Reviewers' conclusions regarding NDA 50-739, Protocol 983-4, Pivotal Study submitted in support of approval for community acquired pneumonia indication.

Multiple methods and outcomes were evaluated, and with respect to both clinical and microbiologic efficacy, cefdinir 300 milligrams po BID is equivalent to cefaclor 500 milligrams po TID in the treatment of community acquired pneumonia.

Study 983-4 alone provides enough microbiologic support the the approval cefdinir to treat community acquired pneumonia caused by *Streptococcus pneumoniae*, β-lactamase (-) *Haemophilus influenzae* and β-lactamase (-) *Haemophilus parainfluenzae*. Insufficient evidence is available to support claims of efficacy against *Staphylococcus aureus* and *Streptococcus pyogenes*. Numbers were entirely insufficient for *Streptococcus pyogenes*; only one patient with *Streptococcus pyogenes* was treated with cefdinir in this study. There is little evidence to solidly support *Staphylococcus aureus* as the sole etiologic agent in the 17 patients from whom this pathogen was isolated.

The safety profile of both treatment arms also is very similar and not unlike other cephalosporins. The singular difference which appears is the greater occurrence of diarrhea in patients treated with cefdinir. A more powerful analysis of safety issues will be offered by an integrated safety analysis which will conclude the review of this NDA. Diarrhea will be evaluated there.

Medical officer's note: *Most of the following text has been duplicated from the Applicant's submission as the CANDA allow for copying pieces of the submission. The medical officer's comments appear in the notes. This is the second and final pivotal study supporting the Applicant's community acquired pneumonia submission.*

Indication: Community Acquired Pneumonia

Title and Study Number: A Phase 3, 10-day, investigator-blind, randomized, comparative, multi center study of cefdinir (CI-983) versus amoxicillin/clavulanate in the treatment of community-acquired bacterial pneumonia (Protocol 983-26)

Objective: The objective of this study was to evaluate the efficacy and safety of cefdinir (300 mg BID) versus amoxicillin/clavulanate (Augmentin®) (500 mg TID) in the treatment of patients with community-acquired bacterial pneumonia.

Study Design: This study was conducted at 35 centers in 9 countries including Canada, Australia and South Africa in addition to centers in western Europe. All centers used similarly amended protocols and identical case report forms (CRFs). This study was conducted in compliance with the Good Clinical Practice Guidelines of the United States Food and Drug Administration (FDA) and European Community Good Clinical Practice Guidelines, and according to the Declaration of Helsinki. An ethics committee or institutional review board (IRB) approval was obtained at each center before the study began. Before enrollment, each patient or guardian was informed of the study objectives and was required to provide written informed consent.

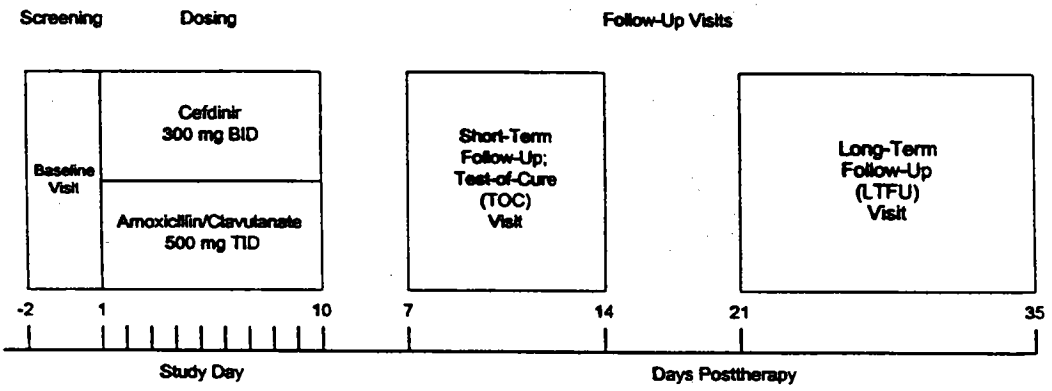

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Figure 3. Protocol 983-26 Study Design

Medical officer's note: *Protocol 983-26, submitted as the Applicant's second pivotal study, is identical to the preceding domestic study in design. There are only three differences: (1) protocol 983-26 took place at centers in Europe, South Africa, Australia and Canada; (2) protocol 983-26 was investigator blinded, whereas protocol 983-4 was double dummy blinded; and (3) protocol 983-26 used amoxicillin/clavulanate 500 mg po TID was used as the comparator arm and protocol 983-4 used cefaclor 300 mg po BID.*

An independent randomization schedule was prepared for each study center. The planned treatment group ratio at each site was 1:1 for cefdinir (300 mg BID) and amoxicllin/clavulanate (500 mg TID). A block size of 4 patients was used, with 2 treatment replicates per block.

Medical officer's note: *Unlike protocol 983-4, protocol 983-26 adhered to original randomization schedule because it was originally designed as a two-armed study, not a three armed study including cefdinir 600 mg po qd.*

Population and Inclusion/Exclusion Criteria: The population is identical to that of protocol 983-4; see review of study 983-4 preceding this review..

The following were the exclusion criteria for protocol 983-26 that differed from the exclusion criteria for protocol 983-4. See review of study 983-4 preceding this review.

Patients with acute pseudomembranous colitis or a history of pseudomembranous colitis;

- Hospitalized or institutionalized patients, as well as patients who had been hospitalized within the preceding 4 weeks;
- Patients who had received another systemic antibacterial agent within a specified time period prior to the anticipated first dose of study medication. The specified period was 48 hours, or 5 half-lives of the antibacterial agent, whichever was longer.

Medical officer's note: *With respect to population evaluated, inclusion and exclusion criteria, protocol 983-26 is identical to protocol 983-4 with the exception of the minor items which are detailed above. Protocol 983-4 did not exclude patients with acute pseudomembranous colitis or a history of pseudomembranous colitis; or hospitalized or institutionalized patients, as well as patients who had been hospitalized within the preceding 4 weeks. In addition, rather than the excluding duration of another systemic antibacterial being less than 48 hours, it was less than 7 days. However, both protocols were amended to include the 5 half-lives and conformed that way. The medical reviewer sees these differences as extremely minor, and the two trials entirely comparable and population studied and inclusion/exclusion criteria are acceptable.*

Evaluability Criteria:

When patients were discontinued early, the following were to be completed: sputum culture and susceptibility testing, chest x-ray, clinical evaluation (i.e., assessment of signs and symptoms as well as an overall assessment of clinical efficacy), physical examination, clinical laboratory tests, as well as records of adverse events.

Medical officer's note: The evaluability criteria for protocol 983-26 are identical to those for protocol 983-4 with the exception of obtaining a chest x-ray on discontinued patients in protocol 983-26 (as bolded and underlined above). On these grounds, the two studies are again directly comparable and evaluability criteria are acceptable.

Laboratories were instructed to use testing procedures that conformed with National Committee for Clinical Laboratory Standards (NCCLS) guidelines. **However, use of other appropriate local guidelines was acceptable, as culture and susceptibility test results from European clinical laboratories have been shown to be similar to those produced with NCCLS reference methods**. MIC trays and discs for cefdinir were supplied by Parke-Davis.

Medical officer's note: The microbiologic breakpoints, by both dilution and diffusion techniques, conform to those adhered to in protocol 983-4. No mention is made in this report of the special case of susceptibility testing for S. pneumoniae (i.e., whether oxacillin disc testing for a zone size of ≥ 20 mm or oxacillin diffusion inhibitory concentration of ≤ 0.06 µg/mL is construed as penicillin susceptible and therefore cefdinir susceptible). Inquiry was made from Dr. Altaie (DAIDP microbiology reviewer) as to the adequacy of the microbiologic evaluation in this protocol. She reviewed the testing, including the susceptibility testing of S. pneumoniae, and believes that the techniques used were adequate and comparable to the studies performed in the United States. Hence, pathogen eradication in 983-26 is comparable to 983-4 and isolates can be used to count for numbers of critical pathogens evaluated.

Endpoints Defined (Clinical and Microbiological): The following table, duplicated form the Applicant's submission, described what data was collected and at what visits.

Table 38. Schedule of Clinical Observations and Laboratory Measurements

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

[a] Prior to treatment (within 48 hours of therapy initiation)
[b] Also to be performed whenever therapy was discontinued early.
[c] Not required for patients showing significant radiologic improvement at previous visit
[d] Parameters to be assessed are listed in the protocol.
[e] Performed only if abnormalities were detected at the previous visit.

Medical officer's note: *See similar schedule for protocol 983-4 on page 45 of this review. The only differences, which are quite minor, present in this schedule are: (1) chest x-ray at LTFU visit was not required among those patients demonstrating significant improvement at TOC in protocol 983-26; and (2) blood cultures could be drawn in 983-26 at the discretion of the investigator; no blood culture data was obtained in protocol 983-26. This reviewer considers these differences to be so minor as to be inconsequential.*

Specimens were collected for culture at the baseline, **Days 3 through 5**, TOC, and LTFU visits.

Medical officer's note: *With respect to microbiologic endpoints, protocol 983-4 is identical to 983-26 except for the additional culture noted above. As this is not an endpoint for analysis, it is of no consequence to outcome.*

Clinical Outcomes.

Medical officer's note: *Protocol 983-26 is similar to protocol 983-4 with respect to the investigator's assessment of clinical endpoints. However, there is a single major difference in*

that protocol 983-26 does not include an "improvement" category assigned by the investigator. Thus, the patient assignment by investigator has no ambiguous clinical outcome between "cure" and "failure". In many ways this is an improvement. However, because the major clinical outcome of interest is the same scoring algorithm employed by the Applicant in protocol 983-4, the studies are directly comparable based on Applicant's use of this clinical scoring system (see protocol 983-4, page 48, Medical officer's note and text following the note up to page 49.

As stated in description of protocol 983-4, the medical reviewer believes this to be a fair and unbiased method with which to assign clinical outcome. Review of protocol 983-4 demonstrated consistent adherence to this clinical algorithm. Thus, the medical reviewer believes this to be an entirely acceptable method. The difference in use of the algorithm is clarified below: there is no category for "improvement" assigned by the investigator. For comparison, see table on page 49 of review for protocol 983-4.

TABLE 39. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU[a,b]

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

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

[a] The combined assessments are shown in bold typeface.

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

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

Medical officer's note: *Protocol 983-26 is almost identical to protocol 983-4 with respect to the clinical endpoints. The singular difference being the elimination of an investigator assigned "improvement" category. However, use of the clinical algorithm is the same and consistent, and this medical reviewer believes these the two protocols are comparable.*

Statistical Considerations: This investigator-blind, comparative study of cefdinir versus amoxicillin/clavulanate was designed with a sample size of 112 evaluable patients per randomized treatment group for a total of 224 evaluable patients based on an assumed 90% microbiologic eradication rate for each randomized group. Equivalence was to be assessed by comparing a one-tailed 95% confidence interval (CI) for the difference (cefdinir minus amoxicillin/clavulanate) in microbiologic eradication rates to a set of predetermined, fixed criteria for equivalence. Sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and amoxicillin/clavulanate microbiologic eradication rates at TOC.

Study centers contributing 8 or fewer patients, or 2 or fewer patients in any treatment group, were pooled for center-adjusted analyses (except that for the ITT analysis by pathogen, the same pooling rule applied to the number of available pathogens).

Medical officer's note: *Statistical treatment for protocol 983-26 was identical to protocol 983-4. The only difference is the smaller size of protocol 983-26.*

Analysis populations for efficacy examined in this report include the evaluable (defined as patients who were microbiologically *and* clinically evaluable), the clinically evaluable, the modified intent-to-treat (MITT), and the intent-to-treat (ITT).

Study Results

Investigators and Numbers Enrolled

Table 40. List of Investigators

Center	Investigator	Country	Number of Patients		
			Randomized to Treatment (N)	Completed TOC Visit (% of N)	Evaluable at TOC (% of N)
1	P. Aldons	Australia	40	30(75)	19(47.5)
2	M. Phillips	Australia	16	15(93.8)	5(31.3)
3	K. Y. Yan	Australia	1	1(100)	0(0)
4	P. Veyssier	France	18	18(100)	9(50)
5	P. Vinceneux	France	7	7(100)	3(42.9)
6	P. Zuck	France	4	4(100)	3(75)
7	D. Le Roux	South Africa	20	15(75)	13(65)
8	P. Frith	Australia	5	5(100)	2(40)
9	P. J. Arens	Germany	5	4(80)	2(40)
10	M. Kunze	Germany	15	15(100)	5(33.3)
12	F. Vogel	Germany	40	30(75)	17(42.5)
13	C. Schoch	Germany	4	4(100)	2(50)
14	G. Dunkhase	Germany	14	14(100)	6(42.9)
16	P. Krupp	Germany	1	1(100)	1(100)
18	C. van Herwaarden	Netherlands	11	11(100)	9(81.8)
19	G. Siemon	Germany	16	16(100)	5(31.3)
20	G. Palmieri	Italy	41	39(95.1)	8(19.5)
21	J. Muir	France	12	10(83.3)	2(16.7)
22	W. Petermann	Germany	37	36(97.3)	15(40.5)
23	S. Fontana	Italy	4	4(100)	0(0)
26	C. K. Chan	Canada	1	1(100)	0(0)
27	C. Laroche	Canada	7	6(85.7)	2(28.6)
28	G. Achyuthan	Canada	9	8(88.9)	5(55.6)
29	L. Latulippe	Canada	6	6(100)	2(33.3)
32	C. St.-Pierre	Canada	12	9(75)	3(25)
33	D. Makinen	Canada	41	38(92.7)	10(24.3)
36	J. S. S. Marx	South Africa	31	22(71)	10(32.3)
37	H. P. Meyer	South Africa	49	42(85.7)	18(36.7)
38	R. Henzgen	Germany	49	46(93.9)	10(20.4)
39	L. Van Schil	Belgium	16	12(75)	10(62.5)
40	A. Volckaert	Belgium	1	0(0)	0(0)
45	J. P. Ducroix	France	8	8(100)	2(25)
47	R. Rimoldi	Italy	4	4(100)	0(0)
51	T. Wanke	Austria	6	4(66.7)	2(33.3)
	Total		554	488(88.1)	201(36.3)

Table 41. Patient Recruitment by Country

Country	Number of Centers That Enrolled Patients	Number of Patients Randomized
Australia	4	62
Austria	2	9
Belgium	2	17
Canada	6	76
France	5	49
Germany	9	181
Italy	3	49
Netherlands	1	11
South Africa	3	100
Total	35	554

Medical officer's note: *There are a large number of centers in different countries with no one center having a huge number of enrollees. The Applicant is providing us with numbers of enrollees that are clinically evaluable, microbiologically and clinically evaluable by treatment arm and investigator.*

Demographics

Table 42. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir N = 277		AmoxClav N = 277		Total N = 554	
Sex						
Male	173	(62.5)	172	(62.1)	345	(62.3)
Female	104	(37.5)	105	(37.9)	209	(37.7)
Race						
White	222	(80.1)	222	(80.1)	444	(80.1)
Black	50	(18.1)	50	(18.1)	100	(18.1)
Asian	2	(0.7)	2	(0.7)	4	(0.7)
Other[a]	3	(1.1)	3	(1.1)	6	(1.1)
Age, yr						
Median	57.0		55.0		56.0	
Range	14 - 94		16 - 99		14 - 99	
Distribution						
13 to <18	5	(1.8)	2	(0.7)	7	(1.3)
18 to <65	161	(58.1)	164	(59.2)	325	(58.7)
≥65	111	(40.1)	111	(40.1)	222	(40.1)

[a] Other = Mixed (3 patients); Metis, North African, Spanish (1 patient each).

TABLE 43. Patient Characteristics - Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir N = 104		Amox/Clav N = 97		Total N = 201	
Sex						
Male	63	(60.6)	66	(68.0)	129	(64.2)
Female	41	(39.4)	31	(32.0)	72	(35.8)
Race						
White	82	(78.8)	74	(76.3)	156	(77.6)
Black	20	(19.2)	21	(21.6)	41	(20.4)
Asian	1	(1.0)	0	(0.0)	1	(0.5)
Other[a]	1	(1.0)	2	(2.1)	3	(1.5)
Age, yr						
Median	55.5		56.0		56.0	
Range	14 - 92		16 - 95		14 - 95	
Distribution						
13 to <18	2	(1.9)	1	(1.0)	3	(1.5)
18 to <65	63	(60.6)	59	(60.8)	122	(60.7)
≥65	39	(37.5)	37	(38.1)	76	(37.8)

[a] Other = Mixed (2 patients), North African (1 patient).

Among all randomized patients, the presence and severity of clinical signs and symptoms were similar for both treatment groups. Most patients presented with cough (100%), sputum production (99%), shortness of breath (86%), and rales (82%). Mean baseline clinical score was 15.0 in the cefdinir treatment group and 14.9 in the amoxicillin/clavulanate treatment group (maximum possible score was 31.5). Among the evaluable and clinically evaluable patients,

mean baseline clinical score was 15.8 for patients randomized to cefdinir and 15.3 for patients randomized to amoxicillin/clavulanate and 14.9 for the cefdinir treatment group and 14.7 for amoxicillin/clavulanate treatment group. Twenty-nine patients (10%) randomized to cefdinir and 26 (9%) randomized to amoxicillin/clavulanate had 1 or more episodes of LRTI within 6 months prior to the start of the study. Seventy-six (27%) patients in the cefdinir group and 83 (30%) patients in the amoxicillin/clavulanate group had a prior or concurrent history of other respiratory ailments that might have predisposed the patient to pneumonia (e.g., asthma, chronic obstructive pulmonary disease, bronchiectasis, emphysema).

Medical officer's note: *The demographic characteristics are fairly evenly distributed by treatment arm among those enrolled and those evaluable.*

Smoking and Past Medical History: Smoking or tobacco use history was obtained in this study. The following Table demonstrates the distribution of this important variable:

Table 44: Smoking Status for All Enrolled Patients

Smoking Status	cefdinir N (%)	amox/clav N (%)
Never	120 (43.3)	116 (41.9)
Past	64 (23.1)	70 (25.3)
Current	93 (33.6)	90 (32.5)
Unknown	0 (0)	1 (0.4)
Total	277 (100.0)	277 (100.0)

Table 45: Years of Smoking for All Enrolled Patients Reporting Past or Present Smoking History

Smoking Status	cefdinir (years)	amox/clav (years)
Past	30.4	23.6
Current	22.9	21.7
Total	25.9	22.5

Table 46: Number of Cigarettes Smoked for All Enrolled Patients Reporting Past or Present Smoking History

Smoking Status	Average number of cigarettes smoked/day	cefdinir N (%)	amox/clav N (%)
Past	light (1-10 per day)	16 (25)	15 (21.4)
	moderate (11-20 per day)	26 (40.6)	34 (48.6)
	heavy (≥ 21 per day)	21 (32.8)	20 (28.6)
	unknown	1 (1.6)	1 (1.4)
Current	light (1-10 per day)	25 (26.9)	26 (28.9)
	moderate (11-20 per day)	44 (47.3)	41 (45.6)
	heavy (≥ 21 per day)	22 (23.7)	22 (22.4)
	unknown	2 (2.2)	1 (1.1)
Total	light (1-10 per day)	41 (26.1)	41 (25.6)
	moderate (11-20 per day)	70 (44.6)	75 (46.9)
	heavy (≥ 21 per day)	43 (27.4)	42 (26.3)
	unknown	3 (1.9)	2 (1.3)

History of existing or prior pulmonary disease was in an open ended inquiry regarding "Past Medical History" which appeared in the questionaire. That question provided the following results for clinically evaluable patients:

Table 47: Prior Pulmonary Diagnoses & Conditions Predisposing to Community Acquired Pneumonia for All Clinically Evaluable Patients

Pulmonary Diagnosis	cefdinir	amox/clav
COPD	29	34
Asthma	38	39
Pneumonia	0	0
Bronchitis	13	9
Lung cancer	0	5
Bronchiectasis	5	6
Pulmonary fibrosis	1	0
Cor pulmonale	2	2
Allergic bronchopul-monary aspergillosis	0	0
Total	88	96

Medical officer's note: *The Applicant is currently evaluating the "past medical history" section of the study questionnaire to determine whether pulmonary diagnoses (i.e., COPD, smoking history, bronchiectasis, prior pneumonia, etc.) are also evenly distributed by treatment arm. The statement above suggests that past medical history is evenly distributed by treatment arm. In addition, the scoring assigned to patients at enrollment for the purposes of assigning the combined investigator-applicant outcome did not differ significantly at enrollment, among evaluable or clinically evaluable patients or by treatment arm. It does look like randomization effectively distributed these potential confounders of pneumonia outcome*

Table 48. Patient Exposure to Study Medication - All Patients
[Number of Patients]

Days on Study Medication	Cefdinir N = 277	Amox/clav N = 277
1	2	5
2	3	2
3	8	3
4	10	5
5	7	6
6	2	5
7	3	6
8	5	9
9	3	4
10	148	99
11	76	123
12	1	2
Median	10.0	10.0

[a] In each treatment group, 1 patient with "unknown" exposure actually took no study medication (0 days).

