar for both groups (16% versus 13%).

Table 35. Summary of Adverse Events -- All Patients
[Number (%) of Patients]

	Cefdinir QD N = 14		Cefdinir BID N = 344		Cefaclor N = 340	
Adverse Events During Study						
All Adverse Events	5	(35.7)	168	(48.8)	130	(38.2)
Associated[a] Adverse Events	3	(21.4)	80	(23.3)	55	(16.2)
Adverse Events by Sex[b]						
All Adverse Events						
Male	3	(42.9)	98	(51.0)	83	(43.7)
Female	2	(28.6)	70	(46.1)	47	(31.3)
Associated Adverse Events						
Male	3	(42.9)	46	(24.0)	35	(18.4)
Female	0	(0.0)	34	(22.4)	20	(13.3)
Adverse Events by Race[c]						
All Adverse Events						
White	4	(33.3)	145	(48.8)	114	(39.9)
Black	1	(50.0)	13	(43.3)	13	(29.5)
Asian	0	(0.0)	3	(100.0)	0	(0.0)
Hispanic	0	(0.0)	5	(41.7)	2	(25.0)
Other	0	(0.0)	2	(100.0)	1	(100.0)
Associated Adverse Events						
White	2	(16.7)	73	(24.6)	51	(17.8)
Black	1	(50.0)	4	(13.3)	3	(6.8)
Asian	0	(0.0)	2	(66.7)	0	(0.0)
Hispanic	0	(0.0)	0	(0.0)	0	(0.0)
Other	0	(0.0)	1	(50.0)	1	(100.0)
Adverse Events by Age[d]						
All Adverse Events						
13 to <18 yr	0	(0.0)	4	(40.0)	3	(37.5)
18 to <65 yr	5	(50.0)	126	(50.0)	92	(35.2)
≥65 yr	0	(0.0)	38	(46.3)	35	(49.3)
Associated Adverse Events						
13 to <18 yr	0	(0.0)	3	(30.0)	1	(12.5)
18 to <65 yr	3	(30.0)	63	(25.0)	43	(16.5)
≥65 yr	0	(0.0)	14	(17.1)	11	(15.5)
Adverse Events by Maximum Intensity[e]						
All Adverse Events						
Mild	4	(28.6)	107	(31.1)	90	(26.5)
Moderate	1	(7.1)	76	(22.1)	54	(15.9)
Severe	0	(0.0)	21	(6.1)	10	(2.9)
Associated Adverse Events						
Mild	2	(14.3)	58	(16.9)	41	(12.1)
Moderate	1	(7.1)	30	(8.7)	17	(5.0)
Severe	0	(0.0)	5	(1.5)	1	(0.3)
Serious Adverse Events[f]	0	(0.0)	17	(4.9)	15	(4.4)

Deaths	0	(0.0)	3	(0.9)	3	(0.9)
Discontinuation of Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	20	(5.8)	15[g]	(4.4)
Associated Adverse Events	0	(0.0)	10	(2.9)	6	(1.8)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	4	(1.2)	4	(1.2)
Associated Adverse Events	0	(0.0)	1	(0.3)	0	(0.0)
Associated Adverse Events	0	(0.0)	10	(2.9)	6	(1.8)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	4	(1.2)	4	(1.2)
Associated Adverse Events	0	(0.0)	1	(0.3)	0	(0.0)

[a] Considered by the investigator to be possibly, probably, or definitely related to study medication.
[b] Percentages based on total numbers of males or females in a treatment group
[c] Percentages based on total numbers of patients of each race in a treatment group
[d] Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.
[e] Patients with multiple adverse events were counted once in each applicable category.
[f] Two additional patients (one cefdinir BID- and one cefaclor-treated) who did not receive study medication experienced a serious adverse event and are not included in the safety summary tables.
[g] One patient discontinued due to a non-TESS adverse event.

Regardless of whether patients received cefdinir or cefaclor, most adverse events were related to the digestive system, body as a whole, the respiratory system, skin and appendages, and the nervous system. Most of the adverse events related to the digestive system were considered drug-associated by the investigator. Significantly more cefdinir BID-treated patients experienced adverse events ($p = 0.004$) and drug-associated adverse events ($p = 0.011$) than cefaclor-treated patients.

The most frequently reported adverse events for patients treated with cefdinir BID included diarrhea (15%), headache (8%), nausea (3%), and rash (3%); and with cefaclor, diarrhea (6%), headache (5%), and rash (3%).

Statistically, there was a significant difference in the rates of diarrhea when the cefdinir BID and cefaclor treatment groups were compared ($p < 0.001$). However, when diarrhea was not included in the analyses, there was no significant difference between the treatment groups in the numbers of patients experiencing adverse events ($p = 0.129$) or drug-associated adverse events ($p = 0.598$).

