TABLE 15. Clinical Cure Rate[a] by Baseline Diagnosis at the Test-of-Cure Visit - Clinically Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	66/83	79.5	73/82	89.0
Infected Traumatic/Surgical Wound	36/44	81.8	39/54	72.2
Paronychia	24/28	85.7	21/25	84.0
Impetigo	21/24	87.5	17/23	73.9
Cellulitis	20/23	87.0	16/21	76.2
Folliculitis	19/25	76.0	23/34	67.6
Infected Dermatitis	18/25	72.0	15/20	75.0
Furuncle	16/18	88.9	18/23	78.3
Carbuncle	9/11	81.8	13/13	100.0
Acutely Infected Ulcer	3/5	60.0	4/5	80.0
Infected Burn	1/1	100.0	3/3	100.0
Across Diagnosis	233/287	81.2	242/303	79.9

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

Clinical reviewer's note: *There were 287 clinically evaluable cefdinir patients with 233 of them clinically cured (81.2%). Of the 303 cephalexin patients, 242 were cured for a 79.9% cure rate.*

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rate by baseline diagnosis for clinically evaluable patients at the TOC visit, the 95% confidence intervals being* $_{287,303}$ *(-0.0541, 0.0805)* $_{81.2\%,79.9\%}$.

Superinfections: Thirty-three patients in the cefdinir BID group and 23 patients in the cephalexin group had superinfections. The following table shows the 54 superinfecting pathogens isolated

from the cefdinir patients and the 31 organisms isolated from the cephalexin patients. Nineteen of the cefdinir pathogens were resistant to it, while 14 of the cephalexin pathogens were resistant to cephalexin.

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

Pathogen	Cefdinir BID N = 476	Cephalexin N = 479
Gram-Positive[a]		
Enterococcus faecalis	2	1
Staphylococcus epidermidis	8	6
Staphylococcus hominis	1	0
Staphylococcus simulans	2	1
Streptococcus agalactiae	0	1
Streptococcus anginosus	1	0
Gram-Negative[a]		
Acinetobacter calcoaceticus var *anitratus*	1	1
Enterobacter cloacae	2	2
Proteus mirabilis	0	1
Pseudomonas aeruginosa	0	1
Pseudomonas fluorescens	0	1
Pseudomonas stutzeri	0	1
Sphingomonas paucimobilis	1	0
Multiple	15	7
Total	33	23

[a] Pathogens appearing as sole superinfecting pathogens

Clinical reviewer's analysis of data: The applicant has requested the approval of an indication for the treatment of uncomplicated skin and skin structure infections caused by

susceptible strains of *S. aureus, S. pyogenes, S. agalactiae,* and *K. pneumoniae.* Therefore, a closer examination of the data concerning these four organisms is necessary. In the analysis of the clinical data presented by the applicant, these four organisms are grouped together with regard to the various baseline diagnoses. In the following tables, the clinical cure rates for each pathogen from the microbiologically evaluable patients is listed, according to the specific SSSI diagnosis.

Table 17. Clinical cure rates - Evaluable patients with *S. aureus* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 143		Cephalexin n = 165	
	Cure	Failure	Cure	Failure
Impetigo	14	2	10	4
Abscess	33	4	29	4
Paronychia	14	3	14	3
Infected Dermatitis	14	3	12	3
Infected Wound	21	4	27	9
Cellulitis	9	1	13	1
Folliculitis	4	2	11	6
Infected Ulcer	2	1	4	0
Furuncle	8	1	8	2
Carbuncle	3	0	3	0
Infected Burn	0	0	2	0
Total	122	21	133	32

Table 17 shows the clinical cure rates, according to baseline diagnosis, for the 143 cefdinir patients and 165 cephalexin

patients with *S. aureus* as a baseline pathogen. There were 122 cefdinir patients (85.3%) and 133 cephalexin patients (80.6%) who were cured. The numbers of patients in both treatment groups for each of the diagnostic categories were very similar with the exception of patients with folliculitis and infected burns.

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to clinical cure rate with* S. aureus, *the 95% confidence interval (with continuity correction) being* $_{143,165}$ *(-0.0432, 0.1373)* $_{85.3\%,80.6\%}$.