Medical officer's note: *Given the chart above, one can conclude that compliance with medication was good and most patients enrolled were exposed to the appropriate amount of treatment assigned by the study.*

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Efficacy

The numbers of patients randomized to treatment are compared to other patients populations in Table 12 as follows:

Table 49. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	N	Cefdinir	Amox/clav
ITT [1]	554 (100.0)	277 (100.0)	277 (100.0)
MITT	263 (47.5)	137 (49.5)	126 (45.5)
Clinically Evaluable	396 (71.5)	201 (72.6)	195 (70.4)
Evaluable	201 (36.3)	104 (37.5)	97 (35.0)
Qualified[a]	123 (22.2)	63 (60.6)	60 (61.9)

[a] As a percentage of the evaluable patient population

[1] Evaluable patients had no known protocol violations that might have affected the efficacy assessments at TOC. Patients became unevaluable if they had no baseline pathogen, had a resistant baseline pathogen, failed to take study drug as prescribed, had off-schedule cultures or clinical assessments, had missing microbiologic or clinical signs/symptoms data at baseline or follow-up, took a concurrent systemic antibacterial therapy not for disease under study, had a concurrent infection, or lacked the required baseline diagnosis. However, patients whose assessments were done early (i.e., before the follow-up visit window) or who took a concurrent antibacterial due to early failure did not become unevaluable for these reasons.

Patients in the clinically evaluable population had the correct indication documented by a baseline chest x-ray and the minimum required clinical signs and symptoms (cough and sputum production) at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy for other concurrent infections; and had their clinical evaluations performed within the range of days specified in the protocol. Patients were not excluded from this data set due to having no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

Data were examined at LTFU for qualified patients. **Qualified patients** were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits (e.g., qualified patients did not take any concurrent systemic antibacterial agents).

Patients in the MITT population had the correct indication, received study medication, had at least 1 baseline pathogen, and had a follow-up culture. The MITT population was the same at TOC and LTFU.

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

Medical officer's note: The medical officer agrees with this evaluable populations which are identical to those defined in protocol 983-4.

Medical officer's note: As compared to protocol 983-4, the percentages of enrollees that are part of the MITT, Evaluable and Qualified population are smaller (see page 57 of this review). The Clinically evaluable population here is a bit larger. These differences are consistent with more patients having microbiologic information. It is unclear how this affects comparability of trials, if at all.

TABLE 50. Patient Disposition - All Patients
[Number (%) of Patients]

Patient Disposition	Cefdinir		Amox/clav		Total	
Randomized to Treatment	277		277		554	
Withdrawn Prior to End of Treatment						
Lack of Efficacy	21	(7.6)	14	(5.1)	35	(6.3)
Adverse Event	9	(3.2)	14	(5.1)	23	(4.2)
Other/Administrative	9[a]	(3.2)	7[b]	(2.5)	16	(2.9)
No Baseline Pathogen	4	(1.4)	9	(3.2)	13	(2.3)
Lack of Compliance	6	(2.2)	14	(5.1)	20	(3.6)
Resistant Baseline Pathogen	4	(1.4)	0	(0.0)	4	(0.7)
Completed Treatment	224	(80.9)	219	(79.1)	443	(80.0)
Completed Follow-Up Visits						
TOC	244	(88.1)	244	(88.1)	488	(88.1)
LTFU	160	(57.8)	181	(65.3)	341	(61.6)

[a] Reasons include: Patient discharged without study medication (3 patients); wrong indication (2 patients); and concurrent antibacterial, study drug dosing error, history of hepatic disease, patient not enrolled (1 patient each).

[b] Reasons include: Wrong indication (4 patients); and inability to swallow capsules, patient request, patient not enrolled (1 patient each).

Medical officer's note: In this study and study 983-4, disposition of patients between cefdinir and comparator are fairly even. Follow-up at TOC is greater here. Withdrawal prior to end of treatment is not dominated by one reason. No important differences between treatment arms are discernable in this study with respect to patient disposition.

TABLE 51. Reasons Patients Were Not Evaluable at TOC or Disqualified at LTFU
(Number of Patients)

	Cefdinir	Amox/clav
Randomized to Treatment	277	277
Reasons Patients Were Not Evaluable for TOC Analyses		
Baseline X-Ray Missed	8	4
Clinical Assessment Missed	12	11
Clinical Evaluation Out-of-Date Range[a]	23	30
Concurrent Antibacterial[a]	5	16
Medication Not as Prescribed	19	24
Prior Antibacterial	21	11
Resistant Baseline Pathogen(s)	11	12
Wrong Indication	6	12
Culture[b] Out-of-Date Range[a]	27	33
Culture[b] Missed	26	26
No Baseline Susceptibility Tests	7	6
No Proven Baseline Pathogen	128	139
Total Not Evaluable	173	180
Patients Who Were Evaluable at TOC[c]	104	97
Reasons Patients Were Disqualified for LTFU Analyses		
Clinical Assessment Missed	26	18
Clinical Evaluation Out-of-Date Range[a]	3	8
Concurrent Antibacterial[a]	6	4
Culture[d] Out of Date Range[a]	3	8
Culture[d] Missed	33	27
Total Disqualified	41	37
Patients Who Were Qualified at LTFU	63	60

[a] Patients who had microbiologic and/or clinical assessments done early or who took a concurrent antibacterial because they were early failures were not removed from the evaluable analyses for these reasons.
[b] Baseline or TOC culture
[c] Only these patients were candidates for qualified analyses at LTFU.
[d] LTFU culture

Medical officer's note: Although reasons patients were not evaluable are justifiable by review of the protocol and appear fairly evenly distributed between treatment arms, the large numbers of patients not evaluable is extremely disappointing. It is fortunate that analysis of patients clinically evaluable does not require a proven baseline pathogen, a very large group among those nonevaluable. Many cases of CAP may be due to pathogens not routinely isolated (i.e., Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, etc.) which would not be expected to be responsive to either treatment arm and it is uncertain how many such

individuals are enrolled here.

Thirteen (4%) of the 333 baseline pathogens with determined susceptibility to cefdinir were resistant to cefdinir, and 13 (4%) of the 332 baseline pathogens with determined susceptibility to amoxicillin/clavulanate were resistant to amoxicillin/clavulanate (Table 11). There were no significant differences between the number of isolates resistant to cefdinir and the number of isolates resistant to amoxicillin/clavualanate for all pathogens combined (p = 1.0), nor for the individual species *H. influenzae, H. parainfluenzae, S. aureus, K. pneumoniae*, and *E. coli*. No *M. catarrhalis* isolates were resistant to either study medication.

Table 52: Distribution of Baseline Pathogens by Susceptibility to Study Medication - Pathogens From All Patients (only those requested in package insert)
(Number of Pathogens)

Baseline Pathogen	N	Cefdinir				Amoxicillin/Clavulanate			
		S	I	R	U	S	I	R	U
Gram-Positive									
Staphylococcus aureus	19	17	0	0	2	15	0	2	2
Streptococcus pneumoniae	117	110	3	1	3	113	0	1	3
Gram-Negative									
Escherichia coli	10	9	0	1	0	8	1	1	0
Haemophilus influenzae									
β-lactamase +	8	8	0	0	0	8	0	0	0
β-lactamase -	69	62	3	2	2	64	0	2	3
β-lactamase unknown	11	6	0	0	5	7	0	0	4
Haemophilus parainfluenzae									
β-lactamase +	2	2	0	0	0	1	0	1	0
β-lactamase -	25	23	1	1	0	25	0	0	0
β-lactamase unknown	8	7	0	0	1	6	0	1	1
Klebsiella pneumoniae	12	11	0	1	0	10	1	1	0
Moraxella catarrhalis									
β-lactamase +	12	10	2	0	0	12	0	0	0
β-lactamase -	2	1	1	0	0	2	0	0	0
β-lactamase unknown	4	4	0	0	0	4	0	0	0

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

Medical officer's note: Once again, there does not appear to be any difference between treatment arms for this evaluation.

Clinical Efficacy

Test of Cure, Clinical Cure

TABLE 53 Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the TOC Visit - Evaluable Patients [Number of Patients].

Investigator Determination	Combined Investigator/Sponsor Determination			
	Cefdinir N = 104		Amoxicillin/Clavulanate N = 97	
	Cure	Failure	Cure	Failure
Cure	83	0	86	0
Failure	0	18	0	9
Not Assessable	0	3	0	2
Cure rate	83/104(80%)		86/97(89%)	

For Clinical Cure Rate among Evaluable Patients at TOC, the lower limit of the one- tailed 95% CI about the difference with continuity correction is (-19.82, 2.11).

Medical officer's note: The changes made by applying the clinical algorithm resulted in reassigning the three investigator deemed "not assessable" patients to the combined sponsor-investigator failure arm in the cefdinir treated group and reassignment of two patients in the amoxicillin/clavulanate group in a similar manner. This would not impact outcome and would slightly favor the amoxicillin/clavulanate arm. Cefdinir failed to meet the predetermined criteria for equivalence against amoxicillin/clavulanate.

Long-Term Follow Up, Clinical Cure

TABLE 54 Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at the LTFU Visit - Qualified Patients

Investigator Determination	Combined Investigator/Sponsor Determination					
	Cefdinir N = 63			Amoxicllin/clavulanate N = 60		
	Cure	Failure[a]	Recurrence	Cure	Failure[a]	Recurrence
Cure	57	2	0	58	0	0
Failure/Recurrence	0	2	2	0	1	1
Cure rate	57/63(90.4%)			58/60(96.7%)		

[a] The patients in this column were automatically clinical failures on the combined scale at LTFU because they had been clinical failures on the combined scale at TOC.

For Clinical Cure Rate among Evaluable Patients at LTFU, the lower limit of the 95% CI about the difference with continuity correction is (-16.37, 3.99).

Medical officer's note: This is not a primary outcome measure and the numbers are smaller.

Thus, the finding is of less significance that the comparison of clinical cure rate among evaluable patients at TOC.

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

TABLE 55 Clinical Efficacy at TOC and LTFU – ITT and MITT Populations by Clinical Cure, Microbiologic Eradication by Patient and Clinical Cure Among Clinically Evaluable Patients

Parameter	Cefdinir BID		Amoxicillin/ Clavulanate	
	n/N	%	n/N	%
TOC/ITT: Microbiologic Eradication by Patient[a]	122/277	44.0	116/277	41.9
TOC/ITT: Clinical Cure[b]	198/277	71.5	221/277	79.8
TOC/MITT: Microbiologic Eradication by Patient[c]	119/137	86.9	115/126	91.3
LTFU/ITT: Microbiologic Eradication by Patient[d]	75/277	27.1	73/277	26.4
LTFU/ITT: Clinical Cure[e]	142/277	51.3	169/277	61.0
Clinical Cure Rate[f] Among Clinically Evaluable Patients	155/201	77.0	166/195	85.0

[a] n/N = Number of patients with eradication/total number of patients.
[b] n/N = Number of patients with combined determination of cure/total number of patients.
[c] n/N = Number of patients with eradication/total number of patients.
[d] n/N = Number of patients with continued microbiologic eradication (i.e., no relapse)/total number of patients.
[e] n/N = Number of patients with combined determination of cure/total number of patients.
[f] n/N= Number of patients with clinical cures divided by all clinically evaluable patients (microbiologic status irrelevant). See footnote on page 95 for more detailed description.

For TOC/ITT, microbiologic eradication rate by patient, the 95% CI about the difference with continuity correction is (-6.44, 10.77).

For TOC/ITT, clinical cure rate, the 95% CI about the difference with continuity correction is (-15.78, -0.83).

For TOC/MITT, microbiologic eradication rate by patient, the 95% CI about the difference with continuity correction is (-12.67, 3.86).

For LTFU/ITT, microbiologic eradication rate by patient, the 95% CI about the difference with continuity correction is (-7.01, 8.45).

For LTFU/ITT, clinical cure rate, the 95% CI about the difference with continuity correction is (-18.33, -1.16).

For Clinical Cure Rate among Clinically Evaluable Patients, the 95% CI about the difference with continuity correction is (-16.18, 0.15).

Medical officer's note: The clinical outcomes above, which are not primary endpoints but evaluate several clinical populations (intent to treat and modified intent to treat for clinical cure and microbiologic eradication by patient at both test of cure and long-term follow up) , are marginal and disappointing. Clinical cure at both TOC and LTFU are failures (or near failures) and clinical cure among clinically evaluable patients is also disappointing. ITT microbiologic eradication rates by patient at TOC and LTFU are equivalent, and MITT microbiologic eradication rates by patient at TOC is also equivalent.

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

Table 56. Clinical Cure Rate[a] by Patient (According to Their Baseline Pathogens) at the TOC Visit - Evaluable Patients

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	1/1	100.0	5/5	100.0	3/4	75.0	1/1	100.0
Streptococcus pneumoniae	29/36	80.6	32/36	88.9	6/7	85.7	7/8	87.5
Haemophilus influenzae	25/29	86.2	19/21	90.5	3/6	50.0	4/5	80.0
Haemophilus parainfluenzae	4/8	50.0	7/8	87.5	2/3	66.7	2/2	100.0
Escherichia coli	0/0	0	0/0	0	0/1	0	0/0	0
Klebsiella pneumoniae	3/4	75.0	1/1	100.0	1/1	100.0	0/0	0
Moraxella catarrhalis	6/6	100.0	3/3	100.0	0/0	0	5/5	100.0
Total	76/96	79.2	77/86	89.5	15/22	68.2	14/21	66.7
Total, single & multiple isolates	91/118	77.1	91/107	85.0				

n/N = Number of patients who were cured/total number of patients.

[a] Based on combined investigator/sponsor clinical assessments.

For TOC, the Clinical Cure Rate by Patient (single isolate) according to Baseline Pathogens, the 95% CI about the difference with continuity correction is (-21.86, 1.12).

Medical officer's note: Again, cefdinir does not meet equivalence against the comparator, amoxicillin/clavulanate. However, enough microbiologic evidence is availabe, when coupled with study 983-4, to provide support for Moraxella catarrhalis to be a pathogen labeled for pneumonia.

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

Table 57. Clinical Cure Rate[a] by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients Who Were Classified as Cures at TOC

Baseline Pathogen	Single Isolate				Multiple Isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	1/1	100.0	5/5	100.0	1/1	100.0	0/0	0
Streptococcus pneumoniae	19/19	100.0	24/25	96.0	3/4	75.0	4/4	100.0
Haemophilus influenzae	21/21	100.0	11/11	100.0	1/2	50.0	3/3	100.0
Haemophilus parainfluenzae	4/4	100.0	6/6	100.0	1/1	100.0	1/1	100.0
Escherichia coli	0/0	0	0/0	0	0/0	0	0/0	0
Klebsiella pneumoniae	2/2	100.0	0/0	--	0/0	0	0/0	0
Moraxella catarrhalis	5/6	83.3	3/3	100.0	0/0	0	4/4	100.0
Total	56/57	98.2	55/56	98.2	6/8	75.0	12/12	100.0
Total, single & multiple isolates	62/65	95.3	77/78	98.7				

n/N = Number of patients who were cured/total number of patients.

a Based on combined investigator/sponsor clinical assessments.

For LTFU, the Clinical Cure Rate by Patient according to Baseline Pathogens (single isolate), the 95% CI about the difference with continuity correction is (-10.42, 3.76).

Medical officer's note: Equivalence is demonstrated in this outcome, which is not primary.

Microbiologic Efficacy

Test-of-Cure, Microbiologic Eradication by Pathogen

Table 58. Microbiologic Eradication Rate by Baseline Pathogen at the TOC Visit - Pathogens From Evaluable Patients

Baseline Pathogen	Cefdinir		Amox/clav	
	n/N	%	n/N	%
Staphylococcus aureus	3/4	75.0	5/6	83.3
Streptococcus pneumoniae	42/44	95.5	43/44	97.7
Escherichia coli	0/1	0.0	0/0	–
Haemophilus influenzae				
β-lactamase +	2/3	66.7	3/3	100.0
β-lactamase -	21/29	72.4	17/21	81.0
β-lactamase unknown	3/3	100.0	1/2	50.0
Haemophilus parainfluenzae				
β-lactamase -	10/10	100.0	11/11	100.0
β-lactamase unknown	1/1	100.0	1/1	100.0
Klebsiella pneumoniae	5/5	100.0	1/1	100.0
Moraxella catarrhalis				
β-lactamase +	4/4	100.0	6/6	100.0
β-lactamase -	1/1	100.0	1/1	100.0
β-lactamase unknown	1/1	100.0	1/1	100.0
Total	93/106	87.7	90/97	92.8

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

For LTFU, the Microbiologic Eradication Rate by Baseline Pathogen, the 95% CI about the difference with continuity correction is (-14.13, 4.03).

Medical officer's note: Acceptable eradication rates are demonstrated in this nonprimary outcome measure.

Long-Term Follow Up. Microbiologic Eradication by Pathogen

TABLE 59. Microbiologic Eradication Rate by Baseline Pathogen at the LTFU Visit - Pathogens From Qualified Patients Who Were Classified as Patients With Eradication at TOC

Baseline Pathogen	Cefdinir		Amox/clav	
	n/N	%	n/N	%
Staphylococcus aureus	1/1	100.0	4/4	100.0
Streptococcus pneumoniae	22/22	100.0	27/27	100.0
Haemophilus influenzae				
β-lactamase +	1/1	100.0	2/2	100.0
β-lactamase -	16/16	100.0	8/8	100.0
β-lactamase unknown	1/1	100.0	0/0	--
Haemophilus parainfluenzae				
β-lactamase -	6/6	100.0	7/7	100.0
Klebsiella pneumoniae	2/2	100.0	0/0	--
Moraxella catarrhalis				
β-lactamase +	4/4	100.0	5/5	100.0
β-lactamase -	1/1	100.0	1/1	100.0
β-lactamase unknown	1/1	100.0	0/0	--
Total	55/55	100.0	54/54	100.0

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

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

Medical officer's note: *Equivalence is clearly evident at this non-primary endpoint.*

Test of Cure, Microbiologic Eradication by Patient

TABLE 60. Microbiologic Eradication Rate by Patient (According to Their Baseline Pathogens) at the TOC Visit - Evaluable Patients

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	0/1	0	4/5	80.0	3/3	100.0	1/1	100.0
Streptococcus pneumoniae	35/36	97.2	35/36	97.2	5/8	62.5	7/8	87.5
Haemophilus influenzae	22/29	75.9	18/21	85.7	3/6	50.0	3/5	60.0
Haemophilus parainfluenzae	8/8	100.0	8/8	100.0	2/3	66.7	3/3	100.0
Escherichia coli	0/0	0	0/0	0	0/1	0	0/0	0
Klebsiella pneumoniae	4/4	100.0	1/1	100.0	1/1	100.0	0/0	0
Moraxella catarrhalis	6/6	100.0	3/3	100.0	0	0	4/5	80.0
Total	75/84	89.2	69/74	93.2	14/22	63.6	18/22	81.8
Total, single & multiple isolates	89/106	84.0	87/96	90.6				

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

For TOC, the Microbiologic Eradication Rate by Patient, the 95% CI about the difference with continuity correction is (-13.97, 6.06).

At the TOC visit, 13 evaluable cefdinir-treated patients had 13 persistent pathogens, and 9 evaluable amoxicillin/clavulanate treated patients had 9 persistent pathogens. All of the persistent pathogens had been susceptible to study medication at baseline and 18/22 remained susceptible at TOC (Appendix E.2). Among cefdinir-treated patients, susceptibility at TOC was intermediate for one isolate of *H. influenzae* and unknown for two isolates of *H. influenzae*. One isolate of *H. influenzae* from an amoxicillin/clavulanate-treated patient was of unknown susceptibility at TOC.

Long-Term Follow Up Visit, Microbiologic Eradication by Patient

Table 61. Microbiologic Eradication by Patient (According to Their Baseline Pathogens) at the LTFU Visit - Qualified Patients Who Were Classified as Patients with Eradication at TOC

Baseline Pathogen	Single isolate				Multiple isolates			
	Cefdinir		Amox/clav		Cefdinir		Amox/clav	
	n/N	%	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	0/0	--	4/4	100.0	1/1	100.0	0/0	0
Streptococcus pneumoniae	19/19	100.0	24/24	100.0	3/3	100.0	3/3	100.0
Haemophilus influenzae	17/17	100.0	9/9	100.0	1/1	100.0	1/1	100.0
Haemophilus parainfluenzae	5/5	100.0	6/6	100.0	1/1	100.0	1/1	100.0
Escherichia coli	0/0	0	0/0	0	0/0	0	0/0	0
Klebsiella pneumoniae	2/2	100.0	0/0	--	0/0	0	0/0	0
Moraxella catarrhalis	6/6	100.0	3/3	100.0	0/0	0	3/3	0
Total	49/49	100.0	46/46	100.0	6/6	100.0	8/8	100.0
Total, multiple & single isolates	55/55	100.0	54/54	100.0				

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

Medical officer's note: *Equivalence is demonstrated around this non-primary endpoint.*

APPEARS THIS WAY
ON ORIGINAL

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

Table 62. Microbiologic Efficacy at TOC and LTFU -- MITT and ITT Populations

Parameter	Cefdinir BID		Amox/clav	
	n/N[a]	%	n/N	%
TOC/MITT: Microbiologic Eradication by Pathogen[a]	151/182	83	140/165	84.8
TOC/ITT: Microbiologic Eradication by Pathogen[a]	146/164	89	139/150	92.7
LTFU/ITT Microbiologic Eradication by Pathogen[a]	93/182	51.1	94/165	57

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

For TOC/MITT, microbiologic eradication rate by pathogen, the 95% CI about the difference with continuity correction is (-10.19, 6.43).