Medical officer's note: The side effect profile of cefdinir is not unexpected. Other newer cephalosporins have also been observed to have higher rates of diarrhea and gastrointestinal effects. The Applicant proposed to evaluate all patients withdrawn from study for diarrhea for Clostridium difficile-associated diarrhea beginning 12/1/92. Three patients were withdrawn but

the investigators failed to perform such testing. Among those patients reporting diarrhea as an ADR, the investigator consider the event mild in 75% of cases and only 2% were characterized as severe. Age and sex did not appear to be related to the occurrence of diarrhea. The remaining ADR profile resembles other cephalosporins, including the comparator arm.

Table 36. All and Associated[a] Adverse Events by Body System - Patients Receiving Study Medication [Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 14				Cefdinir BID[b] N = 344				Cefaclor N = 340			
	All		Associated		All		Associated		All		Associated	
DIGESTIVE SYSTEM	3[c]	(21.4)	3[c]	(21.4)	77[c]	(22.4)	60[c]	(17.4)	41[c]	(12.1)	33	(9.7)
Diarrhea	3	(21.4)	3	(21.4)	52	(15.1)	46	(13.4)	20	(5.9)	1	(5.6)
Nausea	1	(7.1)	1	(7.1)	11	(3.2)	10	(2.9)	7	(2.1)	5	(1.5)
Vomiting	0	(0.0)	0	(0.0)	8	(2.3)	5	(1.5)	5	(1.5)	4	(1.2)
Flatulence	0	(0.0)	0	(0.0)	5	(1.5)	2	(0.6)	1	(0.3)	1	(0.3)
Anorexia	0	(0.0)	0	(0.0)	4	(1.2)	3	(0.9)	4	(1.2)	3	(0.9)
Dyspepsia	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.6)	4	(1.2)	3	(0.9)
Gastroenteritis	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Liver Function Tests Abnormal	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.6)	1	(0.3)	1	(0.3)
Melena	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)
Rectal Hemorrhage	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Constipation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.6)	1	(0.3)
Jaundice	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Mouth Ulceration	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Rectal Disorder	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Aphthous Stomatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Dry Mouth	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Dysphagia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Eructation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
BODY AS A WHOLE	1	(7.1)	0	(0.0)	59[c]	(17.2)	16	(4.7)	41[c]	(12.1)	12[c]	(3.5)
Headache	1	(7.1)	0	(0.0)	26	(7.6)	13	(3.8)	17	(5.0)	7	(2.1)
Back Pain	0	(0.0)	0	(0.0)	6	(1.7)	1	(0.3)	5	(1.5)	1	(0.3)
Infection	0	(0.0)	0	(0.0)	6	(1.7)	0	(0.0)	5	(1.5)	0	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	5	(1.5)	2	(0.6)	4	(1.2)	3	(0.9)
Chest Pain	0	(0.0)	0	(0.0)	4	(1.2)	0	(0.0)	2	(0.6)	0	(0.0)
Neck Pain	0	(0.0)	0	(0.0)	3	(0.9)	0	(0.0)	2	(0.6)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	3	(0.9)	0	(0.0)	4	(1.2)	0	(0.0)
Abscess	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Accidental Injury	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	3	(0.9)	0	(0.0)
Allergic Reaction	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Asthenia	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)	2	(0.6)	1	(0.3)
Cellulitis	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cyst	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Face Edema	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Fever	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Hernia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Photosensitivity Reaction	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Generalized Edema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Malaise	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
RESPIRATORY SYSTEM	1	(7.1)	0	(0.0)	32[c]	(9.3)	0	(0.0)	35	(10.3)	0	(0.0)
Rhinitis	0	(0.0)	0	(0.0)	8	(2.3)	0	(0.0)	9	(2.6)	0	(0.0)