Table 18. Clinical cure rates - Evaluable patients with *S. pyogenes* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 17		Cephalexin n = 11	
	Cure	Failure	Cure	Failure
Impetigo	1	2	0	0
Abscess	0	0	1	0
Paronychia	0	0	3	0
Infected Dermatitis	1	0	1	0
Infected Wound	5	0	2	0
Cellulitis	4	1	2	1
Folliculitis	2	0	1	0
Furuncle	1	0	0	0
Total	14	3	10	1

Table 18 shows the results for the 17 evaluable cefdinir patients and the 11 evaluable cephalexin patients with *S. pyogenes* as a baseline pathogen. There were 14 cures (82.4%) and three failures (17.6%) in the cefdinir group, while the cephalexin

group had 10 cures (90.9%) and one failure (9.1%).

Statistical reviewer's note: Cefdinir fails to establish therapeutic equivalence to cephalexin with respect to the clinical cure rates in evaluable patients with S. pyogenes. *The exact 95% confidence interval is* $_{17,11}$ *(-0.4953, 0.2844)* $_{82.4\%,90.9\%}$, *the asymptoxic 95% confidence interval is* $_{17,11}$ *(-0.3340, 0.1628)* $_{82.4\%,90.9\%}$.

Table 19. Clinical cure rates - Evaluable patients with *S. agalactiae* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 13		Cephalexin n = 18	
	Cure	Failure	Cure	Failure
mpetigo	0	1	2	2
Abscess	3	1	2	1
Paronychia	2	1	0	1
Infected Dermatitis	0	0	1	1
Infected Wound	3	0	3	1
Cellulitis	2	0	0	0
Folliculitis	0	0	0	2
Infected Ulcer	0	0	1	0
Carbuncle	0	0	1	0
Total	10	3	10	8

Among the 13 evaluable cefdinir patients with *S. agalactiae* as a baseline pathogen, there were 10 cures and 3 failures for a 76.9% cure rate. For the 18 evaluable cephalexin patients, there were 10 cures and eight failures for a 55.6% cure rate.

Clinical reviewer's note: *It should be noted that all 13 evaluable cefdinir patients had mixed infections with other microorganisms present. Along with the S. agalactiae, six of these patients had S. aureus, seven patients had a gram negative rod, two had S. epidermidis, one had Enterococcus, and one had C. albicans.*

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to clinical cure rates due to S. agalactiae. The 95% exact confidence interval is* $_{13,18}(-0.1504, 0.5987)_{76.9\%,55.6\%}$ *and the 95% asymptotic confidence interval is* $_{13,18}(-0.1106, 0.5379)_{76.9\%,55.6\%}$. *It is to be noted that the sample sizes are not adequate to ensure acceptable level of power to the statistical inferences obtained.*

Table 20. Clinical cure rates - Evaluable patients with *K. pneumoniae* according to diagnosis.

Baseline Diagnosis	Cefdinir n = 8		Cephalexin n = 9	
	Cure	Failure	Cure	Failure
Impetigo	0	1	1	1
Abscess	1	0	1	0
Paronychia	2	0	1	2
Infected Wound	2	0	0	2
Cellulitis	1	0	0	0
Folliculitis	1	0	0	0
Infected Ulcer	0	0	0	1
Total	7	1	3	6

Among the eight evaluable cefdinir patients with *K. pneumoniae* as a baseline pathogen, there were seven cures (87.5%) and one failure (12.5%). For the nine evaluable cephalexin patients with *K. pneumoniae*, there were three cures (33.3%) and six failures (66.7%).

Clinical reviewer's note: *All of the cefdinir patients, except for one patient with paronychia, had mixed infections with other organisms. The cefdinir patient who failed therapy had impetigo with four organisms (E. faecium, S. aureus, S. agalactiae, and K. pneumoniae).*

Statistical reviewer's note: *It is to be noted that the sample size is not adequate to ensure acceptable power to the statistical inferences.*

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Table 21. Clinical cure rates - Summary of Evaluable patients with requested organisms according to diagnosis.