For TOC/ITT, microbiologic eradication rate by pathogen, the 95% CI about the difference with continuity correction is (-10.63, 3.34).

For LTFU/ITT, microbiologic eradication rate by pathogen, the 95% CI about the difference with contuity correction is (-16.93, 5.19).

Medical officer's note: The Applicant performed adequately in these comparisons, which are non-primary endpoints.

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ON ORIGINAL

Test of Cure, Microbiologic Versus Clinical Response Rates

Table 63. Microbiologic Versus Clinical Response Rates at the TOC Visit - Evaluable Patients [Number (%) of Patients]

Microbiologic Response	Clinical Response[a]	
	Cure	Failure
Cefdinir, N = 104		
Patients With Eradication	77 (74.0)	14 (13.5)
Patients With Persistence	6 (5.8)	7 (6.7)
Amoxicillin/clavulanate, N = 97		
Patients With Eradication	79 (81.4)	9 (9.3)
Patients With Persistence	7 (7.2)	2 (2.1)

[a] Based on combined investigator/sponsor clinical assessment

Medical officer's note: These results demonstrate a trend of lower eradication and greater clinical response with cefdinir treatment.

Superinfections: At TOC, 32 (12%) cefdinir-treated patients and 28 (10%) amoxicillin/clavulanate-treated patients had one or more superinfecting pathogens. In patients treated with cefdinir, 23 of 38 (61%) superinfecting pathogens were susceptible to cefdinir, while among amoxicillin/clavulanate-treated patients, 23 of 41 (56%) superinfecting pathogens were susceptible to amoxicillin/clavulanate.

Table 64. Patients With Superinfections - All Patients
(Number of Patients)

Pathogen	Cefdinir N = 277	Amoxicillin/clavulanate N = 277
Gram-Positive		
Beta-hemolytic *streptococcus* (not group A, B, or D)	1	0
Staphylococcus epidermidis	0	1
Streptococcus mitis	1	1
Streptococcus pneumoniae	2	0
Streptococcus (viridans groups)	2	0
Group C *streptococcus*	1	0
Group F *streptococcus*	1	0
Gram-Negative		
Citrobacter freundii	0	1
Enterobacter cloacae	1	1
Escherichia coli	0	2
Haemophilus influenzae	6	1
Haemophilus parainfluenzae	5	6
Klebsiella pneumoniae	0	1
Moraxella catarrhalis	3	0
Neisseria species	0	2
Pseudomonas aeruginosa	2	2
Proteus vulgaris	1	0
Multiple	6	10
Total	32	28

Medical officer's note: Study 983-4 had superinfection rates of 3.5% and 5.8% for the cefdinir and cefaclor arms respectively. It is difficult to know what to make of the superinfection rates of 12% cefdinir and 10% for amoxicillin/clavulanate seen here. In addition, the pathogens identified by the studies are quite different. There is only on gram positive isolate (S. pneumoniae) identified as a superinfection in study 983-4. Here there are many more; some of questionable significance as pathogens in the setting of CAP without strong documentation. One wonders whether this points to differences in microbiologic judgements on the part of those interpreting culture results. What is evident is that superinfection rates appear to be equivalent across treatment and control arms is both studies. Thus, there seems to be no increased rate attributable to study drug.

Reinfections: One cefdinir-treated patient was reinfected with *H. influenzae*; and one patient in the amoxicillin/clavulanate ~~treatment group was reinfected with Group C *Streptococcus*~~.

Medical officer's note: *Reinfections rates are similar and unremarkable across both treatment arms.*

Safety

Medical officer's note: *With the exception of the following items, safety for protocol 983-27 was evaluated with the same methodology of safety for protocol 983-4. In protocol 983-4, abnormal laboratory values were designated as adverse events at the discretion of the investigator whereas in protocol 983-27, abnormal clinical laboratory values were designated as adverse events if they were confirmed by repeat testing, suggested a disease or organ toxicity, or required active management (e.g., discontinuation of drug, more frequent follow-up, diagnostic investigation, etc. It is noteworthy that both protocols required that patients discontinuing treatment due to diarrhea in protocol 983-4 were to be tested for C. difficile as well.*

Safety data were evaluated for 276 patients who took cefdinir and 276 patients who took amoxicillin/clavulanate because one patient in each treatment group was randomized but did not take study drug. Forty-one (15%) cefdinir-treated patients and 43 (16%) amoxicillin/clavulanate-treated patients had one or more adverse events that the investigator considered drug-associated. Eleven (4%) patients who received cefdinir and 14 (5%) who received amoxicillin/clavulanate discontinued treatment due to adverse events; an additional three patients in the cefdinir group and one patient in the amoxicillin/clavulanate group withdrew from the study due to an adverse event after completing treatment. Fourteen (5%) patients who received cefdinir and 15 (5%) amoxicillin/clavulanate-treated patients experienced a serious adverse event. Seven patients died: four who received cefdinir, and three who received amoxicillin/clavulanate.

Medical officer's note: *There appears to be no difference between rates of ADRs in the cefdinir and amoxicillin clavulanate arms with respect to overall rates of drug associated ADR, rates of patients discontinuing therapy due to an ADRs, rates of serious ADRs or overall death rate in study.*

Table 65. Summary of Adverse Events - All Patients Who Received Study Medication
[Number (%) of Patients]

	cefdinir (n=276)	amox/clav (n=276)
Adverse Events During Study		
All Adverse Events	97 (31.5)	97 (35.1)
Associated[a] Adverse Events	41 (14.9)	43 (15.6)
Adverse Events During Treatment		
All Adverse Events	59 (21.4)	71 (25.7)
Adverse Events by Sex[b]		
All Adverse Events		
Male	47 (27.3)	53 (30.8)
Female	40 (38.5)	44 (42.3)
Associated Adverse Events		
Male	23 (13.4)	20 (11.6)
Female	18 (17.3)	23 (22.1)
Adverse Events by Race[c]		
All Adverse Events		
White	75 (33.9)	82 (37.1)
Black	11 (22.0)	13 (26.0)
Asian	1 (50.0)	0 (0.0)
Hispanic	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (66.7)
Associated Adverse Events		
White	40 (18.1)	41 (18.6)
Black	1 (2.0)	2 (4.0)
Asian	0 (0.0)	0 (0.0)
Hispanic	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Adverse Events by Age[d]		
13 to <18 yr	0 (0.0)	1 (50.0)
18 to <65 yr	53 (33.1)	58 (35.4)
≥65 yr	34 (30.6)	38 (34.5)
Associated Adverse Events		
13 to <18 yr	0 (0.0)	1 (50.0)
18 to <65 yr	30 (18.8)	30 (18.3)
≥65 yr	11 (9.9)	12 (10.9)

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

All and Drug-Associated Adverse Events

Table 66. All and Associated[a] Adverse Events by Body System[b] - Patients Who Received Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir N = 276				Amoxicillin/Clavulanate N = 276			
	All		Associated		All		Associated	
DIGESTIVE SYSTEM	40	(14.5)	31	(11.2)	47	(17.0)	31	(11.2)
Diarrhea	23	(8.3)	22	(8.0)	22	(8.0)	19	(6.9)
Dyspepsia	7	(2.5)	3	(1.1)	2	(0.7)	2	(0.7)
Constipation	3	(1.1)	0	(0.0)	3	(1.1)	0	(0.0)
Gastritis	3	(1.1)	2	(0.7)	4	(1.4)	1	(0.4)
Liver Function Tests Abnormal	3	(1.1)	3	(1.1)	1	(0.4)	1	(0.4)
Nausea	2	(0.7)	1	(0.4)	8	(2.9)	4	(1.4)
Vomiting	2	(0.7)	1	(0.4)	7	(2.5)	4	(1.4)
Abnormal Stools	1	(0.4)	1	(0.4)	1	(0.4)	1	(0.4)
Anorexia	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Dry Mouth	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenal Ulcer	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hemorrhagic Colitis	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Melena	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Rectal Disorder	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Stomach Ulcer	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Biliary Pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Dysphagia	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Flatulence	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Gastrointestinal Disorder	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Rectal Hemorrhage	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
BODY AS A WHOLE	28	(10.1)	6	(2.2)	28	(10.1)	6	(2.2)
Headache	11	(4.0)	0	(0.0)	10	(3.6)	3	(1.1)
Infection	7	(2.5)	2	(0.7)	1	(0.4)	1	(0.4)
Abdominal Pain	6	(2.2)	4	(1.4)	1	(0.4)	1	(0.4)
Accidental Injury	3	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Asthenia	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Back Pain	2	(0.7)	0	(0.0)	3	(1.1)	0	(0.0)
Flu Syndrome	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Abscess	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Chest Pain	1	(0.4)	0	(0.0)	2	(0.7)	0	(0.0)
Chest Pain Substernal	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sudden Death	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Allergic Reaction	0	(0.0)	0	(0.0)	2	(0.7)	1	(0.4)
Cellulitis	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Fever	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
HIV Test Positive	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	4	(1.4)	0	(0.0)
RESPIRATORY SYSTEM	16	(5.8)	2	(0.7)	14	(5.1)	0	(0.0)
Pharyngitis	3	(1.1)	0	(0.0)	2	(0.7)	0	(0.0)

Rhinitis	3	(1.1)	0	(0.0)	1	(0.4)	0	(0.0)
Dyspnea	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)

[a] Associated adverse events are those considered possibly, probably, or definitely related to treatment.
[b] The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have >1 adverse event per system.

Medical officer's note: The ADR rates are identical for cefdinir and amoxicillin/clavulanate. Of note, gastrointestinal complaints, particularly diarrhea, are prominent but equal across treatment arms. Interestingly, the incidence of adverse events, including diarrhea, was greater in certain groups in both treatment arms. See the following chart:

Table 67: Variation in Rates of Adverse Events among Different Groups

	Overall Adverse Events		Diarrhea Rates	
Demographic group	cefdinir	amox/clav	cefdinir	amox/clav
Sex				
Male	27%	31%	5%	6%
Female	39%	42%	14%	11%
Race				
Whites	34%	37%	10%	10%
Blacks	22%	26%	2%	0%

It will be interesting to see whether the integrated safety analysis supports higher overall rates of ADRs, and in particular diarrhea, among females and blacks.

Table 68. All and Associated[a] Adverse Events by Body System[b] - Patients Who Received Study Medication [Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir N = 276				Amox/Clav N = 276			
	All		Associated		All		Associated	
DIGESTIVE SYSTEM	40	(14.5)	31	(11.2)	47	(17.0)	31	(11.2)
Diarrhea	23	(8.3)	22	(8.0)	22	(8.0)	19	(6.9)
Dyspepsia	7	(2.5)	3	(1.1)	2	(0.7)	2	(0.7)
Constipation	3	(1.1)	0	(0.0)	3	(1.1)	0	(0.0)
Gastritis	3	(1.1)	2	(0.7)	4	(1.4)	1	(0.4)
Liver Function Tests Abnormal	3	(1.1)	3	(1.1)	1	(0.4)	1	(0.4)
Nausea	2	(0.7)	1	(0.4)	8	(2.9)	4	(1.4)
Vomiting	2	(0.7)	1	(0.4)	7	(2.5)	4	(1.4)
Abnormal Stools	1	(0.4)	1	(0.4)	1	(0.4)	1	(0.4)
Anorexia	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Dry Mouth	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenal Ulcer	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hemorrhagic Colitis	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Melena	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Rectal Disorder	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)

Stomach Ulcer	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Biliary Pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Dysphagia	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Flatulence	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Gastrointestinal Disorder	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Rectal Hemorrhage	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
BODY AS A WHOLE	28	(10.1)	6	(2.2)	28	(10.1)	6	(2.2)
Headache	11	(4.0)	0	(0.0)	10	(3.6)	3	(1.1)
Infection	7	(2.5)	2	(0.7)	1	(0.4)	1	(0.4)
Abdominal Pain	6	(2.2)	4	(1.4)	1	(0.4)	1	(0.4)
Accidental Injury	3	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
Asthenia	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Back Pain	2	(0.7)	0	(0.0)	3	(1.1)	0	(0.0)
Flu Syndrome	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Abscess	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Chest Pain	1	(0.4)	0	(0.0)	2	(0.7)	0	(0.0)
Chest Pain Substernal	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sudden Death	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Allergic Reaction	0	(0.0)	0	(0.0)	2	(0.7)	1	(0.4)
Cellulitis	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Fever	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
HIV Test Positive	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	4	(1.4)	0	(0.0)
RESPIRATORY SYSTEM	16	(5.8)	2	(0.7)	14	(5.1)	0	(0.0)
Pharyngitis	3	(1.1)	0	(0.0)	2	(0.7)	0	(0.0)
Rhinitis	3	(1.1)	0	(0.0)	1	(0.4)	0	(0.0)
Dyspnea	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Pleural Disorder	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	2	(0.7)	2	(0.7)	1	(0.4)	0	(0.0)
Asthma	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Carcinoma of Lung	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Epistaxis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumothorax	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory Disorder	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Lung Disorder	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Lung Edema	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pleural Effusion	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
NERVOUS SYSTEM	12	(4.3)	3	(1.1)	6	(2.2)	0	(0.0)
Insomnia	3	(1.1)	1	(0.4)	2	(0.7)	0	(0.0)
Dizziness	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
Personality Disorder	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Somnolence	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
Convulsion	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sleep Disorder	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Twitching	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Agitation	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)

Delirium	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Paresthesia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
CARDIOVASCULAR SYSTEM	10	(3.6)	1	(0.4)	6	(2.2)	0	(0.0)
Postural Hypotension	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Atrial Fibrillation	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Atrial Flutter	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Heart Arrest	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Heart Failure	1	(0.4)	0	(0.0)	2	(0.7)	0	(0.0)
Hypertension	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hypotension	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Palpitation	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Tachycardia	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Electrocardiogram Abnormal	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Phlebitis	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
Thrombophlebitis	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
SKIN AND APPENDAGES	8	(2.9)	5	(1.8)	9	(3.3)	7	(2.5)
Herpes Simplex	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	2	(0.7)	2	(0.7)	1	(0.4)	0	(0.0)
Acne	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Dry Skin	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Maculopapular Rash	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Rash	1	(0.4)	1	(0.4)	7	(2.5)	6	(2.2)
Eczema	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Urticaria	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
UROGENITAL SYSTEM	6	(2.2)	2	(0.7)	9	(3.3)	3	(1.1)
Vaginitis	2	(0.7)	2	(0.7)	0	(0.0)	0	(0.0)
Albuminuria	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hematuria	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Kidney Failure	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Orchitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary Tract Infection	1	(0.4)	0	(0.0)	4	(1.4)	1	(0.4)
Breast Carcinoma	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pyelonephritis	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Urinary Retention	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Vaginal Moniliasis	0	(0.0)	0	(0.0)	2	(0.7)	2	(0.7)
SPECIAL SENSES	4	(1.4)	2	(0.7)	4	(1.4)	0	(0.0)
Conjunctivitis	2	(0.7)	0	(0.0)	1	(0.4)	0	(0.0)
Taste Perversion	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Uveitis	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Amblyopia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Ear Pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Otitis Media	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
METABOLIC AND NUTRITIONAL	3	(1.1)	1	(0.4)	7	(2.5)	1	(0.4)
Hyperuricemia	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Lactate Dehydrogenase Increase	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
NPN Increased	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Bilirubinemia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Hyperglycemia	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)

Peripheral Edema	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
SGPT Increased	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
MUSCULOSKELETAL SYSTEM	3	(1.1)	0	(0.0)	1	(0.4)	0	(0.0)
Arthralgia	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Rheumatoid Arthritis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
HEMIC AND LYMPHATIC SYSTEM	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Anemia	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
ENDOCRINE SYSTEM	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Diabetes Mellitus	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)

NPN = Nonprotein nitrogen

[a] Associated adverse events are those considered possibly, probably, or definately related to treatment.

[b] The totals for each body system may be less than the number of patients with adverse events in that body system 1 adverse event per system.

Deaths: Seven patients, four in the cefdinir treatment group and three in the amoxicllin/clavulanate group, died during the study. None of the deaths were considered related to study medication by the investigator.

Table 69. All Patient Deaths

Treatment	Center	Patient No.	Age (yr), Sex	Cause of Death[a]	Relationship to Study Medication[b]	Study Day Drug Discontinued	Study Day Patient Died
Cefdinir							
	19	3	57, M	Respiratory Insufficiency (Respiratory Disorder) Lung-Cancer (Carcinoma of Lung)	Definitely Not Definitely Not	10	23
	21	1	87, M	Sudden Death of Probable Cardiac Origin (Sudden Death)	Unlikely	1	1
	38	44	85, F	Acute Cardiac Failure (Heart Failure)	Definitely Not	5	36
	39	4	80, F	Dyspnoea (Dyspnea)	Unlikely	11	38
Amox/Clav							
	33	2	39, F	Probable Metastatic Ca Breast (Breast Carcinoma)	Definitely Not	6	25
	38	1	84, M	Sudden Death	Definitely Not	11	38
	51	4	68, M	Cardiac Failure (Heart Failure)	Definitely Not	4	4

[a] When the investigator term and COSTART term differ, the COSTART term appears in parentheses.

[b] Relationship to study medication of adverse event leading to death, in the opinion of the investigator

Medical officer's note: Review of case summaries for these patients, found in Applicant's Appendix B.2 does not suggest any deaths attributable to drug.

Serious Adverse Events: Twenty-nine patients, 14 (5%) treated with cefdinir and 15 (5%)

treated with amoxicillin/clavulanate, experienced serious adverse events during this study. Serious adverse events that the investigator considered related to cefdinir were exacerbation of pneumonia in two patients, and hemorrhagic colitis in one patient. No serious adverse events were considered to be related to amoxicillin/clavulanate. Eight cefdinir-treated patients and five amoxicillin/clavulanate-treated patients withdrew from the study due to these serious events.

Medical officer's note: Review of case summaries for these patients, found in Applicant's Appendix B.2, does not suggest that the drug was related to the outcomes.

Withdrawals Due to Adverse Events: Fourteen (5%) patients treated with cefdinir and 15 (5%) treated with amoxicillin/clavulanate withdrew from the study due to adverse events. Of these, 11 (4%) patients treated with cefdinir and 14 (5%) patients treated with amoxicillin/clavulanate discontinued treatment due to adverse events. The remaining three cefdinir-treated patients and one amoxicillin/clavulanate-treated patient withdrew after completing treatment but before the LTFU visit. There was no significant difference between the treatment groups in the number of patients discontinuing treatment due to adverse events ($p = 0.30$).

Diarrhea resulted in withdrawal of two patients in each treatment group; pneumonia and carcinoma of lung each resulted in withdrawal of two patients in the cefdinir treatment group; and rash led to withdrawal of two patients in the amoxicillin/clavulanate group. All other adverse events that led to withdrawal did so in only one patient each.

Medical officer's note: Review of case summaries for these patients, found in Applicant's Appendix B.2 does not differ with respect to withdrawal by treatment arm.

Table 69. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Who Received Study Medication {Number % of Patients}

BODY SYSTEM/ - Adverse Event	Cefdinir N = 276	Amox/Clav N = 276
RESPIRATORY SYSTEM	4 (1.4)	3 (1.1)
Pneumonia	2 (0.7)	0 (0.0)
Carcinoma of Lung	2 (0.7)	0 (0.0)
Lung Disorder	0 (0.0)	1 (0.4)
Lung Edema	0 (0.0)	1 (0.4)
Pleural Effusion	0 (0.0)	1 (0.4)
BODY AS A WHOLE	3 (1.1)	2 (0.7)
Abscess	1 (0.4)	0 (0.0)
Infection	1 (0.4)	0 (0.0)
Sudden Death	1 (0.4)	0 (0.0)
Cellulitis	0 (0.0)	1 (0.4)
Headache	0 (0.0)	1 (0.4)
DIGESTIVE SYSTEM	2 (0.7)	4 (1.4)
Diarrhea	2 (0.7)	2 (0.7)
Dysphagia	0 (0.0)	1 (0.4)

Vomiting	0 (0.0)	1 (0.4)
NERVOUS SYSTEM	2 (0.7)	0 (0.0)
Convulsion	1 (0.4)	0 (0.0)
Somnolence	1 (0.4)	0 (0.0)
SKIN AND APPENDAGES	2 (0.7)	3 (1.1)
Acne	1 (0.4)	0 (0.0)
Pruritus	1 (0.4)	0 (0.0)
Rash	0 (0.0)	2 (0.7)
Urticaria	0 (0.0)	1 (0.4)
CARDIOVASCULAR SYSTEM	1 (0.4)	1 (0.4)
Heart Arrest	1 (0.4)	0 (0.0)
Heart Failure	0 (0.0)	1 (0.4)
SPECIAL SENSES	1 (0.4)	0 (0.0)
Uveitis	1 (0.4)	0 (0.0)
UROGENITAL SYSTEM	0 (0.0)	3 (1.1)
Breast Carcinoma	0 (0.0)	1 (0.4)
Pyelonephritis	0 (0.0)	1 (0.4)
Urinary Tract Infection	0 (0.0)	1 (0.4)

Medical officer's note: *Review of the above table suggests no important differences by treatment arm with respect to treatment discontinuations and study withdrawals.*

Clostridium difficile-Associated Diarrhea: Although *Clostridium difficile* testing was to have been done for patients discontinuing study medication due to diarrhea, none of the four patients who discontinued therapy due to diarrhea were tested. one patient developed hemorrhagic colitis 17 days after completing the 10-day course of treatment with cefdinir but *Clostridium difficile* toxin tests conducted on stool samples collected Days 30 and 35 were negative.