Sinusitis	1	(7.1)	0	(0.0)	7	(2.0)	0	(0.0)	3	(0.9)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	4	(1.2)	0	(0.0)	3	(0.9)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	4	(1.2)	0	(0.0)	5	(1.5)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	3	(0.9)	0	(0.0)	3	(0.9)	0	(0.0)
Carcinoma of Lung	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	2	(0.6)	0	(0.0)
Epistaxis	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Asthma	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	5	(1.5)	0	(0.0)
Dyspnea	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Lung Disorder	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Sputum Increased	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cough Increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Pleural Effusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Voice Alteration	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
SKIN AND APPENDAGES	0	(0.0)	0	(0.0)	19	(5.5)	10	(2.9)	12[c]	(3.5)	6	(1.8)
Rash	0	(0.0)	0	(0.0)	10	(2.9)	6	(1.7)	10	(2.9)	5	(1.5)
Sweating	0	(0.0)	0	(0.0)	4	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	3	(0.9)	3	(0.9)	1	(0.3)	0	(0.0)
Urticaria	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)
Acne	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Contact Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
NERVOUS SYSTEM	0	(0.0)	0	(0.0)	15[c]	(4.4)	4[c]	(1.2)	13[c]	(3.8)	2	(0.6)
Dizziness	0	(0.0)	0	(0.0)	3	(0.9)	2	(0.6)	7	(2.1)	2	(0.6)
Insomnia	0	(0.0)	0	(0.0)	3	(0.9)	1	(0.3)	2	(0.6)	0	(0.0)
Abnormal Dreams	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Acute Brain Syndrome	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Confusion	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Depersonalization	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Hallucinations	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hemiplegia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertonia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Hypesthesia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Anxiety	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Tremor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
SPECIAL SENSES	0	(0.0)	0	(0.0)	9[c]	(2.6)	1	(0.3)	15	(4.4)	3	(0.9)
Ear Disorder	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Eye Pain	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis Media	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)	2	(0.6)	0	(0.0)
Abnormal Vision	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Amblyopia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Pain	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	6	(1.8)	0	(0.0)
Tinnitus	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)
Eye Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Otitis Externa	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Taste Perversion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
METABOLIC AND NUTRITIONAL DISORDERS	0	(0.0)	0	(0.0)	8[c]	(2.3)	2[c]	(0.6)	6	(1.8)	3	(0.9)
Dehydration	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral Edema	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Blood Urea Nitrogen Increased	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Hyperglycemia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
AST Increased	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)

ALT Increased	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	1	(0.3)	1	(0.3)
Weight Gain	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Edema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Gout	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Hypoglycemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
UROGENITAL SYSTEM	1[c]	(7.1)	0	(0.0)	8[c]	(2.3)	2	(0.6)	6	(1.8)	3	(0.9)
Urinary Tract Infection	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Vaginal Moniliasis	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.6)	3	(0.9)	3	(0.9)
Kidney Calculus	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Prostatic Disorder	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary Frequency	1	(7.1)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Urination Impaired	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dysmenorrhea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Polyuria	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR SYSTEM	1	(7.1)	0	(0.0)	5[c]	(1.5)	0	(0.0)	9[c]	(2.6)	3	(0.9)
Atrial Fibrillation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)
Hypotension	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial Infarct	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial Ischemia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Palpitation	1	(7.1)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.3)
Arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Cardiomyopathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Congestive Heart Failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Heart Arrest	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Heart Failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Vasodilation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
HEMIC AND LYMPHATIC SYSTEM	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	3	(0.9)	1	(0.3)
Lymphadenopathy	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cyanosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Ecchymosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Thrombocythemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
MUSCULOSKELETAL SYSTEM	0	(0.0)	0	(0.0)	1[c]	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)
Arthralgia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0	0	(0.0)
Myopathy	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Bone Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)

[a] Possibly, probably, or definitely related to treatment

[b] All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.

[c] The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Deaths: Six deaths occurred in the study; three in each arm. All were believed definitely unrelated to treatment by the investigators.

Table 37. Deaths - All Patients

Treatment	Center	Patient Number	Age (yr), Sex	Cause of Death[a]	Relationship to Study Medication[b]	Study Day Drug Discontinued	Study Day Patient Died
Cefdinir BID	7	12	29, M	Left Upper Lobe Pneumonia (Pneumonia)	Definitely Not	10	49
	13	2	69, M	Adenocarcinoma of the Lung (Carcinoma of Lung)	Definitely Not	11	212
	27	58	75, M	Jakob-Creutzfeldt Disease (Acute Brain Syndrome	Definitely Not	10	41
Cefaclor	13	7	78, M	Pulmonary Edema (Lung Edema)	Definitely Not	—[c]	—[c]
	27	5	86, M	Cardiopulmonary Arrest (Heart Arrest)	Definitely Not	11	15
	63	85	68, M	Lung Cancer (Carcinoma of Lung)	Definitely Not	3	3

[a] When the investigator term and COSTART term differ, the COSTART adverse event term appears in parentheses.
[b] As determined by the investigator
[c] Patient died before receiving study medication.

Medical officer's note: The only death of concern is patient 12 at center 7. The patient had an uncomplicated medical history and review of the CRF suggests patient presented with a LLL pneumonia due to Haemophilus influenzae which responded to therapy. About 29 days after discharge, patient presented with a LUL pneumonia and died 10 days later. It appears the events are entirely unrelated.