Medical officer's note: *Diarrhea rates are high among participants of protocol 983-27 in both study arms. Among patients receiving cefdinir in protocol 983-4, diarrhea rates were high. Testing for C. difficile toxin was intended but not carried through. All cephalosporins marketed in the United States currently bear labeling regarding pseudomembranous colitis. Although these two protocols provide little information, and the integrated safety summary may be helpful and will be completed at a later date, this reviewer believes the language found in the other cephalosporin package inserts regarding this ADR would be appropriate.*

Clinical Laboratory Values.

Medical officer's note: *Analysis of clinical laboratory values was identical to that performed in protocol 983-4 (median changes from baseline, category shift changes, and markedly abnormal values at first posttherapy visit). There were no abnormal values or changes associated with cefdinir therapy; abnormalities most typically were consistent with resolving infection*

(resolution of leukocytosis), and were similar across both treatment arms.

CONCLUSIONS

- Overall, cefdinir 300 mg BID for 10 days was not as effective as amoxicillin/clavulanate 500 mg TID for 10 days in treating adult patients with community-acquired bacterial pneumonia. Differences were observed in the clinical response rate. Although not equivalent, all responses were good. Microbiologic response rates were equivalent.

- Cefidinir demonstrated efficacy against *Streptococcus pneumoniae* (35/36, 97.2%), *Haemophilus influenzae* (22/29, 75.9%) and *Moraxella catarrhalis* (6/6, 100%). The additional isolates of *Moraxella catarrhalis* successfully treated in this study, when coupled with those from study 983-4 provide a requisite number to allow to efficacy labeling. Insufficient evidence is available to support claims of efficacy for CAP due to *Streptococcus pyogenes* or *Staphylococcus aureus*.

- No difference was observed between cefdinir and amoxicillin/clavulanate with respect to incidence of drug-associated adverse events, including diarrhea, during treatment. There was no difference between the treatments in the rate of treatment discontinuation due to adverse events.

RECOMMENDATIONS REGARDING TWO PIVOTAL CAP TRIALS (983-4 & 983-26)

- Cefdinir 300 mg po bid for 10 days be approved for the treatment of CAP.

- Cefidinir be approved for CAP due to *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta lactamase producing), *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*.

/S/

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Medical Officer
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/S/

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Concurrences:
HFD-520/TL/Jan Soreth, MD
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Concurrence:
HFD-725/TL/DLin, PhD

cc: Orig NDAs 50-674 & 50-675
HFD-520/Division File
HFD-520/CSO BDuvall-Miller
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague
HFD-40/DDMAC/J Spearmon
HFD-520/Pharm/FPelsor
HFD-520/MO/HHamilton
HFD-520/TL/JSoreth
HFD-725/Stat/AChakravarty
HFD-725/Stat/TL/DLin

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information

Acute Exacerbation of Chronic Bronchitis

A double-blind, randomized, multicenter (N=36, U.S. and international sites) study of cefdinir (CI-983) versus cefuroxime axetil in the treatment of patients with acute exacerbations of chronic bronchitis (Protocol 983-5).

Medical officer's note: This reviewer believes that the clinical outcome is the critical measure in this indication. Microbiological outcome makes little sense. Evaluation of clinical trials reveals that most studies demonstrate a benefit to the administration of antibiotic therapy in patients with acute exacerbation of chronic bronchitis[1]. However, this benefit is largely clinical. Microbiologic outcomes are murky; patients often carry the same microorganisms before and after therapy.

This issue was addressed by the Advisory Commitee Meeting which convened in March, 1997:

> *Dr. Thompson: ... In discussing the acute exacerbation of chronic bronchitis, it is important to realize that Haemophilus influenzae and Strep. pneumoniae are present in the sputum in 30 to 50 percent of patients with chronic bronchitis, and this is true whether or not patients are undergoing an acute episode at the time.*
>
> *In addition, it has been clearly shown in the literature that there is no specific correlation with the development of AECB in terms of development of purulence of the sputum.*
>
> *Again, briefly, referred to already this morning is isolation of other organisms from the sputum of these patients -- viridans streptococci, Staph aureus, gram-negative enteric bacilli. All of these can be isolated occasionally from the sputum of patients who are undergoing an acute exacerbation of chronic bronchitis, and the question of course is whether these represent simply oropharyngeal contamination or whether they may occasionally be playing a pathogenic role.*
>
> *Lastly, and probably most importantly, the failure to eradicate putative pathogens including, of course, the major three organisms that I have already mentioned int he face [error omitted] of clinical improvement is very common.*
>
> ...
>
> *...The first is that we would suggest that clinical outcome is the primary determinant of efficacy for the indication of bronchitis.*

Exacerbations of Chronic Bronchitis" by John G. Bartlett in Infectious Diseases, 2d., eds. Sherwood L. Gorbach, John G. Bartlett, and Neil R. Blackow (W.B. Saunders Co.: Philadelphia) 1998:584-586

Medical officer's note: Understood in the above description is that in order to have AECB one must have have underlying chronic bronchitis. The above inclusion critieria are acceptable although minimally restrictive. This is unfortunate because it becomes a lax test of efficacy as equivalence is easy to demonstrate.

Exclusion Criteria: Patients were to be excluded from participating in the study for any of the following reasons:

- Evidence of pneumonia on a prescreen x-ray;
- Diseases that would preclude evaluation of the therapeutic response, including cystic fibrosis, bronchiectasis, carcinoma of the bronchus, or significant pulmonary structural defects;
- History or clinical evidence of significant cardiovascular, renal, hepatic, hematological, gastrointestinal, neurological, psychiatric, or other chronic disease;
- Hepatic disease, obstruction of the biliary tract, or baseline bilirubin or hepatic enzyme levels (AST, ALT) >2 times the upper limit of normal;
- Baseline serum creatinine >2 times the upper limit of normal or creatinine clearance <30 mL/min;
- Hypersensitivity to β-lactams (including penicillins and cephalosporins);
- A baseline pathogen known to be resistant to either study drug prior to randomization;
- Concomitant infections requiring systemic antibacterial therapy;
- Prior participation in this or any other cefdinir study;
- Receipt of any other investigational compound within 4 weeks of study entry; or
- Receipt of another systemic antibacterial agent in the 48 hours prior to the first dose of study medication, or if the time interval between the last dose of the prior antibacterial and the first dose of cefdinir would be less than 5 half-lives of the prior antibacterial agent.

Medical officer's note: The above exclusion criteria are acceptable. Many are general to other studies in the application.

Evaluability Critieria: The Applicant analyzed several populations: intent-to-treat (ITT), modified intent-to-treat (MITT), evaluable (those patients both microbiologically and clinically evaluable), and clinically evaluable (those patients who were clinically but not necessarily microbiologically evaluable). Each is described below.[2]

Medical officer's note: Violations which eliminated patients from various populations are described below. As this reviewer has stated earlier, clinical outcome is of the most interest. This reviewer only analyzed those subjects with bacterial cultures deemed likely to be etiologic in AECB. This is the population included in this review. *See Medical officer's note on page 164.*

The criteria for evaluability are reasonable, and uncertainties and failures are carried forward as appropriate. The populations analyzed are the same as those evaluated in the community acquired pneumonia study. The reviewer agrees that these populations are acceptable for analysis; however, microbiologically evaluable patients probably have little meaning in AECB.

---

[2] Evaluable patients had no known protocol violations that might have affected the efficacy assessments at TOC using specific, predefined criteria. Patients became unevaluable if they had no baseline pathogen, had a resistant baseline pathogen, failed to take study drug as prescribed, had off-schedule cultures or clinical assessments, had missing microbiologic or clinical signs/symptoms data at baseline or follow-up, took a concurrent systemic antibacterial therapy not for disease under study, had a concurrent infection, or lacked the required baseline diagnosis. Patients whose TOC assessments were done early (ie, before the follow-up visit window) or who took a concurrent antibacterial due to early failure did not become unevaluable for these reasons.

A subset of evaluable patients identified as "qualified patients" was examined at LTFU. Qualified patients were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits. Patients whose LTFU assessments were done early or who took a concurrent antibacterial between the TOC and LTFU visits due to recurrence were not disqualified for these reasons.

Patients in the clinically evaluable population had the correct indication, a productive cough with mucopurulent or purulent sputum, and no resistant pathogens at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy for other concurrent infections; and had their clinical evaluations performed within the range of days specified in the protocol. Patients were not excluded from this data set due to having no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

A subset of clinically evaluable patients identified as "clinically qualified patients" was examined at LTFU. Clinically qualified patients were clinically evaluable patients who did not have any additional protocol variations between the TOC and LTFU visits. Patients whose LTFU assessments were done early or who took a concurrent antibacterial between the TOC and LTFU visits due to recurrence were not disqualified for these reasons.

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

Endpoints defined: The sponsor had three primary endpoints -- microbiologic eradication rate summarized by pathogen, microbiologic eradication rate summarized by patient, and clinical cure rate summarized by patient. A secondary endpoint was the appearance of new pathogens.

Clinical endpoints: The investigator assessed the following clinical signs and symptoms at the baseline, TOC, and LTFU visits: cough, sputum production, sputum appearance, dyspnea, fever, and chest sounds. The recorded signs and symptoms provided the basis for all assessments of patient clinical response.

The investigator's impression of patient clinical response used the following protocol-specified definitions.

Investigator's Assessment of Clinical Response at TOC:
- **Cure:** Absence or satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- **Failure:** No significant remission of baseline signs and symptoms; further antibacterial therapy required; or
- **Not Assessable:** Unable to assess patient; no data.

Investigator's Assessment of Clinical Response at LTFU:
- **Cure:** Absence of satisfactory remission of all baseline signs and symptoms; no further antibacterial therapy required;
- **Failure/Recurrence:** Worsening or no significant remission of baseline signs and symptoms since the previous visit; further antibacterial therapy required; or
- **Not Assessable:** Unable to assess patient; no data.

Sponsor's Assessment of Clinical Response at TOC:
- **Cure:** ≥50% decrease in clinical score at TOC relative to baseline;
- **Failure:** <50% decrease in clinical score at TOC relative to baseline; or
- **Not Assessable:** No baseline signs/symptoms or no follow-up data.

Sponsor's Assessment of Clinical Response at LTFU:
- **Cure:** Cure at TOC and <2-point increase in clinical score at LTFU relative to TOC and ≥50% decrease in clinical score at LTFU relative to baseline;
- **Recurrence:** Cure at TOC and either ≥2-point increase in clinical score at LTFU relative to TOC or <50% decrease in clinical score at LTFU relative to baseline;
- **Failure:** Failure at TOC; or
- **Not Assessable:** No baseline signs/symptoms or no follow-up data.

Table 98. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU[a,b]

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

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

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

Microbiologic Response by Pathogen: Specimens were collected for culture at baseline, 3 to 5 days after initiation of therapy, and at the TOC and LTFU visits. Sputum samples were taken most commonly, but samples of bronchial fluid, lung tissue, or transtracheal aspirate were also allowed.

At the TOC and LTFU visits, the microbiologic response of each baseline pathogen was classified as:

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

Microbiologic eradication rate by pathogen was defined as the percentage of baseline pathogens that were absent from specimens obtained at the TOC or LTFU visits. Patients with multiple baseline pathogens provided multiple observations in the analyses of microbiologic efficacy on a per pathogen basis. The eradication rate by pathogen was calculated separately for each of the follow-up visits.

Qualified patients who had persistent pathogens at TOC were automatically considered to have persistent pathogens at the LTFU visit. Patients without baseline pathogens could become superinfected.

Microbiologic Response by Patient: At the TOC visit, patients were classified by their overall microbiologic response based on the baseline and 7- to 14-day posttherapy culture results as:

- **Patients With Eradication** — All baseline pathogens eradicated at TOC *or* no material available to culture at TOC (presumed eradication);
- **Patients With Persistence** — Presence of at least 1 baseline pathogen in the TOC culture; or
- **Not Assessable** — No proven baseline pathogen *or* no follow-up data.

At the LTFU visit, patients were classified by their microbiologic response based on the baseline, 7- to 14-day posttherapy, and 21- to 35-day posttherapy culture results as:

- **No Relapse** — Patients with Eradication at TOC *and* either continued eradication of all baseline pathogens at LTFU or no material available to culture at LTFU;
- **Relapse** — Patients with Eradication at TOC *and* reappearance of at least 1 baseline pathogen at LTFU;
- **Patient With Persistence** — Patients with Persistence at TOC; or
- **Not Assessable** — No proven baseline pathogen *or* no follow-up data.

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

Medical officer's note: The above outcomes are reasonable assignments. As discussed earlier in this review, greater weight is given to clinical outcome; this reviewer questions the utility of microbiologic outcome in AECB. A category of "Patient with Relapse" is reasonable at LTFU. This reviewer is pleased that no "improved" categories are included in the final outcome measures. Relapse and persistence are appropriate assignments at LTFU. Although a sort of failure, it is a very common outcome in AECB. In fact, microbiologic eradication is probably not a reasonable expectation.

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

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

The appearance of a new pathogen together with a clinical worsening or failure at the corresponding clinical assessment also constituted a superinfection or a reinfection.

If a patient had a new organism(s) isolated in any postbaseline culture, but had no corresponding clinical assessment of signs and symptoms, the determination of pathogenicity was made by the sponsor.

Medical officer's note: These assignments are reasonable and important to monitor.

Statistical Considerations: This double-blind, randomized, comparative study of cefdinir versus cefuroxime was designed with a sample size of 190 evaluable patients per randomized group (570 total evaluable patients).

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

The following are the fixed criteria for establishing equivalence utilizing a two-tailed, 95% confidence interval for each treatment difference, using a standard normal approximation.

Table 99. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Response Rate	Treatments Are Equivalent If 95% Confidence Interval for Treatment Difference Is Within Bounds
≥90%	-10%, +10%
80%-89%	-15%, +15%
70%-79%	-20%, +20%

Medical officer's note: The above is the Applicant's strategy for analysis. The reviewer believes that 90% microbiologic eradication rate is probably not realistic; clinical outcome is more important. Thus, the clinical outcome will be tantamount.

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

Medical officer's note: The above represents the Applicant's analysis plan for safety data; this reviewer finds it acceptable.

Medical officer's note: Review of a subset of case report forms convinced this reviewer that outcome assignments were appropriately made. Therefore the Applicant's outcome assignments will be used in the analysis. Populations differ only with respect to those patients microbiologically evaluable. *See Medical officer's note on page 164.*

Demographics

Demographics, Evaluability

The following demonstrates the numbers of the populations analyzed:

Table 100. Patients With Data Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir 600 mg QD		Cefdinir 300 mg BID		Cefuroxime	
Intent-to-Treat (ITT)[a]	349	(100.0)	347	(100.0)	349	(100.0)
Clinically Evaluable[b]	278	(79.7)	286	(82.4)	286	(81.9)
Evaluable[c]	119	(34.1)	120	(34.6)	110	(31.5)
Qualified[d]	78	(22.3)	68	(19.6)	66	(18.9)

[a] All patients who were randomized to treatment
[b] Total number of patients who were clinically evaluable at TOC
[c] Total number of patients who were microbiologically and clinically evaluable at TOC
[d] Total number of evaluable patients who were microbiologically and clinically qualified at LTFU

Table 101. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir 600 mg QD N = 349		Cefdinir 300 mg BID N = 347		Cefuroxime N = 349		Total N = 1045	
Sex								
Men	223	(63.9)	202	(58.2)	210	(60.2)	635	(60.8)
Women	126	(36.1)	145	(41.8)	139	(39.8)	410	(39.2)
Race								
White	321	(92.0)	326	(93.9)	327	(93.7)	974	(93.2)
Black	17	(4.9)	17	(4.9)	21	(6.0)	55	(5.3)
Asian	7	(2.0)	2	(0.6)	1	(0.3)	10	(1.0)
Other[a]	4	(1.1)	2	(0.6)	0	(0.0)	6	(0.6)
Age, yr								
Median	59		59		61		59	
Range	18-91		15-88		20-92		15-92	
Distribution								
13 to <18	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
18 to <65	221	(63.3)	233	(67.1)	209	(59.9)	663	(63.4)
≥65	128	(36.7)	113	(32.6)	140	(40.1)	381	(36.5)

[a] Arabian, Gypsy, Mixed

Of all patients randomized to treatment, about 60% were men and over 90% were white. Although there was a wide age range (15 to 92 years), only one patient was under 18 years old, and most patients were in the 18 to <65 years-old age bracket. Just over one-third of patients were 65 years of age or older.

Medical officer's note: The demographic provide adequate representation by sex, but racial variation is extremely limited. DAIDP's Guidelines recommends that adults aged 18 and over be evaluated for this indication. Although the protocol had allowed for adolescence to be enrolled, so very few were that the reviewer need not eliminate this patient from analysis.

Smoking History:

Table 104: Smoking Status for All Enrolled Patients

Smoking Status	cefdinir bid N (%)	cefdinir qd N (%)	cefuroxime N (%)
Never	124(35.7)	133(38.1)	117(33.5)
Past	117(33.7)	118(33.8)	120(34.4)
Avg yrs	27.7	33.8	28.2
Current	106(30.5)	98(28.1)	112(32.1)
Avg yrs	33.2	28.1	33.0
Total	347 (100.0)	349(100.0)	349(100.0)
Avg yrs	30.3	31.6	30.5

Table 105: Number of Cigarettes Smoked for All Enrolled Patients Reporting Past or Present Smoking History

Smoking Status	Average number of cigarettes smoked/day	cefdinir bid N (%)	cefdinir qd N (%)	cefuroxime N(%)
Past	light (1-10 per day)	19(16.2)	15(12.7)	16(13.3)
	moderate (11-20 per day)	64(54.7)	60(50.8)	63(52.5)
	heavy (≥ 21 per day)	34(29.1)	43(36.4)	41(34.2)
Current	light (1-10 per day)	18(17.0)	17(17.3)	28(25.0)
	moderate (11-20 per day)	45(42.5)	51(52.0)	45(40.2)
	heavy (≥ 21 per day)	42(39.6)	30(30.6)	39(34.8)
	unknown	1(0.9)	0	0
Total	light (1-10 per day)	37(16.6)	32(14.8)	44(19.0)
	moderate (11-20 per day)	109(48.9)	111(51.4)	108(46.6)
	heavy (≥ 21 per day)	76(34.1)	73(33.8)	80(34.5)
	unknown	1(0.4)	0	0

Medical officer's note: It is surprising that such a great number of subjects have no prior smoking history. Roughly a third are past smokers, a third are current smokers and a third have never smoked. Although environmental factors can cause AECB, the failure of this submission to collect such critical information which would provide more compelling evidence for the diagnosis is extremely unfortunate. Among those who smoke

or smoked, the vast majority are moderate to heavy smokers. Because smokers are very apt to underestimate their habit, these subjects probably have a very significant exposure. The amount of exposure reported by the subjects is reassuing to this reviewer.

Concomittant Medical Conditions: In addition to chronic bronchitis, nearly half of the patients had other respiratory tract conditions. Common conditions were chronic obstructive pulmonary disease (COPD), asthma, and emphysema. Similar numbers of patients in each treatment group had experienced one or more lower respiratory tract infections during the year prior to the study: 63% in the cefdinir QD group, 70% in the cefdinir BID group, and 72% in the cefuroxime group. Thirty-four percent of patients in each treatment group were past smokers and 28% to 32% of patients in each treatment group were current smokers.

Table 106: Prior Pulmonary Diagnoses & Conditions Predisposing to Acute Exacerbation of Chronic Bronchitis for All Clinically Evaluable Patients

Diagnosis	cef qd	cef bid	cefurox
Aspergillosis	1		
Asthma	43	45	42
Tuberculosis	8	14	10
Emphysema/COPD	96	108	104
Pulmonary cancer	2	1	2
Allergic bronchitis	1	1	
Cold	2		
Pulmonary embolus	1		2
Bronchiectasis	1	4	1
Pulmonary abscess	1		
Pneumonia	2		2
Collapsed lung	1		
Chronic inhalant allergies	1		
Chronic airflow obstruction		1	
Silicosis			1
Sarcoidosis		1	2
Pleurisy		1	
Interstitial pulmonary fibrosis		2	2
Pigeon Fancier's Lung			1
History of pneumothorax		2	1

Medical officer's note: Because the information of prior and current pulmonary diagnoses was generated by an open ended question regarding medical history, the information obtained is extremely limited. Although the diagnoses of emphysema/COPD and asthma are the most common, many of the other diagnoses do not provide an insight into the etiology of the subjects' AECB. It would have been preferable to have obtained this important data in a more structured fashion that would provide more information into the subjects' chronic bronchitis. In addition, information regarding recent prior therapy for exacerbations would have been useful. The Applicant provides in his report

the following: "Similar numbers of patients in each treatment group had experienced 1 or more lower respiratory tract infections during the year prior to the study: 63% in the cefdinir QD group, 70% in the cefdinir BID group, and 72% in the cefuroxime group." More details on the range, severity and exact diagnosis would have been helpful.

Pathogens Isolated

The most common pathogens were *Haemophilus influenzae* (218 patients), *Streptococcus pneumoniae* (82 patients), *Haemophilus parainfluenzae* (72 patients), and *Moraxella catarrhalis* (53 patients). Multiple pathogens were cultured from 115 patients, of which 31 (27%) had *S. pneumoniae* and *H. influenzae.*

Table 108. Distribution of Patients by Baseline Pathogen
(Number of Patients)

	Cefdinir		*Cefuroxime*
	600 mg QD	*300 mg BID*	
Gram-Positive			
Streptococcus pneumoniae	*37*	*22*	*23*
Gram-Negative			
Haemophilus influenzae	*74*	*74*	*70*
Haemophilus parainfluenzae	*21*	*28*	*23*
Moraxella catarrhalis	*20*	*15*	*18*

Medical officer's note: The Applicant submitted a long list of pathogens that included many Enterobacteriaciae species and commensal Neisseria species. This Reviewer believes that the above pathogens are of interest and that it would be very difficult, if not impossible to prove that any of the other pathogens listed by the Applicant were truly responsible for the subject's symptoms.

Of *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis* isolates with documented β-lactamase results, 29/272 (11%), 10/73 (14%), and 37/74 (50%), respectively, were β-lactamase positive. Of the β-lactamase-positive isolates, only one *H. parainfluenzae* isolate was resistant to cefdinir and none were resistant to cefuroxime.

Medical officer's note: It greatly suprises this Reivewer that such a small percent of isolates were obtained. Nationwide, beta lactamase resistant occurs in about 95% of Moraxella catarrhalis isolates and 40% of Haemophilus influenzae isolates.

Clinical Signs and Symptoms

At baseline, productive cough and purulent or mucopurulent sputum were required for eligible patients. Over 95% of patients enrolled in the study had a moderate or severe

cough at baseline, and over 90% of patients had moderate or severe sputum production at baseline. The majority of patients also presented with rhonchi, wheezing, and some degree of dyspnea. Approximately one third of the patients presented with rales, 20% with fever, and less than 10% with fremitus or pleural rub at baseline.. There were no apparent differences between treatment groups or between the ITT and evaluable patient populations.

Table 109. Patient Disposition - All Patients (Number of Patients)

Patient Disposition	*Cefdinir*		*Cefuroxime*	*Total*
	600 mg QD	*300 mg BID*		
Randomized to Treatment	*349*	*347*	*349*	*1045*
Discontinued Treatment				
Adverse Event	*17[a]*	*15*	*13*	*44[b]*
No Baseline Pathogen	*5*	*3*	*8*	*16*
Lack of Compliance	*5*	*3*	*7*	*15*
Resistant Baseline Pathogen	*3[a]*	*3*	*7*	*13*
Failure at End of Therapy[c]	*4*	*4*	*3*	*11*
Other/Administrative[d]	*2*	*2*	*2*	*6*
Completed Treatment[e]	*314*	*317*	*309*	*940*

[a] *Patient 40, Center 20, discontinued treatment with cefdinir QD because her baseline pathogen was resistant to both study drugs (CRF 10) and also because she experienced severe diarrhea beginning on the first day of treatment (CRF 8).*

[b] *Another 9 patients were withdrawn from the study due to an adverse event that occurred after treatment ended but before LTFU.*

[c] *These patients did not complete treatment. They discontinued due to lack of efficacy.*

[d] *Patient choice (2 patients), lost to follow-up (1 patient), lost sputum sample (1 patient), history of epilepsy (1 patient), patient died during the study and the day of death was unknown (1 patient).*

[e] *Based on the investigator assessment of patient status at the end of treatment (Case Report Form 10)*

Medical officer's note: The above table provides reasonable explanation of patient outcome. It is unfortunate, but many studies have this much loss to follow up. There does not appear to be bias by treatment arm. The "No baseline pathogen" category is derived by Applicant and includes many microorganisms that the reviewer does not consider undisputed pathogens in AECB.

Table 110. Reasons Patients Were Not Evaluable at TOC or Were Disqualified at LTFU

(Number of Patients)

	Cefdinir		Cefuroxime
	QD	BID	
Test-of-Cure Visit			
Exclusions From Evaluable Analyses[a]			
No Proven Baseline Pathogen	158	144	163
Culture Out of Time Range[b]	45	23	39
Clinical Assessment Out of Range[b]	35	21	29
Culture Missed	15	20	23
Baseline Pathogen(s) Resistant to Either Study Drug	12	20	15
Medication Not Taken as Prescribed[b]	13	11	16
Baseline X-Ray Missed	9	10	12
No Baseline Susceptibility Tests	4	9	5
Disallowed Prior Antibacterial	7	8	5
Clinical Assessment Missed	5	4	5
Concurrent Antibacterial[b]	7	3	5
Randomization Violation	4	1	2
No Baseline Signs or Symptoms	0	2	0
Condition Prevented Assessment	0	1	0
Wrong Indication	0	1	1
Long-Term Follow-Up Visit			
Disqualifications From Qualified Analyses[a]			
Culture Missed	33	39	34
Clinical Assessment Missed	33	36	31
Concurrent Antibacterial[b]	9	17	16
Clinical Assessment Out of Range[b]	11	9	7
Culture Out of Range[b]	11	9	6
Total Disqualified	54	65	54

[a] *Patients who had multiple reasons for exclusion or disqualification are displayed for each reason that applied.*

[b] *Patients who had cultures or assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early failures/recurrences were not removed from the analyses for these reasons.*

Medical officer's note: It is unfortunate that such emphasis was placed on microbiologic outcomes for evaluability: the clinical outcomes are of greater interest. However, this Reviewer spot finds the above reasons acceptable and discerns no bias by

treatment arm. "No baseline pathogens" eliminates all pathogens but Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Haemophilus parainfluenzae.

Table 111. Patients With Data Included in Efficacy Summaries
[Number (%) of Patients]

Patient Population	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
Intent-to-Treat (ITT)[a]	349	(100.0)	347	(100.0)	349	(100.0)
Clinically Evaluable [b]	278	(79.7)	286	(82.4)	286	(81.9)
Evaluable[c]	119	(34.1)	120	(34.6)	110	(31.5)
Qualified[d]	78	(22.3)	68	(19.6)	66	(18.9)

[a] *All patients who were randomized to treatment*
[b] *Total number of patients who were clinically evaluable at TOC*
[c] *Total number of patients who were microbiologically and clinically evaluable at TOC*
[c] *Total number of evaluable patients who were microbiologically and clinically qualified at LTFU*

Medical officer's note: The FDA and Applicant populations are identical in the ITT and clinically evaluable populations. However, the reviewer only evaluated those patients with bacterial pathogens reasonably likely to be etiologic in AECB. This includes Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. Although the role of Haemophilus parainfluenzae is a subject of debate, the Applicant has demonstrated efficacy against this pathogen in CAP and was therefore considered here. Staphylococcus aureus was eliminated because it is impossible to determine whether this agent is a contaminant, colonizer or pathogen. Series that have evaluated Staphylococcus aureus in AECB have concluded it to be an uncommon cause. The Applicant's submission identified it as a fairly common cause. Thus, the reviewer feels justified in her conclusion that the data provided does not support. It is extremely difficult to imagine assigning causality to many of the other bacteria, such as Enterobacteriaciae, other streptococci, and commensal Neisseria species, which were incorporated into the Applicant's analysis.

Safety Evaluations

Patient 17, Center 6, and Patient 17, Center 7, both randomized to cefdinir BID, did not receive study medication and are not included in the safety evaluations.

Medical officer's note: This is acceptable.

Efficacy

Table 112. Microbiologic Eradication Rate by Baseline Pathogen at the Test-of-Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir 600 mg QD		Cefdinir 300 mg BID		Cefuroxime	
	n/N	%	n/N	%	n/N	%
Streptococcus pneumoniae	34/38	89.5	35/40	87.5	30/30	100.0
Haemophilus influenzae	56/70	80.0	58/74	78.4	52/71	73.2
β-Lactamase positive	4/4	100.0	4/7	57.1	8/10	80.0
β-Lactamase negative	51/65	78.4	53/66	80.3	43/60	71.7
β-Lactamase unknown	1/1	100.0	1/1	100.0	1/1	100.0
Haemophilus parainfluenzae	19/19	100.0	27/30	90.0	20/21	95.2
β-Lactamase positive	2/2	100.0	3/3	100.0	3/3	100.0
β-Lactamase negative	13/13	100.0	21/24	87.5	15/16	93.8
β-Lactamase unknown	4/4	100.0	3/3	100.0 1	2/2	100.0
Moraxella catarrhalis	19/19	100.0	17/20	85.0	20/21	95.2
β-lactamase positive	14/14	100.0	4/6	66.7	8/9	88.9
β-lactamase negative	5/5	100.0	13/14	92.9	12/12	100.0
Total	222/254	87.4	239/288	82.9	214/256	83.6

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

Table 113 displays the 95% confidence intervals with continuity correction.

Table 113. Comparisons of Microbiologic Eradication Rates by Pathogen for Evaluable Patients at TOC

Comparison	95% CI	Criterion	Result
Cefdinir QD-Cefuroxime	*(-2.69, 10.30)*	*15%*	*Equiv.*
Cefdinir BID-Cefuroxime	*(-7.25, 6.04)*	*15%*	*Equiv.*
Cefdinir QD-Cefdinir BID	*(-1.91, 10.74)*	*15%*	*Equiv.*

Medical officer's note: Equivalence is demonstrated by these comparisons.

Microbiologic Eradication by Patient

Table 114. Microbiologic Eradication Rate by Patient According to Baseline Pathogen at the Test-of Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Streptococcus pneumoniae	25/27	92.6	19/21	90.5	19/19	100.0
Gram-Negative						
Haemophilus influenzae	49/59	83.1	45/58	77.6	40/56	71.4
Haemophilus parainfluenzae	17/17	100.0	24/27	88.9	18/19	94.7
Moraxella catarrhalis	16/16	100.0	11/14	78.6	15/16	93.8
Total	107/119	89.9	99/120	82.5	92/110	83.6

n/N = Number of patients with baseline pathogens eradicated/total number of patients.

Table 115 displays the 95% confidence intervals with continuity correction.

Table 115. Comparisons of Microbiologic Eradication Rates by Patient for Evaluable Patients at TOC

Comparison	Pooled Rates		
	95% CI	Criterion	Result
Cefdinir QD-Cefuroxime	(-3.37, 15.93)	15%	Equiv.
Cefdinir BID-Cefuroxime	(-11.70, 9.43)	15%	Equiv.
Cefdinir QD-Cefdinir BID	(-2.11,16.94)	15%	Equiv.

Medical officer's note: Cefdinir qd and bid compare favorably to cefuroxime; cefdinir qd appears superior to cefdinir bid by this analysis. Good numbers of the pathogens of interest have been isolated in this study.

Clinical Cure by Patient

Table 116. Clinical Cure Rate[a] by Patient According to Baseline Pathogen at the Test-of Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Streptococcus pneumoniae	25/27	92.6	15/21	71.4	15/19	78.9
Gram-Negative						
Haemophilus influenzae	44/59	74.6	40/58	69.0	41/56	73.2
Haemophilus parainfluenzae	15/17	88.2	22/27	81.5	15/19	78.9
Moraxella catarrhalis	13/16	81.3	9/14	64.3	13/16	81.3
Total	97/119	81.5	86/120	71.7	84/110	76.4

n/N = Number of patients with a clinical cure at TOC/total number of patients.
[a] *Combined investigator/sponsor determination*

Table 117. Comparisons of Clinical Cure Rates by Patient for Microbiologically-Clinically Evaluable Patients at TOC

Comparison	Pooled Rates		
	95% CI	Criterion	Result
Cefdinir QD-Cefuroxime	*(-6.29, 16.59)*	*20%*	*Equiv*
Cefdinir BID-Cefuroxime	*(-16.88, 7.49)*	*20%*	*Equiv*
Cefdinir QD-Cefdinir BID	*(-1.65, 21.34)*	*20%*	*Equiv*

Medical officer's note: Equivalence is demonstrated by in both cefdinir regimens against cefuroxime. Inexplicably, the cefdinir bid regimen is inferior to the cefinir qd regimen by this analysis.

Long-Term Follow-Up Visit (21-35 Days Posttherapy): Microbiologic Eradication by Pathogen and Patient

Evaluable patients who continued to satisfy necessary protocol requirements between the TOC and LTFU visits were considered qualified at LTFU. Qualified patients who had persistent pathogens at the TOC visit were automatically considered to have persistent pathogens at the LTFU visit.

Table 119. Microbiologic Eradication Rate by Baseline Pathogen at the Long-Term Follow-Up Visit - Evaluable Patients Who Qualified for Long-Term Analysis

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Streptococcus pneumoniae	23/27	85.2	27/27	100.0	21/21	100.0
Gram-Negative						
Haemophilus influenzae	38/42	90.5	40/40	100.0	38/39	97.4
Haemophilus parainfluenzae	13/13	100.0	19/19	100.0	13/13	100.0
Moraxella catarrhalis	15/15	100.0	11/11	100.0	14/14	100.0
Total	89/97	91.8	77/77	100.0	86/87	98.8

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

Table 120. Microbiologic Eradication Rate by Patient According to Baseline Pathogen at the Long-Term Follow-Up Visit - Evaluable Patients Who Qualified for Long-Term Analysis

Baseline Pathogen	Cefdinir				Cefuroxime	
	600 mg QD		300 mg BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Streptococcus pneumoniae	18/20	90.0	15/15	100.0	14/14	100.0
Streptococcus pyogenes	3/3	100.0	3/3	100.0	1/1	100.0
Gram-Negative						
Haemophilus influenzae	32/35	91.4	30/30	100.0	28/28	100.0
Haemophilus parainfluenzae	11/11	100.0	17/17	100.0	13/13	100.0
Moraxella catarrhalis	12/12	100.0	6/6	100.0	11/11	100.0
Total	73/78	93.6	68/68	100.0	66/66	100.0

n/N = Number of patients with baseline pathogens eradicated/total number of patients.

Medical officer's note: Acceptable rates of microbiologic eradication rates by patient and pathogens are seen in every treatment arm. By these analyses, cefdinir qd performs worse than either cefdinir bid or cefuroxime. However, these are not primary outcome measures and all the rates are acceptable.

Clinically Evaluable and Clinically Qualified Analyses

TOC Visit (7-14 Days Posttherapy)

Clinical Cure Rate

In the clinically evaluable patient population at the TOC visit, the clinical cure rates were 229/278 (82%) in the cefdinir qd group, 225/286 (79%) in the cefdinir bid group, and

232/286 (81%) in the cefuroxime group. Table 121 displays the 95% confidence intervals with continuity correction

Table 121. Comparisons of Clinical Cure Rates by Patient (Clinically Evaluable Population) at TOC

Comparison	*95% CI*	*Criterion*	*Result*
Cefdinir QD-Cefuroxime	*(-5.47, 7.98)*	*15%*	*Equiv*
Cefdinir BID-Cefuroxime	*(-9.36, 4.47)*	*20%*	*Equiv*
Cefdinir QD-Cefdinir BID	*(-3.18, 10.58)*	*20%*	*Equiv*

Medical officer's note: *This reviewer considers this outcome measure the most important. No differences in cure rates by treatment arm are detected among clinically evaluable patients.*

LTFU Visit (21-35 Days Posttherapy)

Clinical Cure

Among clinically qualified patients who were classified as cures at the TOC visit, the overall clinical cure rates at the LTFU visit (ie, no clinical recurrence) were similar in all three groups: 181/192 (94%) in the cefdinir QD group, 185/194 (95%) in the cefdinir BID group, and 186/195 (95%) in the cefuroxime group.

Medical officer's note: *No differences are detected in clinical cure rate among the clinically evaluable population qualified at long term follow up. All cure rates at LTFU are very acceptable.*

Table 122. Investigator Versus Combined Investigator/Sponsor Clinical Response Determination at LTFU - Clinically Qualified Patients

Investigator Determination	*Combined Investigator/Sponsor Determination*								
	Cefdinir								
	QD N = 200			*BID N = 202*			*Cefuroxime N = 203*		
	Cure	*Failure*	*Recurrence*	*Cure*	*Failure*	*Recurrence*	*Cure*	*Failure*	*Recurrence*
Cure	*181*	*5*	*0*	*184*	*2*	*0*	*186*	*4*	*0*
Failure/Recurrence	*0*	*3*	*11*	*0*	*6*	*9*	*0*	*4*	*9*
Not Assessable	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*

Medical officer's note: *It is reassuring that application of the combined investigator/sponsor determination shows little discrepancy from the investigatory determination alone.*

Intent-to-Treat Analyses

Test-of-Cure Visit (7-14 Days Posttherapy)

Table 123. Clinical Efficacy Results at TOC - ITT Patients

	Clinical Cure Rate	
	n/N	%
Cefdinir QD	229/349	65.6
Cefdinir BID	225/347	64.8
Cefuroxime	232/349	66.5

n/N = Number of patients with combined determination of cure/total number of patients.

Medical officer's note: *As would be expected in the intent to treat analysis, clinical cure rate is lower than in evaluable population. However, all three treatment arms demonstrate similar efficacy.*

Long-Term Follow-Up Visit (21-35 Days Posttherapy)

Table 124. Clinical Cure Rate by Patient Results at LTFU - ITT Population

	Clinical Cure Rate by Patient	
	n/N	%
Cefdinir QD	181/349	51.9
Cefdinir BID	185/347	53.3
Cefuroxime	186/349	53.3

n/N = Number of patients with combined investigator/sponsor determination of cure (ie, no recurrence) at LTFU/total number of patients.

Medical officer's note: *As would be expected, the further out the follow up, the smaller the population. Once again, all three treatment arms demonstrate similar efficacy.*

Patients With Cefdinir-Resistant Streptococcus pneumoniae

Three patients who were treated with cefdinir had cefdinir-resistant *S. pneumoniae* at baseline. All three patients completed treatment and were assessed as clinically cured at TOC. One patient (Patient 5, Center 28; cefdinir 600 mg QD) had microbiologic persistence. The other two patients (Patient 34, Center 35, cefdinir 600 mg QD; Patient 46, Center 35, cefdinir 300 mg BID) had microbiologic eradication at TOC. All three patients had a second, cefdinir-sensitive pathogen at baseline, each of which had the same microbiologic response as the resistant *S. pneumoniae*. There were no known penicillin-resistant *S. pneumoniae* isolates at baseline.

Medical officer's note: The numbers are too small to draw any conclusions. In addition, because microbiologic outcomes are problematic in AECB, it would be dangerous to conclude efficacy based on this indication.

Appearance of New Pathogens During the Study

Reinfections

Seven patients were reinfected after the TOC visit with pathogens not present at baseline.

Table 125. Patients With Reinfections - ITT Patients (Number of Patients)

Pathogen(s)	Cefdinir		Cefuroxime
	QD	BID	
Gram-Positive			
Streptococcus pneumoniae	0	1	0
Gram-Negative			
Haemophilus influenzae	0	1	0
Moraxella catarrhalis	2	3	0
Total	2	5	0

Medical officer's note: The Applicant appears to have included the appearance of any new bacterial species in its analysis of this topic. This reviewer limited this analysis only to the pathogens of interest. The numbers are too small to draw conclusions.

Safety

All and Drug-Associated Adverse Events

More patients in all three treatment groups experienced adverse events in the gastro-intestinal system than in any other body system. Diarrhea was the most frequently occurring adverse event, occurring in 10% of cefdinir QD-treated patients, 8% of cefdinir BID-treated patients, and 6% of cefuroxime-treated patients. There was no significant difference between the treatment groups in the rates of patients who experienced diarrhea ($p = 0.281$). Diarrhea was generally considered drug-associated. Other adverse events that occurred in at least 2% of patients in any treatment group were headache, nausea, rash, and accidental injury.