Serious Adverse Events. Seventeen (5%) patients receiving cefdinir BID and 15 (4%) receiving cefaclor experienced serious adverse events. Only was one patient believed to have a serious adverse event related due to cefdinir; this was a patient with multiple other medical problems who experienced abdominal pain, diarrhea, nausea and vomiting characterized by the investigator as "mild". No serious adverse events were attributed to cefaclor.

Withdrawals due to Adverse Events. The following table summarizes adverse events leading to study discontinuations and withdrawals. Diarrhea, nausea, vomiting and pneumonia were the most common reasons for discontinuing treatment with cefdinir; pneumonia and rash were the most common reasons for discontinuing cefaclor. Overall, 20 (6%) of patients on cefdinir withdrew due to an adverse event and 14 (4%) on cefaclor withdrew due to an adverse event. Four patients in each treatment arm with between end of therapy and LTFU; half of these patients required additional antibiotics for respiratory infection.

Table 38. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Receiving Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir BID N = 344		Cefaclor N = 340	
DIGESTIVE SYSTEM	7[a]	(2.0)	3[a]	(0.9)
Diarrhea	3	(0.9)	0	(0.0)
Nausea	3	(0.9)	2	(0.6)
Vomiting	3	(0.9)	2	(0.6)
Dyspepsia	1	(0.3)	0	(0.0)
Liver Function Tests Abnormal	1	(0.3)	0	(0.0)
RESPIRATORY SYSTEM	6[a]	(1.7)	8	(2.4)
Pneumonia	3	(0.9)	3	(0.9)
Carcinoma of Lung	1	(0.3)	1	(0.3)
Dyspnea	1	(0.3)	0	(0.0)
Lung Disorder	1	(0.3)	1	(0.3)
Sinusitis	1	(0.3)	1	(0.3)
Bronchitis	0	(0.0)	1	(0.3)
Pleural Effusion	0	(0.0)	1	(0.3)
BODY AS A WHOLE	4	(1.2)	2	(0.6)
Abdominal Pain	2	(0.6)	0	(0.0)
Accidental Injury	1	(0.3)	0	(0.0)
Hernia	1	(0.3)	0	(0.0)
Abscess	0	(0.0)	1	(0.3)
Infection	0	(0.0)	1	(0.3)
CARDIOVASCULAR SYSTEM	3	(0.9)	1	(0.3)
Atrial Fibrillation	1	(0.3)	0	(0.0
Myocardial Infarct	1	(0.3)	0	(0.0)
Myocardial Ischemia	1	(0.3)	0	(0.0)
Heart Arrest	0	(0.0)	1	(0.3)
METABOLIC AND NUTRITIONAL	3	(0.9)	1	(0.3)
Dehydration	1	(0.3)	0	(0.0)
Hyperglycemia	1	(0.3)	0	(0.0)
Weight Gain	1	(0.3)	0	(0.0)
Gout	0	(0.0)	1	(0.3)
NERVOUS SYSTEM	3	(0.9)	0	(0.0)
Confusion	1	(0.3)	0	(0.0)
Hallucinations	1	(0.3)	0	(0.0)
Somnolence	1	(0.3)	0	(0.0)
SKIN AND APPENDAGES	2	(0.6)	4	(1.2)
Rash	2	(0.6)	3	(0.9)

Contact Dermatitis	0 (0.0)	1 (0.3)

* The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Medical officer's note: There are no unexpected findings here; abdominal complaints are again prominent in the cefdinir arm.

Clinical Laboratory Values. Baseline specimens for each patient's clinical laboratory parameters (hematology, blood chemistry, and urinalysis) were to be collected prior to the receipt of study medication. At the TOC visit, clinical laboratory tests were repeated and these values were compared to standard normal values and the patient's baseline values. Significantly abnormal values at TOC visit were repeated until the abnormality resolved or a reason for the abnormality was determined.

Clinical laboratory test results were examined by three methods: median changes from baseline, category shift changes, and markedly abnormal values at the first posttherapy visit (i.e., typically the TOC visit).

Medical officer's note: No clinically significant changes were noted that were attributed to cefdinir alone; there were slightly more increases and decreases in platelet counts and bicarbonate levels and more decreases than increases in bacterial urine count. Most changes observed in this analysis related to resolution of infection, such as decreases in white blood cell count and PMNs and were seen across both arms. Although all patients who received medication were evaluated for safety in this study, the total number enrolled is only 704. There are no safety signals detectable upon review of this study. This reviewer will perform an integrated safety for this formulation on all submitted studies which will offer more ability to detect smaller changes.