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Table 126. All and Associated Adverse Events by Body System - All Patients Who Received Study Medication
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir 600 mg QD N = 349				Cefdinir 300 mg BID N = 345				Cefuroxime N = 349			
	All		Assoc		All		Assoc		All		Assoc	
DIGESTIVE SYSTEM	44*	(12.6)	37*	(10.6)	43*	(12.5)	36*	(10.4)	40*	(11.5)	31*	(8.9)
Diarrhea	33	(9.5)	29	(8.3)	28	(8.1)	27	(7.8)	22	(6.3)	19	(5.4)
Nausea	9	(2.6)	7	(2.0)	5	(1.4)	3	(0.9)	9	(2.6)	8	(2.3)
Constipation	1	(0.3)	0	(0.0)	3	(0.9)	2	(0.6)	1	(0.3)	0	(0.0)
Dyspepsia	2	(0.6)	2	(0.6)	3	(0.9)	2	(0.6)	2	(0.6)	1	(0.3)
Gastritis	0	(0.0)	0	(0.0)	3	(0.9)	2	(0.6)	1	(0.3)	0	(0.0)
Abnormal Stools	2	(0.6)	2	(0.6)	2	(0.6)	2	(0.6)	0	(0.0)	0	(0.0)
Vomiting	1	(0.3)	0	(0.0)	2	(0.6)	1	(0.3)	3	(0.9)	2	(0.3)
Dry Mouth	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Flatulence	1	(0.3)	1	(0.3)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Increased Appetite	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Melena	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Anorexia	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastroenteritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Gastrointestinal Hemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Hepatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	1	(0.3)
Intestinal Obstruction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Periodontal Abscess	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rectal Hemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
BODY AS A WHOLE	18*	(5.2)	7*	(2.0)	17*	(4.9)	4	(1.2)	25*	(7.2)	7	(2.0)
Headache	2	(0.6)	1	(0.3)	7	(2.0)	1	(0.3)	8	(2.3)	4	(1.1)
Abdominal Pain	6	(1.7)	6	(1.7)	3	(0.9)	1	(0.3)	4	(1.1)	3	(0.9)
Back Pain	1	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Moniliasis	1	(0.3)	1	(0.3)	2	(0.6)	2	(0.6)	0	(0.0)	0	(0.0)
Pain	1	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Accidental Injury	3	(0.9)	0	(0.0)	1	(0.3)	0	(0.0)	7	(2.0)	0	(0.0)
Asthenia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Flu Syndrome	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Generalized Edema	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Abscess	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Chest Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Infection	4	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Intentional Injury	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neck Pain	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
RESPIRATORY SYSTEM	11	(3.2)	0	(0.0)	15	(4.3)	0	(0.0)	10*	(2.9)	0	(0.0)
Bronchitis	1	(0.3)	0	(0.0)	4	(1.2)	0	(0.0)	2	(0.6)	0	(0.0)
Pneumonia	1	(0.3)	0	(0.0)	3	(0.9)	0	(0.0)	2	(0.6)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)

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

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

Table 126. All and Associated Adverse Events by Body System - All Patients Who Received Study Medication
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir 600 mg QD N = 349				Cefdinir 300 mg BID N = 345				Cefuroxime N = 349			
	All		Assoc		All		Assoc		All		Assoc	
RESPIRATORY SYSTEM (continued)												
Rhinitis	5	(1.4)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Asthma	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Epistaxis	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Sinusitis	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Lung Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Lung Edema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Respiratory Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Voice Alteration	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
SKIN AND APPENDAGES	11	(3.2)	9	(2.6)	9	(2.6)	6	(1.7)	4	(1.1)	1	(0.3)
Rash	7	(2.0)	5	(1.4)	5	(1.4)	4	(1.2)	1	(0.3)	0	(0.0)
Herpes Zoster	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.6)	1	(0.3)	1	(0.3)
Cutaneous Moniliasis	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fungal Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Herpes Simplex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Sweating	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	2	(0.6)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR SYSTEM	5	(1.4)	0	(0.0)	5	(1.4)	0	(0.0)	3*	(0.9)	0	(0.0)
Pulmonary Embolus	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Palpitation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Vasodilation	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Angina Pectoris	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Atrial Fibrillation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Congestive Heart Failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Cor Pulmonale	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Heart Failure	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial Infarction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Syncope	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tachycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
METABOLIC AND NUTRITIONAL	1*	(0.3)	0	(0.0)	4	(1.2)	1	(0.3)	1	(0.3)	0	(0.0)
Alkaline Phosphatase Increased	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dehydration	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Edema	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Hyperuricemia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Hypokalemia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral Edema	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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

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

TABLE 126. All and Associated Adverse Events by Body System - All Patients Who Received Study Medication

[Number (%) of Patients]

(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir 600 mg QD N = 349				Cefdinir 300 mg BID N = 345				Cefuroxime N = 349			
	All		Assoc		All		Assoc		All		Assoc	
HEMIC AND LYMPHATIC SYSTEM	0	(0.0)	0	(0.0)	3	(0.9)	0	(0.0)	1	(0.3)	0	(0.0)
Leukopenia	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Eosinophilia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Ecchymosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
NERVOUS SYSTEM	3	(0.9)	1	(0.3)	3	(0.9)	0	(0.0)	5[a]	(1.4)	1	(0.3)
Delirium	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dizziness	1	(0.3)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Neuralgia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Agitation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Anxiety	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hallucinations	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Insomnia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Nervousness	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Paresthesia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
UROGENITAL SYSTEM	8	(2.3)	3	(0.9)	3	(0.9)	1	(0.3)	6	(1.7)	1	(0.3)
Urinary Tract Disorder	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Urinary Tract Infection	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Vaginal Moniliasis[b]	2	(1.6)	2	(1.6)	1	(0.7)	1	(0.7)	1	(0.7)	1	(0.7)
Albuminuria	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cystitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Dysuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Glycosuria	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urine Abnormality	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Vaginitis[b]	1	(0.8)	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
MUSCULOSKELETAL SYSTEM	2	(0.6)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.3)	0	(0.0)
Arthralgia	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Myalgia	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Arthritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
SPECIAL SENSES	1	(0.3)	1	(0.3)	2	(0.6)	1	(0.3)	6	(1.7)	2	(0.6)
Ear Pain	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Tinnitus	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)
Conjunctivitis	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Ear Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
Otitis Media	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Taste Loss	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)
Taste Perversion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.3)

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

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

[b] *The percentages are based on the number of women in each treatment group: 126 in the cefdinir QD group, 144 in the cefdinir BID group, and 139 in the cefuroxime group.*

Adverse Events by Age, Sex and Race

Overall, there was very little difference in adverse event or associated adverse event rates between patients 18 to <65 years of age and patients ≥65 years of age. The incidence of diarrhea was somewhat lower in older patients treated with either cefdinir BID or cefuroxime (4% and 5%, respectively, versus 10% and 7% in younger patients). The incidence of diarrhea in patients receiving cefdinir QD was approximately the same in patients 18 to <65 or ≥65 years of age (10% vs 9%). Other adverse events occurred with such low frequency that there were no obvious differences between the two age groups. Women had a slightly higher overall incidence of adverse events than men in all treatment groups. This was partly due to a higher incidence of adverse events in the urogenital system, including urinary tract infection, vaginal moniliasis, and vaginitis. Other than this, no particular body system or event appeared to be responsible for the difference. The rates of associated adverse events were more similar between the sexes: 14% of both men and women treated with cefdinir QD experienced an associated adverse event, and 11% of men and women treated with cefuroxime experienced an associated adverse event. In the cefdinir BID group, 10% of men versus 17% of women experienced an associated adverse event. This difference was primarily due to small differences in adverse event rates in the body as a whole (moniliasis, headache abdominal pain), digestive system (diarrhea), and urogenital system (vaginal moniliasis, vaginitis). Over 90% of patients in the study were white. No clinically important differences in adverse event profiles were apparent based on race.

Medical officer's note: *This safety data is consistent with that submitted in other sections of this application and resembles other extended spectrum cephalosporins. There are no surprises.*

Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events

Deaths

Seven patients died during this study. None of the deaths was considered to be associated with study medication.

Table 127. Patients Who Died During the Study

Center	Patient Number	Age (yr), Sex	Cause of Death	Day of Last Dose of Study Drug	Day of Death
Cefdinir 600 mg QD					
6	*7*	*53, M*	*Murder*[a]	*Unknown*	*Unknown (≤16)*
26	*10*	*80, M*	*Cardiopulmonary Decompensation*	*8*	*12*
Cefdinir 300 mg BID					
3	*10*	*78, M*	*Pulmonary Embolism*	*1*	*2*
17	*118*	*80, M*	*Respiratory Failure*[b]	*7*	*11*
Cefuroxime Axetil 250 mg BID					
24	*11*	*74, M*	*Respiratory Failure*[b]	*10*	*21*
28	*6*	*83, M*	*Cardiopulmonary Arrest*	*4*	*4*
34	*4*	*68, F*	*Cerebral Embolism*	*10*	*48*

[a] *This patient was presumed to have been a murder victim. His body was found some time after death occurred, so the time of death and number of doses of cefdinir taken are not known.*

[b] *Due to AECB*

Medical officer's note: Review of the narratives submitted by the Applicant show no suggestion of treatment effect in the deaths. All but one of the deaths (i.e., the murder) occurred in seriously debilitated patients and were not unexpected.

Serious Adverse Events

Twenty patients experienced a serious, nonfatal adverse event. Only one was considered by the investigator to be treatment-associated: Patient 91, Center 17, experienced a severe gastrointestinal hemorrhage after four days of treatment with cefuroxime that the investigator considered possibly related to study drug.

Patient 4, Center 34, was hospitalized for a myocardial infarction on Day 16 after completing treatment with cefuroxime. While still hospitalized, she experienced a probable cerebral embolism and died. Thus, although her myocardial infarction was a serious adverse event and not directly fatal, this patient is listed in the deaths section of this report.

Medical officer's note: Review of the narratives submitted by the Applicant do not convincingly suggest that the treatment was etiologic.

Table 128. Nonfatal Serious Adverse Events
(Page 1 of 2)

Center	Patient Number	Age (yr), Sex	Adverse Event[a]	Intensity	Relationship to Study Medication[b]	Study Day of Onset	Management of Study Drug	Outcome[c]
Cefdinir 600 mg QD								
20	4	66, M	Asthma	Severe	Definitely Not	31	None	Not Yet Recovered
24	8	60, M	Pneumonia	Moderate	Unlikely	11	None	Recovered
34	31	70, F	Angina (Angina Pectoris)	Moderate	Definitely Not	32	None	Recovered
35	11	53, F	Exacerbation of Chronic Bronchitis (Bronchitis)	Severe	Definitely Not	4	Discontinued	Recovered
	48	42, F	Syncope	Moderate	Definitely Not	3	None	Recovered
36	3	19, M	Asthma	Severe	Definitely Not	11	None	Recovered
	12	41, F	Congestive Heart Failure	Severe	Definitely Not	20	None	Recovered
Cefdinir 300 mg BID								
1	21	75, M	Bronchitis	Severe	Definitely Not	5	Discontinued	Recovered
17	67	67, M	Epistaxis	Severe	Unlikely	21	None	Recovered
26	2	73, M	Tonsillitis (Pharyngitis)	Moderate	Unlikely	15	None	Recovered
	14	64, M	Pneumonia	Moderate	Definitely Not	16	None	Recovered
34	22	79, M	Exacerbation of Bronchitis (Bronchitis)	Moderate	Definitely Not	35	None	Recovered
			Chronic Obstructive Pulmonary Disease (Lung Disorder)	Moderate	Definitely Not	35	None	Recovered
35	40	75, M	Worsening of AECB (Bronchitis)	Severe	Definitely Not	15	None	Recovered
			Ear Ache (Ear Pain)	Severe	Definitely Not	15	None	Recovered

[a] When the investigator and COSTART terms differ, the COSTART term appears in parentheses.
[b] According to the investigator
[c] As of the last study visit

TABLE 128. Nonfatal Serious Adverse Events
(Page 2 of 2)

Center	Patient Number	Age (yr), Sex	Adverse Event[a]	Intensity	Relationship to Study Medication[b]	Study Day of Onset	Management of Study Drug	Outcome[c]
Cefuroxime 250 mg BID								
1	13	77, M	Chronic Bronchitis (Bronchitis)	Moderate	Definitely Not	4	Discontinued	Recovered
17	91	34, M	Gastrointestinal Bleed (Gastrointestinal Hemorrhage)	Severe	Possibly	4	Discontinued	Recovered
	134	78, M	Laceration of Eyebrow Area (Accidental Injury)	Moderate	Definitely Not	39	None	Recovered
			Laceration of Chin (Accidental Injury)	Moderate	Definitely Not	39	None	Recovered
			Bruising of Hand (Ecchymosis)	Moderate	Definitely Not	39	None	Recovered
24	4	72, M	Atypical Chest Pain (Chest Pain)	Moderate	Unlikely	4	None	Recovered
	5	90, M	Hip Fracture (Accidental Injury)	Severe	Unlikely	12	None	Recovered/ Sequelae
31	6	83, F	Lung Oedema (Lung Edema)	Moderate	Definitely Not	24	None	Recovered
			Pneumonia	Mild	Definitely Not	24	None	Recovered
35	1	81, F	Atrial Fibrillation	Moderate	Definitely Not	5	None	Recovered

[a] When the investigator and COSTART terms differ, the COSTART term appears in parentheses.
[b] According to the investigator
[c] As of the last study visit

Withdrawals Due to Adverse Events

Forty-five patients discontinued treatment because of an adverse event; 17 (5%) from the cefdinir QD group, 15 (4%) from the cefdinir BID group, and 13 (4%) from the cefuroxime group. Nine patients withdrew from the study after completing treatment but before the LTFU because of an adverse event; 3 (1%) from the cefdinir QD group, 2 (1%) from the cefdinir BID group, and 4 (1%) from the cefuroxime group.

Diarrhea, which occurred in all three treatment groups, was the most common reason patients discontinued medication. Two percent of cefdinir QD-treated patients, 2% of cefdinir BID-treated patients, and 1% of cefuroxime-treated patients discontinued treatment because of diarrhea.

Rash caused discontinuation in 1% of both cefdinir treatment groups, and in none of cefuroxime-treated patients. Other events that caused discontinuation or withdrawal in two or more patients included abdominal pain, headache, pulmonary embolus, dyspepsia, nausea, bronchitis, sinusitis, and urticaria.

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 1 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event[a]	Relationship to Study Medication[b]	Study Day of Onset	Study Day Drug Discontinued	Outcome[c]
Cefdinir 600 mg QD							
11	12	47, F	Melaena (Melena)	Unlikely	7	7	Recovered
17	42	49, M	Diarrhoea (Diarrhea)	Probably	2	7	Recovered
	107	74, M	Abdominal Pain	Possibly	3	3	Recovered
	115	67, F	Diarrhoea (Diarrhea)	Probably	2	6	Recovered
	129	70, M	Diarrhoea (Diarrhea)	Probably	2	5	Recovered
	136	46, M	Dyspepsia	Probably	3	5	Recovered
	142	43, F	Diarrhoea (Diarrhea)	Probably	3	4	Recovered
18	2	40, M	Diarrhoea (Diarrhea)	Probably	7	7	Recovered
	5	63, M	Urticarial Rash (Urticaria)	Probably	6	6	Recovered
20	18	57, M	Conjunctivitis	Probably	4	6	Recovered
			Exanthema (Rash)	Probably	5		Recovered
	40	22, F	Diarrhoea (Diarrhea)	Definitely	1	2	Recovered
	60	38, M	Gastralgia (Abdominal Pain)	Probably	1	2	Recovered
			Diarrhoea (Diarrhea)	Probably	1		Recovered
			Cephalgia (Headache)	Probably	1		Recovered

[a] *If the investigator and COSTART terms differ, the COSTART term appears in parentheses.*
[b] *According to the investigator*
[c] *As of the last study visit*

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TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 2 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event[a]	Relationship to Study Medication[b]	Study Day of Onset	Study Day Drug Discontinued	Outcome[c]
Cefdinir 600 mg QD (cont)							
20	66	44, F	Diarrhoea (Diarrhea)	Possibly	4	6	Recovered
			Exanthema (Rash)	Possibly	5		Recovered
	67	55, M	Allergic Exanthema (Rash)	Probably	5	7	Recovered
	83	50, M	Gastralgia (Abdominal Pain)	Possibly	2	3	Recovered
			Nausea	Possibly	2		Recovered
32	35	43, M	Sinusitis	Definitely Not	12	Completed Medication	Recovered
34	28	71, F	Urinary Tract Infection	Definitely Not	18	Completed Medication	Recovered
	31	70, F	Angina (Angina Pectoris)	Definitely Not	32	Completed Medication	Recovered
35	11	53, F	Exacerbation of Chronic Bronchitis (Bronchitis)	Definitely Not	4	4	Recovered
	59	50, F	Urticaria	Definitely	1	1	Recovered
Cefdinir 300 mg BID							
1	21	75, M	Bronchitis	Definitely Not	5	5	Recovered
3	10	78, M	Pulmonary Embolism (Pulmonary Embolus)	Definitely Not	2	1	Died
6	32	31, F	Diarrhoea (Diarrhea)	Probably	3	8	Recovered
			Allergic Exanthema (Rash)	Probably	5		Recovered
	39	56, F	Neuralgia	Unlikely	2	3	Recovered

[a] If the investigator and COSTART terms differ, the COSTART term appears in parentheses.
[b] According to the investigator
[c] As of the last study visit

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 3 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event[a]	Relationship to Study Medication[b]	Study Day of Onset	Study Day Drug Discontinued	Outcome[c]
Cefdinir 300 mg BID (cont)							
11	16	68, M	Herpes Zoster	Unlikely	6	6	Recovered/Sequelae
	24	56, F	Diarrhoea (Diarrhea)	Probably	4	4	Recovered
	29	72, M	Pyrosis (Dyspepsia)	Possibly	2	2	Recovered
17	87	33, F	Erythematous Rash (Rash)	Probably	5	5	Recovered
	90	52, F	Flatulence	Possibly	6	8	Recovered
	113	42, M	Diarrhoea (Diarrhea)	Possibly	4	3	Recovered
20	9	75, M	Diarrhoea (Diarrhea)	Probably	2	5	Not Yet Recovered
	51	55, F	Allergic Exanthema (Rash	Definitely	1	2	Recovered
	62	64, F	Gastralgia (Abdominal Pain)	Unlikely	5	6	Recovered
			Diarrhoea (Diarrhea)	Possibly	5		Recovered
			Cephalgia (Headache)	Unlikely	5		Recovered
			Palpitation	Unlikely	5		Recovered
			Exanthema (Rash)	Unlikely	5		Recovered
22	7	34, M	Dysphagia	Definitely Not	2[d]	2	Not Yet Recovered
25	7	58, F	Pulmonary Embolism (Pulmonary Embolus)	Definitely Not	8	Completed Medication	Recovered

[a] *If the investigator and COSTART terms differ, the COSTART term appears in parentheses.*
[b] *According to the investigator*
[c] *As of the last study visit*
[d] *Present at baseline, not treatment-emergent*

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 4 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event[a]	Relationship to Study Medication[b]	Study Day of Onset	Study Day Drug Discontinued	Outcome[c]
Cefdinir 300 mg BID (cont)							
30	11	26, F	Diarrhoea (Diarrhea)	Definitely	3	4	Recovered
			Nausea	Definitely	3		Recovered
35	40	75, M	Worsening of AECB (Bronchitis)	Definitely Not	15	Completed Medication	Recovered
Cefuroxime 250 mg BID							
1	13	77, M	Chronic Bronchitis (Bronchitis)	Definitely Not	4	5	Recovered
11	33	74, M	Nausea	Probably	2	5	Recovered
17	91	34, M	Gastrointestinal Bleed (Gastrointestinal Hemorrhage)	Possibly	4	4	Recovered
	94	57, M	Nausea	Possibly	1	3	Recovered
	102	57, F	Diarrhoea (Diarrhea)	Probably	2	4	Recovered
18	1	75, F	Diarrhoea (Diarrhea)	Probably	10	10	Recovered
20	32	67, M	Diarrhoea (Diarrhea)	Probably	3	5	Recovered
24	11	74, M	COPD Exacerbation (Lung Disorder)	Unlikely	13	Completed Medication	Died
25	6	72, M	Diarrhea	Possibly	2	5	Recovered
28	6	83, M	Bronchoaspiration (Respiratory Disorder)	Definitely Not	4	4	Died
29	6	75, M	Epigastralgia (Abdominal Pain)	Probably	2	6	Recovered
32	34	50, M	Sinusitis	Definitely Not	19	Completed Medication	Recovered

[a] If the investigator and COSTART terms differ, the COSTART term appears in parentheses.
[b] According to the investigator
[c] As of the last study visit

TABLE 129. Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
(Page 5 of 5)

Center	Patient Number	Age (yr), Sex	Adverse Event[a]	Relationship to Study Medication[b]	Study Day of Onset	Study Day Drug Discontinued	Outcome[c]
Cefuroxime 250 mg BID (cont)							
34	4	68, F	Myocardial Infarction (Myocardial Infarct)	Definitely Not	16	Completed Medication	Died[d]
35	12	55, F	Chest Discomfort (Chest Pain)	Definitely Not	7	7	Recovered
			Otitis Media	Definitely Not	7		Recovered
	62	67, F	Hallucinations	Definitely	3	3	Recovered
			Itching (Pruritus)	Definitely	3		Recovered
37	8	83, M	Tachycardia	Unlikely	9	9	Recovered
	32	52, M	Sinusitis	Definitely Not	20	Completed Medication	Recovered

[a] *If the investigator and COSTART terms differ, the COSTART term appears in parentheses.*
[b] *According to the investigator*
[c] *As of the last study visit*
[d] *Died of a pulmonary embolism following coronary bypass surgery*

TABLE 130. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Who Received Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir 600 mg QD N = 349		Cefdinir 300 mg BID N = 345		Cefuroxime N = 349	
BODY AS A WHOLE	3[a]	(0.9)	1[a]	(0.3)	2	(0.6)
Abdominal Pain	3	(0.9)	1	(0.3)	1	(0.3)
Headache	1	(0.3)	1	(0.3)	0	(0.0)
Chest Pain	0	(0.0)	0	(0.0)	1	(0.3)
CARDIOVASCULAR SYSTEM	1	(0.3)	3	(0.9)	2	(0.6)
Pulmonary Embolus	0	(0.0)	2	(0.6)	0	(0.0)
Palpitation	0	(0.0)	1	(0.3)	0	(0.0)
Angina Pectoris	1	(0.3)	0	(0.0)	0	(0.0)
Myocardial Infarction	0	(0.0)	0	(0.0)	1	(0.3)
Tachycardia	0	(0.0)	0	(0.0)	1	(0.3)
DIGESTIVE SYSTEM	11	(3.2)	9[a]	(2.6)	7	(2.0)
Diarrhea	8	(2.3)	6	(1.7)	4	(1.1)
Dyspepsia	1	(0.3)	1	(0.3)	0	(0.0)
Dysphagia	0	(0.0)	1	(0.3)	0	(0.0)
Flatulence	0	(0.0)	1	(0.3)	0	(0.0)
Nausea	1	(0.3)	1	(0.3)	2	(0.6)
Gastrointestinal Hemorrhage	0	(0.0)	0	(0.0)	1	(0.3)
Melena	1	(0.3)	0	(0.0)	0	(0.0)
NERVOUS SYSTEM	0	(0.0)	1	(0.3)	1	(0.3)
Neuralgia	0	(0.0)	1	(0.3)	0	(0.0)
Hallucinations	0	(0.0)	0	(0.0)	1	(0.3)
RESPIRATORY SYSTEM	2	(0.6)	2	(0.6)	5	(1.4)
Bronchitis	1	(0.3)	2	(0.6)	1	(0.3)
Lung Disorder	0	(0.0)	0	(0.0)	1	(0.3)
Respiratory Disorder	0	(0.0)	0	(0.0)	1	(0.3)
Sinusitis	1	(0.3)	0	(0.0)	2	(0.6)
SKIN AND APPENDAGES	5	(1.4)	5	(1.4)	1	(0.3)
Rash	3	(0.9)	4	(1.2)	0	(0.0)
Herpes Zoster	0	(0.0)	1	(0.3)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	1	(0.3)
Urticaria	2	(0.6)	0	(0.0)	0	(0.0)
SPECIAL SENSES	1	(0.3)	0	(0.0)	1	(0.3)
Conjunctivitis	1	(0.3)	0	(0.0)	0	(0.0)
Otitis Media	0	(0.0)	0	(0.0)	1	(0.3)
UROGENITAL SYSTEM	1	(0.3)	0	(0.0)	0	(0.0)
Urinary Tract Infection	1	(0.3)	0	(0.0)	0	(0.0)

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

Medical officer's note: Review of this information shows no unexpected findings: all are consistent with administration of extended spectrum cephalosporins.

Clostridium difficile-Associated Diarrhea

Only one patient who discontinued treatment because of diarrhea was tested for *C. difficile*. Patient 6, Center 25, discontinued treatment with cefuroxime on Day 5 and later had a positive test for *C. difficile* toxin. An endoscopy was not performed.

***Medical officer's note**: This is not unexpected with the adminstration of extended spectrum cephalosporins.*

CONCLUSIONS

- Cefdinir 600 mg qd and cefdinir 300 mg bid are as effective in the treatment of AECB as cefuroxime.

- Cefdinir 600 mg qd and cefdinir 300 mg bid demonstrated adequate efficacy against the pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Moraxella catarrhalis* in the treatment of AECB. In addition, the Applicant has submitted two adequated and well controlled pivotal clinical trials in support of the CAP indication. These add significant strength to this single trial in support of the AECB indication.

- Cefdinir and cefuroxime are equally well-tolerated by most patients. Most adverse events experienced by cefdinir-treated patients are mild and do not require treatment discontinuation.

/S/

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Concurrences:
HFD-520/TL/Jan Soreth, MD
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Concurrence:
HFD-725/TL/DLin, PhD

cc: Orig NDAs 50-674 & 50-675
HFD-520/Division File
HFD-520/CSO Bduvall-Miller
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague
HFD-520/Pharm/FPelsor
HFD-520/MO/HHamilton
HFD-520/TL/JSoreth
HFD-725/Stat/AChakravarty
HFD-725/Stat/TL/DLin
HFD-40/DDMAC/S. Spearmon

Introduction to the Skin and Skin Structure Infection Indications

The applicant is requesting approval of an NDA for Omnicef Capsules and Omnicef Suspension for the treatment of uncomplicated skin and skin structure infections caused by *S. aureus, S. pyogenes, S. agalactiae,* and *K. pneumoniae.* In support of this request, data from two clinical trials, an adult study with 34 investigators and 975 patients, and a pediatric study with 18 investigators and 394 patients, were submitted.

Both studies were randomized, comparative, multicenter studies with two parallel treatment groups. The adult study involved therapy with the capsule formulation and was double-blinded. The pediatric study involved therapy with the oral suspension and was investigator-blinded. In both studies, cephalexin was the comparator agent.

In the adult study, according to the applicant, there were 178 evaluable patients with 215 pathogens in the cefdinir treatment group and 204 evaluable patients with 247 pathogens in the cephalexin treatment group. The eradication rate for all pathogens in the cefdinir group was 200/215 (93.0%) compared to 221/247 (89.5%) for all pathogens in the cephalexin treatment group. The clinical cure rates for cefdinir and cephalexin were 148/178 (83.1%) and 163/204 (79.9%), respectively. Based on the 95% confidence interval, the two treatment arms were shown to be therapeutically equivalent.

In the FDA clinical reviewer's analysis of the data, the results were evaluated according to the specific organisms requested and the baseline diagnoses. There was a total of 181 evaluable cefdinir patients and 203 evaluable cephalexin patients with skin and skin structure infections caused by the four organisms requested. The overall clinical cure rates for cefdinir and cephalexin were 153/181 (84.5%0 and 156/203 (76.8%), respectively.

The clinical cure rate for cefdinir patients with infections caused by *S. aureus* was 122/143 (85.3%) compared to 133/165

(80.6%) for cephalexin patients with similar infections due to *S. aureus*. The clinical cure rates for cefdinir patients and cephalexin patients with infections due to *S. pyogenes* were 14/17 (82.4%) and 10/11 (90.9%), respectively. For the evaluable patients with infections due to *S. agalactiae*, the clinical cure rates were 10/13 (76.9%) for the cefdinir group and 10/18 (55.6%) for the comparator group. Likewise, the clinical cure rates for cefdinir patients and cephalexin patients with infections caused by *K. pneumoniae* were 7/8 (87.5%) and 3/9 (33.3%), respectively.

In the pediatric study, according to the applicant, there were 118 evaluable patients with 166 pathogens in the cefdinir treatment group and 113 evaluable patients with 156 pathogens in the cephalexin treatment group. The eradication rate for all pathogens in the cefdinir group was 165/166 (99.4%) compared to 152/156 (97.4%) for all pathogens in the cephalexin group. The clinical cure rates for cefdinir and cephalexin were 116/118 (98.3%) and 106/113 (93.8%), respectively. Based on the 95% confidence interval, the two treatment arms were shown to be therapeutically equivalent.

In the FDA clinical reviewer's analysis, there was a total of 116 evaluable cefdinir patients and 116 evaluable cephalexin patients with skin and skin structure infections caused by the four organisms requested. The overall clinical cure rates for cefdinir and cephalexin were 114/116 (98.3%) and 110/116 (94.8%), respectively.

The clinical cure rate for pediatric cefdinir patients with infections caused by *S. aureus* was 73/75 (97.3%) compared to 73/77 (94.8%) for cephalexin patients with similar infections. The clinical cure rates for pediatric cefdinir patients and cephalexin patients with infections due to *S. pyogenes* were 34/34 (100%) and 31/33 (93.9%), respectively. For the evaluable pediatric patients with infections due to *S. agalactiae*, the clinical cure rates were 4/4 (100%) for the cefdinir group and 6/6 (100%) for the cephalexin group. The clinical cure rate for cefdinir pediatric patients with infections due to *K. pneumoniae* was 3/3 (100%); while in the comparator group, there were no evaluable patients with an infection caused by *K. pneumoniae*.

In both studies, diarrhea was the most frequently reported adverse event among the cefdinir patients. There were 78 reports (16.5%) of diarrhea in the adult study and 15 cases (10.6%)

reported in the pediatric study. Other frequently reported adverse events included nausea with 17 reports (~~3~~.6%) and moniliasis with 14 reports (7.3%) in the adult study. Infection with 13 cases (9.2%) was the second most frequently reported adverse event, following diarrhea, in the pediatric study.

The applicant has submitted sufficient data to show that cefdinir is safe and effective in the treatment of uncomplicated skin and skin structure infections in both an adult and pediatric population. Data from both clinical trials show the drug to be effective in the eradication of various types of skin and skin structure infections caused by *S. aureus* and *S. pyogenes*, when used as directed. The data regarding *S. agalactiae* and *K. pneumoniae* are insufficient because of the much smaller number of cases involving these organisms, their occurrence primarily in polymicrobial infections, and their questionable role at this time as pathogens or contaminants in these infections.

Therefore, it is recommended that cefdinir capsules and cefdinir suspension be approved for the treatment of uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*.

NDA 50-739 (Cefdinir 300 mg capsules)
NDA 50-749 (Cefdinir oral suspension, 125 mg/mL)

Clinical Review of Studies for Skin and Skin Structure Infections (SSSI)

Indication: Uncomplicated Skin and Skin Structure Infections.

Title and Study Number: A phase 3, 10-day, double-blind, randomized, comparative, multi center study of cefdinir (CI-983) versus cephalexin in the treatment of patients with skin and skin structure infections (SSSI) (protocol 983-8).

Objective: To evaluate the efficacy and safety of cefdinir (300 mg bid or 600 mg qd) and cephalexin (500 mg qid) in the treatment of adults and adolescents with SSSI.

Clinical reviewer's note: *Originally, patients were randomly assigned to 1 of 3 treatment groups to receive cefdinir 600 mg QD or 300 mg BID, or cephalexin 500 mg QID for 10 days. The 600 mg cefdinir QD treatment group in the original study was discontinued due to a theoretical concern about maintaining therapeutic blood and tissue concentrations of cefdinir for extended periods, i.e., QD dosing might not be adequate for treating serious, potentially life-threatening SSSIs. After the protocol was amended to stop cefdinir QD enrollment, patients continued to be randomized to cefdinir BID and cephalexin. Subsequent patient numbers associated with cefdinir QD were skipped and the next sequential patient number was used. A second deviation from the original protocol involved changing the test-of-cure determination from the short-term follow-up visit (3 to 7 days posttherapy) to a longer term follow-up visit (7 to 16 days posttherapy).*

Study Design: This was a double-blind, randomized, comparative, multi center study with 2 parallel treatment groups. Patients were assigned by a blinded randomization code to receive one of two dosage regimens of cefdinir or cephalexin for 10 days. Screening, dosing, follow-up visits, and the test-of-cure (TOC) visit window used in data analyses are illustrated in Figure 1. The short-term follow-up (STFU) and long-term follow-up (LTFU) visits are defined in the figure. The TOC visit window shown in the figure was determined after the study was completed; it provided a more stringent test of the study medication.

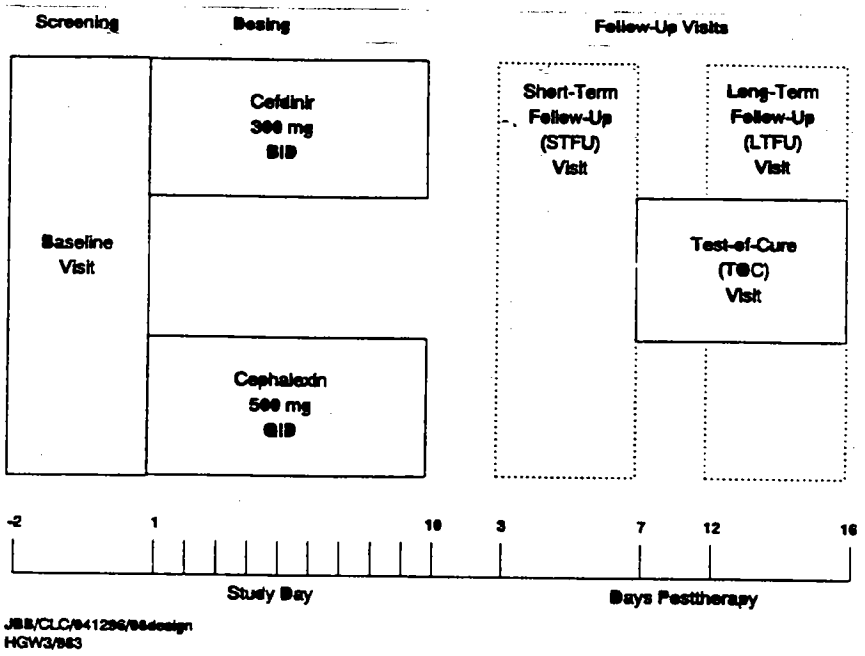

FIGURE 1. Protocol 983-8 Study Design

Protocol Overview

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

Population: Participants included males and nonpregnant, nonlactating females aged 13 years or older. Females were also to be either adolescent and not sexually active, using an effective means of contraception and have a negative pregnancy test at baseline, postmenopausal, or surgically sterilized.

Inclusion Criteria: Eligible patients had acute bacterial SSSIs serious enough to warrant oral antimicrobial therapy. SSSIs could include: abscess, infected burn, carbuncle, cellulitis, infected dermatitis, erysipelas, folliculitis, furuncle, impetigo, paronychia, acutely infected ulcer, or an infected traumatic/surgical wound. Bacterial etiology of the infection from a skin or wound aspirate, biopsy, or swab was to be confirmed by a positive culture.

Eligible patients were also required to have at least 2 clinical signs and symptoms for study entry including pain/tenderness, erythema/warmth, swelling, induration, fluctuation, or drainage.

Exclusion Criteria: Patients were to be excluded from participating in the study for any of the following reasons:

- A disease or condition that precluded evaluation of the therapeutic response, including a terminal illness;
- Pregnancy or lactation;
- Hepatic disease, obstruction of the biliary tract, bilirubin or hepatic enzyme levels (AST ALT) >2 times the upper limit of normal;
- Baseline serum creatinine >1.5 times the upper limit of normal or creatinine clearance <30 mL/min;
- Previous antibacterial therapy within 7 days of the start of study medication, *except* for patients who had no more than a 24-hour course of therapy within that 7-day period provided that at least 5 half-lives of the previous antibacterial had passed;
- Hypersensitivity to β-lactams;
- Baseline pathogen(s) known to be resistant to either study medication prior to randomization;
- Concomitant infection(s) requiring systemic or topical antibacterial therapy, *except* metronidazole administered when a mixed aerobic/anaerobic infection was suspected;
- An infection thought to be *purely* anaerobic;
- Prior participation in this or any other cefdinir study;
- Radiographic evidence of the presence of osteomyelitis;
- Taking iron-containing medications concomitantly, including multivitamins with iron;
- Seeking treatment for the primary diagnosis of acne;
- Taking any other investigational compound within 4 weeks of study entry; or
- Taking probenecid concomitantly.

Clinical reviewer's note: *Both the patient inclusion and exclusion criteria are consistent with the guidelines recently developed by the DAIDP.*

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

Confirmation of bacteriological etiology and lack of *in vitro* resistance to study medication was required for a patient to be

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 resistant to cefdinir or cephalexin (but not both) provided, in his or her judgement, they were exhibiting satisfactory clinical improvement.

When treatment was discontinued early, the following were to be completed: skin culture (from the baseline site of infection) and susceptibility testing, a clinical evaluation, a physical examination, clinical laboratory tests, as well as records of adverse events and concurrent medications. If additional antibiotics were not required at the time study medication was discontinued and the patient had received at least 3 days of study medication, both follow-up visits were scheduled to be completed. If additional antibiotics were required or if the patient had no baseline pathogen, follow-up visits were not requested.

Assessments of specific microbiologic and clinical parameters at the TOC visit, 7 to 16 days posttherapy, were used to evaluate the efficacy of cefdinir. Efficacy measures used included microbiologic eradication rate by pathogen, microbiologic eradication rate by patient, and clinical cure rate by patient.

Clinical reviewer's note: *The reviewer agrees with the above evaluability criteria. The applicant strictly adhered to these criteria when determining patient outcome.*

Endpoints Defined (Clinical and Microbiological)

The schedule of visits, examinations and evaluations for the patients in this study is shown in Table 1.

Each patient had a baseline evaluation within 48 hours prior to the initiation of therapy. This included a medical history, a physical examination, a clinical assessment of signs and symptoms (classified as absent, mild, moderate, or severe at each visit), specimen collection from the SSSI site, and clinical laboratory tests.

TABLE 1. Schedule of Clinical Observations and Laboratory Measurements

Procedure/Observation	Baseline	Day 1	Days 3-5	Day 10	Posttherapy Visits: 3 to 7 Days	Posttherapy Visits: 12 to 16 Days
Medical History	X					
Physical Examination[c]	X				X	X
Clinical Assessment of Signs and Symptoms[c]	X		X		X	X
Skin Culture from Baseline Site of Infection and Susceptibility Testing[c]	X				X	X
Adverse Events		X	———	———	X	X
Clinical Laboratory Testing[c,d]	X				X	X[e]
Investigator Assessment of Clinical Efficacy[c]					X	X
Radiographic Evaluation[f]	X					
Pharmacokinetic Specimen Collection[g]			X			
Dosing		X	———	X		

[a] Prior to treatment (within 48 hours) or Day 1
[b] Test-of-cure visit occurred 7 to 16 days posttherapy and was not defined in terms of the posttherapy visits.
[c] Performed whenever a patient was withdrawn
[d] Tests performed are listed in the protocol (Appendix A.2).
[e] Performed only if abnormalities were detected at the previous visit
[f] Only to rule out osteomyelitis
[g] Optional; at selected centers, blood was collected 4 hours after the morning dose of study medication for analysis of plasma-drug concentration (Addendum A, Appendix A.2).

Microbiological endpoints: Specimens were collected for culture and susceptibility testing at baseline, STFU and TOC, if material was available. If multiple sites of infection existed at baseline, the most severely affected (ie, the largest, most purulent, or most erythematous) site was to be chosen and followed throughout the entire length of the study. All isolated bacteria suspected of being pathogens were identified to genus and species, and testing for β-lactamase production was performed when appropriate. Organisms cultured from SSSI sites and classified as contaminants or not otherwise speciated were not considered pathogens in this study.

All isolates were tested for susceptibility to cefdinir and cephalexin using both broth microdilution and Kirby-Bauer disk diffusion methods. Test procedures as well as minimum inhibitory concentration (MIC) and zone diameter standards conformed with National Committee for Clinical Laboratory Standards (NCCLS) guidelines.

Microbiologic Response by Pathogen: At the TOC visit, the microbiologic response of each baseline pathogen was classified as:

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

Patients with multiple pathogens provided multiple observations in the analysis of microbiological efficacy on a per pathogen basis. A patient's microbiologic response was evaluated based on baseline and posttherapy culture results. The microbiologic eradication rate by pathogen was defined as the percentage of pathogens present in baseline specimens that were eliminated (or presumed to be eliminated) from specimens obtained at the TOC visit.

Microbiologic Response by Patient: At the TOC visit, patients were classified by their overall microbiologic response based on the baseline and 7- to 16-day posttherapy culture results as:

- **Patients With Eradication** - All baseline pathogens eradicated or no material available to culture at follow-up (ie, presumed eradication);
- **Patients With Persistence** - Presence of at least 1 baseline pathogen in the TOC culture; or
- **Not Assessable** - No proven baseline pathogen or no follow-up data.

The microbiologic eradication rate by patient was the percentage of patients in whom all baseline pathogens were eradicated. Each patient provided 1 observation.

Superinfection - The appearance of a nonbaseline pathogen at any time during treatment through the TOC visit *and* a clinical worsening or failure at the corresponding clinical assessment.

If a patient had a nonbaseline pathogen at follow-up, the sponsor reviewed the progress of the patient's clinical signs and symptoms and determined whether or not the patient had experienced a superinfection.

Clinical reviewer's note: *The reviewer agrees with these definitions which are consistent with guidelines requiring the complete eradication of an organism to establish efficacy.*

Clinical endpoints: An evaluation of each patient's signs and symptoms was made at baseline, after 3-5 days of therapy, at the short term follow up, and the long term follow up (TOC). The following criteria were used by each investigator at both the STFU and the TOC visits:

- **Cure** -Disappearance of all baseline site signs and symptoms
- **Improvement** - Satisfactory remission but not complete disappearance of baseline site signs and symptoms
- **Failure** - Worsening or no significant remission of baseline site signs and symptoms
- **Not assessable** - Cannot assess the patient

Clinical reviewer's note: *The reviewer accepts the applicant's definitions for these endpoints which are very similar to those recently proposed by the DAIDP in its draft document. It is important to note that most of the clinical failures were patients who showed no improvement; their conditions did not necessarily worsen.*

The protocol specified that investigator and sponsor assessments of patient clinical response would be made. Based on the investigator's assessment of signs and symptoms at the TOC and before unblinding, the sponsor used a scoring algorithm to calculate an assessment of clinical efficacy.

A combination of investigator and sponsor assessments, referred to as the combined investigator/sponsor clinical assessment in this report, was used as the primary measure of patient clinical response in the efficacy analyses (Table 2). The purpose of the combined investigator/sponsor clinical assessment was to address patients who were classified as improvement or not assessable by the investigator and reclassify them as cure, failure, or not assessable using the sponsor assessment.

TABLE 2. Determination of Combined Investigator/Sponsor Clinical Assessment

Sponsor Assessment	Investigator Assessment: Cure Disappearance of all baseline site clinical signs and symptoms	Improvement Satisfactory remission but not complete disappearance of baseline site clinical signs and symptoms	Failure Worsening or no significant remission of baseline site clinical signs and symptoms	Not Assessable Cannot assess the patient
Cure ≥50% decrease in clinical score at TOC relative to baseline	Cure	Cure[a]	Failure	Cure[a]
Failure <50% decrease in clinical score at TOC relative to baseline	Cure	Failure[a]	Failure	Failure[a]
Not Assessable No baseline clinical signs and symptoms or no follow-up clinical assessment	Cure	Not Assessable[a]	Failure	Not Assessable[a]

TOC = Test-of-cure.
[a] The sponsor assessment was substituted for the investigator assessment.

The clinical cure rate was the percentage of patients identified as cured using the combined investigator/sponsor clinical assessment. All patients who had postbaseline surgical intervention were considered treatment failures by the sponsor. Since only TOC data were used in these analyses, follow-up clinical scores were only calculated for the TOC visit, not for the STFU and LTFU visits.

Clinical reviewer's note: *The reviewer finds the definitions and clinical assessment method to be acceptable.*

Statistical Considerations:

Sample Size: This study was designed to use two-tailed 95% confidence intervals (CI) to assess the equivalence of response rates from evaluable patients without surgical intervention at admission who were treated with cefdinir BID or cephalexin. An overall response rate of 85% regardless of treatment was assumed.

This provided an 80% probability (power) that the limits of the 95% CI for the difference between the response rates (cefdinir BID minus cephalexin) would fall within the accepted equivalence range (±15 percentage points) if the treatments were truly equivalent.

Originally this was a multi center study with three treatment arms: cefdinir 600 mg QD; cefdinir 300 mg BID; and cephalexin 500 mg QID. Each treatment arm was supposed to have 160 microbiologically evaluable patients for a total enrollment of 480 patients. When the cefdinir QD dosing arm was stopped, patients continued to be enrolled in the other two arms using a 1:1 randomization. A total of 476 patients were enrolled in the cefdinir BID arm and 479 in the cephalexin arm.

At TOC, the microbiologic eradication rates by pathogen and by patient were calculated for each treatment group in the evaluable (with and without surgical intervention), MITT, and ITT patient populations. Clinical cure rates were calculated for each treatment group in the evaluable (with and without surgical intervention), clinically evaluable, and the ITT patient populations.

Methods: Statistical analyses were performed across all diagnoses for the cefdinir BID and cephalexin treatment groups. Efficacy data summaries by baseline diagnosis were generated for each treatment group. No statistical analyses were performed on the efficacy or safety data collected from patients in the cefdinir QD treatment group; descriptive statistics, however, were calculated. All analyses and data summaries were prepared using SAS Version 6.

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

of cases.

The second method used estimates of the response rates in which each center was given equal weight. These center-adjusted estimates and their standard errors were obtained from a model which contained terms for treatment group, study center, and treatment by center interaction.

The treatment difference was defined as cefdinir BID minus cephalexin. The estimated response rate differences and their standard errors were used to construct a two-tailed 95% confidence interval for the treatment difference, using a standard normal approximation. Each 95% confidence interval was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the 2 rates (pooled or center-adjusted) under comparison (Table 3). To demonstrate equivalence, each 95% confidence interval must contain 0 and its limits must fall within the indicated bounds.

TABLE 3. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Treatments are Equivalent if 95% Confidence Interval for Treatment Difference is Within Bounds
90% or greater	-10%, +10%
80%-89%	-15%, +15%
70%-79%	-20%, +20%

Statistical reviewer's note: *The criteria for equivalence (Table 3) are to be clarified to be the following:*

The maximum estimated response rates to be restated as greater than 90%, between 80% and 90%, and less than 80%, respectively. It is also to be noted that the upper boundary of the confidence interval is not held to a fixed percentage; the lower boundary is of critical importance. As stated by the sponsor, the confidence

interval must contain zero to demonstrate therapeutic equivalence.

The confidence intervals will be expressed as: $_{nt,nc}$*(lower limit, upper limit)*$_{pt,pc}$*, where nt = number of subjects in the treatment arm; nc = number of subjects in the control arm; pt = number of successes in the treatment arm; nc = number of successes in the control arm. Yaates' continuity correction will be applied to the calculation of the confidence intervals.*

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

Study Results

Demographics, Evaluability

The cefdinir group consisted of 20 patients who received a dosage of 600 mg QD and 476 patients who received a dosage of 300 mg BID. The QD dosing arm of the study was discontinued shortly after initiation due to a concern regarding appropriate therapeutic concentrations of cefdinir for extended periods. The following table shows the patient disposition, including the number of patients who were considered evaluable by each investigator.

TABLE 4. List of Investigators

Center	Investigator	Number of Patients		
		Entered[a]	Completed[b]	Evaluable[c]
1	J. Applegate	22	12	5
2	R. Chiulli	25	9	9
3	H. Collins	4	1	1
4	K. Dowd	6	3	3
5	B. Lipsky	24	11	6
6	T. Littlejohn	71	40	22
7	Y. Lynfield	2	1	0
8	L. Parish	47	21	20[d]
9	R. Paster	48	30	27
10	A. Puopolo	62	41	30
11	C. Rich	60	37	28
12	M. Sperling	59	28	13
13	S. Weakley	41	32	23
15	P. DiLorenzo	86	60	34
16	R. Smith	4	4	3
17	R. Snow	24	10	5
18	R. Schwartz	15	13	7
19	A. Herbert	43	29	22
20	Z. Munk	52	34	19
21	V. Elinoff	37	23	14[d]
22	A. Balin	47	36	21
23	D. Stewart	32	23	12
24	S. Davis	30	24	14
25	C. Mathias	5	4	1
28	A. Rosenthal	2	1	0
29	R. McCabe	2	2	1
30	C. Khurana	3	2	1
31	D. Stryker	5	4	4
32	R. Margolis	31	26	21
33	C. DeAbate	7	3	0
36	D. Williams	27	12	7
49	R. Herdener	4	2	2
50	M. Goldman	23	14	7
52	W. Gooch	25	16	15
	Total	975	608	391

[a] Randomized to treatment
[b] Completed treatment and long-term follow-up visit (12-16 days posttherapy)
[c] Included in evaluable patient analyses
[d] Some patients in this total completed the test-of-cure visit (7-16 days posttherapy) and met all evaluability criteria, but withdrew prior to the long-term follow-up visit window. These patients do not appear in the completed column.

Patient Demographics: The patient demographics for all patients (ITT) and evaluable patients according to the sponsor are summarized in the following tables.

TABLE 5. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 20		Cefdinir BID N = 476		Cephalexin N = 479		Total N = 975	
Sex								
Male	13	(65.0)	282	(59.2)	283	(59.1)	578	(59.3)
Female	7	(35.0)	194	(40.8)	196	(40.9)	397	(40.7)
Race								
White	12	(60.0)	383	(80.5)	400	(83.5)	795	(81.5)
Black	4	(20.0)	49	(10.3)	40	(8.4)	93	(9.5)
Asian	0	(0.0)	4	(0.8)	1	(0.2)	5	(0.5)
Other	4	(20.0)	40	(8.4)	38	(7.9)	82	(8.4)
Age, yr								
Median	36.0		36.0		37.0		36.0	
Range	15 - 81		13 - 88		13 - 86		13 - 88	
Distribution								
13 to <18	1	(5.0)	23	(4.8)	34	(7.1)	58	(5.9)
18 to <65	18	(90.0)	381	(80.0)	375	(78.3)	774	(79.4)
≥65	1	(5.0)	72	(15.1)	70	(14.6)	143	(14.7)
Baseline Diagnosis*								
Abscess	4	(20.0)	146	(30.7)	129	(26.9)	279	(28.6)
Infected Traumatic/Surgical Wound	4	(20.0)	80	(16.8)	96	(20.0)	180	(18.5)
Folliculitis	7	(35.0)	42	(8.8)	37	(7.7)	86	(8.8)
Cellulitis	3	(15.0)	35	(7.4)	43	(9.0)	81	(8.3)
Paronychia	0	(0.0)	41	(8.6)	39	(8.1)	80	(8.2)
Infected Dermatitis	1	(5.0)	39	(8.2)	33	(6.9)	73	(7.5)
Furuncle	0	(0.0)	31	(6.5)	38	(7.9)	69	(7.1)
Impetigo	0	(0.0)	32	(6.7)	30	(6.3)	62	(6.4)
Carbuncle	0	(0.0)	17	(3.6)	19	(4.0)	36	(3.7)
Acutely Infected Ulcer	1	(5.0)	10	(2.1)	11	(2.3)	22	(2.3)
Infected Burn	0	(0.0)	3	(0.6)	4	(0.8)	7	(0.7)

Other = Cuban, Hawaiian, Hispanic/Latin, Indian, Native American, Pacific Islander, Persian, Spanish, Syrian, Tongan.

* A total of 113 patients had conditions predisposing them to SSSIs: 3 treated with cefdinir QD, 47 treated with cefdinir BID, and 63 treated with cephalexin. Section 5.1.4 contains information about patients with predisposing conditions.

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

Variable	Cefdinir QD N = 9		Cefdinir BID N = 178		Cephalexin N = 204		Total N = 391	
Sex								
Male	6	(66.7)	111	(62.4)	118	(57.8)	235	(60.1)
Female	3	(33.3)	67	(37.6)	86	(42.2)	156	(39.9)
Race								
White	5	(55.6)	139	(78.1)	165	(80.9)	309	(79.0)
Black	2	(22.2)	15	(8.4)	18	(8.8)	35	(9.0)
Asian	0	(0.0)	4	(2.2)	1	(0.5)	5	(1.3)
Other	2	(22.2)	20	(11.2)	20	(9.8)	42	(10.7)
Age, yr								
Median	32.0		35.0		35.0		35.0	
Range	15 - 43		13 - 88		14 - 82		13 - 88	
Distribution								
13 to <18	1	(11.1)	13	(7.3)	14	(6.9)	28	(7.2)
18 to <65	8	(88.9)	142	(79.8)	171	(83.8)	321	(82.1)
≥65	0	(0.0)	23	(12.9)	19	(9.3)	42	(10.7)
Baseline Diagnosis								
Abscess	1	(11.1)	44	(24.7)	44	(21.6)	89	(22.8)
Infected Traumatic/Surgical Wound	3	(33.3)	32	(18.0)	44	(21.6)	79	(20.2)
Paronychia	0	(0.0)	23	(12.9)	22	(10.8)	45	(11.5)
Impetigo	0	(0.0)	18	(10.1)	17	(8.3)	35	(9.0)
Cellulitis	1	(11.1)	17	(9.6)	17	(8.3)	35	(9.0)
Infected Dermatitis	1	(11.1)	19	(10.7)	15	(7.4)	35	(9.0)
Folliculitis	3	(33.3)	9	(5.1)	20	(9.8)	32	(8.2)
Furuncle	0	(0.0)	10	(5.6)	12	(5.9)	22	(5.6)
Carbuncle	0	(0.0)	3	(1.7)	6	(2.9)	9	(2.3)
Acutely Infected Ulcer	0	(0.0)	3	(1.7)	5	(2.5)	8	(2.0)
Infected Burn	0	(0.0)	0	(0.0)	2	(1.0)	2	(0.5)

Other = Hawaiian, Hispanic/Latin, Indian, Pacific Islander, Spanish, Syrian, Tongan.

Clinical reviewer's note: *The study arms (cefdinir bid and cephalexin qid) appear balanced with regard to gender, race, age*

and baseline diagnoses.

Statistical reviewer's note: *Cefdinir BID and cephalexin are balanced with regard to demographic characteristics - sex (p-value = 0.369), race (p-value = 0.446), and age (p-value = 0.466).*

Drug Administration: The distribution for the duration of therapy for all patients according to the applicant is provided in the table below.

TABLE 7. Patient Exposure to Study Medication - All Patients (Number of Patients)

Days on Study Medication	Cefdinir QD N = 20	Cefdinir BID N = 476	Cephalexin N = 479
1	1	2	2
2	1	8	6
3	1	14	8
4	3	12	17
5	1	30	27
6	1	25	19
7	0	14	19
8	0	16	12
9	0	4	4
10	3	116	133
11	9	218	215
12	0	1	4
13	0	1	1
14	0	0	1
Median	10	10	10
Unknown	0	15	11

Clinical reviewer's note: *The median patient exposure to cefdinir was 10 days, the treatment duration proposed in the label. Among the cefdinir BID group, 334 (70%) patients received 10-11 days of therapy. Patients who started cefdinir or*

cephalexin at or after noon on Day 1 finished medication on the morning of or later on Day 11, which accounts for the number of patients with 11 days of treatment.

Unevaluable Patients: The following patients were excluded from all efficacy analysis by the applicant, and the reasons for exclusion were as follows:

TABLE 8. Reasons Patients Were Not Evaluable at TOC
(Number of Patients)

	Cefdinir		Cephalexin
	QD	BID	
Randomized to Treatment	20	476	479
Reasons Patients Were Excluded From Evaluable Analyses[a]			
Clinical Evaluation Out of Date Range[b]	5	123	104
Culture[c] Out of Date Range[b]	6	112	104
Medication Not As Prescribed	7	100	91
No Proven Baseline Pathogen	7	195	177
Resistant Baseline Pathogen(s)	1	64	65
Culture[c] Missed	0	28	20
Clinical Evaluation Missed	1	18	14
Prior Antibacterial	0	7	6
Concurrent Antibacterial[b]	1	5	8
No Baseline Susceptibility Tests	0	1	0
Wrong Indication	0	0	1
Not Evaluable	11	298	275

[a] Patients who had multiple reasons for being excluded from efficacy analyses are included under each reason that applied.

[b] Patients who had microbiologic and/or clinical assessments done early or who took a concurrent antibacterial because they were early failures were not removed from the evaluable analyses for this reason.

[c] Baseline or TOC culture

Of the 476 patients in the cefdinir BID group, 298 were not

evaluable for both microbiological and clinical analysis, leaving a total of 178 evaluable cefdinir patients. In the cephalexin group, 275 patients out of 479 enrolled patients were unevaluable, leaving a total of 204 evaluable cephalexin patients. In both drug treatment groups, the absence of a baseline pathogen was the most common reason for exclusion.

Efficacy

Table 9 compares the number of patients randomized to treatment (i.e., the ITT population) to the number of patients in the other populations. Four different patient groups were analyzed for efficacy as follows:

TABLE 9. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	Cefdinir				Cephalexin	
	QD		BID			
Intent-to-Treat (ITT)[a]	20	(100.0)	476	(100.0)	479	(100.0)
Modified Intent-to-Treat (MITT)[b]	13	(65.0)	273	(57.4)	292	(61.0)
Clinically Evaluable[c]	11	(55.0)	287	(60.3)	303	(63.3)
Evaluable[d]	9	(45.0)	178	(37.4)	204	(42.6)
With Uncomplicated SSSIs	5	(25.0)	124	(26.1)	138	(28.8)
Without Surgical Intervention at Admission	9	(45.0)	138	(29.0)	159	(33.2)
With Surgical Intervention at Admission	0	(0.0)	40	(8.4)	45	(9.4)

[a] All patients who were randomized to treatment
[b] Total number of patients who had the correct indication and received study medication, at least 1 baseline pathogen, and a follow-up skin culture attempted
[c] Total number of patients who were evaluable without regard to microbiologic evaluability criteria
[d] Total number of patients who were microbiologically and clinically evaluable at TOC

Clinical reviewer's note: *The reviewer examined all case report forms and summaries for patients considered to be nonevaluable and clinical failures. The summaries for all patients with pathogens requested for inclusion in the SSSI indication were reviewed along with case report forms when necessary. All of the data was found to be consistent with that presented in the sponsor's report.*

Clinical Efficacy

A summary of the clinical response rates by patient according to the investigators is shown in Table 10. The investigators rated patients on the basis of improvements in sign/symptoms as cures, improvements, failures, and not assessable. The results show the cefdinir 300 mg BID regimen to be comparable to the control drug in the response rates for all categories.

Table 10. Summary of clinical response rates by patient as determined by investigators at the test of cure visit - All patients.

Clinical Response	Number (%) of Patients			
	Cefdinir 300 mg BID		Cephalexin	
	N	%	N	%
Cure	269	56.5	285	59.5
Improvement	117	24.6	118	24.6
Failure	59	12.4	55	11.5
Not Assessable	31	6.5	21	4.4
Total	476	100.0	479	100.0

The primary measure of patient clinical response in the following tables for efficacy analysis was a combination of investigator and sponsor assessments referred to as the combined investigator/sponsor clinical assessment. The purpose for this combined assessment was to account for patients considered as improvements or not assessable by the investigators. The sponsor reclassified them as cures, failures, or not assessable using the sponsor's criteria. Table 11 shows the results of this reclassification for the patients who are both microbiologically and clinically evaluable.

TABLE 11. Investigator vs Combined Investigator/Sponsor Clinical Assessments at the Test-of-Cure Visit - Evaluable Patients

Investigator Assessment	Combined Investigator/Sponsor Clinical Assessment			
	Cefdinir BID N = 178		Cephalexin N = 204	
	Cure	Failure	Cure	Failure
Cure	132	0	145	0
Improvement	16	9	18	14
Failure	0	21	0	27

TABLE 12. Clinical Cure Rate[a] by Patient (According to Their Baseline Pathogens) Across Baseline Diagnoses at the Test-of-Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
Staphylococcus aureus	103/118	87.3	110/133	82.7
Streptococcus agalactiae	2/3	66.7	5/6	83.3
Streptococcus pyogenes	8/10	80.0	4/5	80.0
Streptococcus Group G	1/1	100.0	0/1	0.0
Gram-Negative				
Acinetobacter calcoaceticus var *lwoffi*	2/2	100.0	1/1	100.0
Citrobacter amalonaticus	1/1	100.0	0/0	—
Citrobacter diversus	0/1	0.0	0/0	—
Enterobacter agglomerans	0/0	—	1/1	100.0
Escherichia coli	1/2	50.0	5/6	83.3
Escherichia hermanii	0/1	0.0	0/0	—
Haemophilus parahaemolyticus	0/0	—	1/1	100.0
Haemophilus parainfluenzae	1/2	50.0	1/1	100.0
Klebsiella oxytoca	0/0	—	1/1	100.0
Klebsiella pneumoniae	1/1	100.0	1/3	33.3
Pasteurella multocida	1/1	100.0	0/0	—
Proteus mirabilis	3/4	75.0	6/6	100.0
Providencia rettgeri	0/0	—	1/1	100.0
Xanthomonas maltophilia	0/0	—	1/1	100.0
Multiple	24/31	77.4	25/37	67.6
Total	148/178	83.1	163/204	79.9

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

In Table 12 the clinical cure rates for all microbiologically evaluable patients according to the baseline pathogen isolated is shown. For the 178 cefdinir patients, 148 (83.1%) were cures, while 163 of the 204 (79.9%) cephalexin patients were cured.

Clinical reviewer's note: *The data presented in Table 12 are based on the assignment of one organism as the primary pathogen for each evaluable patient. In reality, the majority of the patients in the study had mixed or polymicrobial infections consisting of two or more organisms, both pathogenic and non-pathogenic species. For example, Table 12 shows three cefdinir patients who had infections with positive cultures for Streptococcus agalactiae only. There were 25 cefdinir patients with infections involving Streptococcus agalactiae, 13 of them evaluable patients. All of those patients had mixed infections with other microorganisms.*

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rate by patients at the TOC visit, the 95% confidence intervals being* $_{178,204}$ *(-0.0506, 0.1155)* $_{83.1\%,79.9\%}$.

TABLE 13. Clinical Cure Rate[a] by Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	38/44	86.4	39/44	88.6
Infected Traumatic/Surgical Wound	27/32	84.4	32/44	72.7
Paronychia	19/23	82.6	18/22	81.8
Impetigo	15/18	83.3	12/17	70.6
Cellulitis	15/17	88.2	15/17	88.2
Infected Dermatitis	14/19	73.7	12/15	80.0
Furuncle	9/10	90.0	9/12	75.0
Folliculitis	6/9	66.7	14/20	70.0
Carbuncle	3/3	100.0	6/6	100.0
Acutely Infected Ulcer	2/3	66.7	4/5	80.0
Infected Burn	0/0	—	2/2	100.0
Across Diagnosis	148/178	83.1	163/204	79.9

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

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rate by baseline diagnosis at the TOC visit, the 95% confidence intervals being* $_{178,204}$ *(-0.0506, 0.1155)* $_{83.1\%,79.9\%}$.

TABLE 14. Microbiologic vs Clinical Response Rates at the Test-of-Cure Visit - Evaluable Patients
[Number (%) of Patients]

Microbiologic Response	Clinical Response[a]			
	Cure		Failure	
Cefdinir BID, N = 178				
Patients With Eradication	144	(80.9)	20	(11.2)
Patients With Persistence	4	(2.2)	10	(5.6)
Cephalexin, N = 204				
Patients With Eradication	158	(77.5)	23	(11.3)
Patients With Persistence	5	(2.5)	18	(8.8)

[a] Based on combined investigator/sponsor clinical assessments

Clinical reviewer's note: *There were four cefdinir patients who had persistent S. aureus, obtained from swabs, present at the TOC visit. All were clinical cures and devoid of all signs/symptoms associated with their infections. Two of the patients had impetigo, one had an abscess, and the fourth had paronychia. There were five cephalexin patients who were clinical cures with persistent pathogens at the TOC visit. Three patients had S. aureus, one patient had S. aureus and P. mirabilis, and the fifth patient had P. mirabilis and S. haemolyticus isolated from their baseline cultures. All clinical signs/symptoms were absent at the TOC visit.*

Clinically evaluable patients: The following table shows the clinical cure rate for all clinically evaluable patients, without regard to the presence or absence of a baseline pathogen, according to their diagnosis.