Baseline Diagnosis	Cefdinir n = 181		Cephalexin n = 203	
	Cure	Failure	Cure	Failure
Impetigo	15	6	13	7
Abscess	37	5	33	5
Paronychia	18	4	18	6
Infected Dermatitis	15	3	14	4
Infected Wound	31	4	32	12
Cellulitis	16	2	15	2
Folliculitis	7	2	12	8
Furuncle	9	1	8	2
Infected Burn	0	0	2	0
Infected Ulcer	2	1	5	1
Carbuncle	3	0	4	0
Total	153	28	156	47

Table 21 shows a summary of the evaluable patients with all of the requested organisms according to diagnosis and their outcomes. Among the patients treated with cefdinir, there were 153 cures (84.5%) and 28 failures (15.5%). For the cephalexin patients, there were 156 cures (76.8) and 47 failures (23.2%).

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rates with the requested organisms, the 95% confidence interval being* $_{181,203}$ *(-0.0067, 0.1604)* $_{84.5\%,76.8\%}$.

Microbiology

Table 22 shows the eradication rates for the applicant's proposed baseline pathogens at the Test of Cure visit for the 178 evaluable patients in the cefdinir group and the 204 evaluable patients in the cephalexin group.

TABLE 22 Microbiologic Eradication Rate by Baseline Isolate at the Test-of-Cure Visit Evaluable Patients

Baseline Pathogen	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
Enterococcus faecalis	0/0	–	1/1	100.0
Enterococcus faecium	1/1	100.0	0/0	–
Staphylococcus aureus	131/143	91.6	145/165	87.9
Streptococcus agalactiae	13/13	100.0	16/18	88.9
Streptococcus pyogenes	17/17	100.0	11/11	100.0
Streptococcus Group G	2/2	100.0	5/6	83.3
Gram-Negative				
Acinetobacter calcoaceticus var *lwoffi*	4/4	100.0	4/4	100.0
Alcaligenes faecalis	0/0	–	1/1	100.0
Citrobacter amalonaticus	1/1	100.0	0/0	–
Citrobacter diversus	½	50.0	0/0	–
Citrobacter freundii	1/1	100.0	1/1	100.0
Enterobacter agglomerans	4/4	100.0	4/4	100.0
Escherichia coli	4/4	100.0	12/13	92.3
Escherichia hermanii	1/1	100.0	0/0	–
Haemophilus parahaemolyticus	0/0	–	1/1	100.0
Haemophilus parainfluenzae	2/2	100.0	1/1	100.0
Klebsiella oxytoca	2/2	100.0	2/2	100.0
Klebsiella pneumoniae	8/8	100.0	8/9	88.9
Pasteurella multocida	1/1	100.0	0/0	–
Proteus mirabilis	6/8	75.0	7/8	87.5
Proteus vulgaris	1/1	100.0	0/0	–
Providencia rettgeri	0/0	–	1/1	100.0
Xanthomonas maltophilia	0/0	–	1/1	100.0
Total	200/215	93.0	221/247	89.4

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

In the cefdinir group, 200 of 215 (93.0%) isolates were eradicated at the test of cure visit, while in the comparator

drug group, 221 of 247 (89.5%) isolates were eradicated.

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with regard to overall microbiologic eradication by baseline isolate at the test of cure visit. When overall eradication is considered [95% confidence interval being* $_{215,247}$ *(-0.0201, 0.0911)* $_{93\%,89.4\%}$*] as well as when only patients with S. aureus as a baseline pathogen are considered [95% confidence interval is* $_{143,165}$ *(-0.0366, 0.1112)* $_{91.6\%,87.9\%}$*]*

TABLE 23. Microbiologic Eradication Rate by Isolate and Baseline Diagnosis at the Test-of-Cure Visit - Isolates From Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	44/48	91.7	48/50	96.0
Infected Traumatic/Surgical Wound	36/40	90.0	43/53	81.1
Paronychia	28/30	93.3	31/33	93.9
Cellulitis	22/22	100.0	21/21	100.0
Infected Dermatitis	22/23	95.7	18/19	94.7
Impetigo	20/23	87.0	15/21	71.4
Folliculitis	12/12	100.0	19/23	82.6
Furuncle	11/11	100.0	12/12	100.0
Carbuncle	3/3	100.0	6/6	100.0
Acutely Infected Ulcer	2/3	66.7	6/7	85.7
Infected Burn	0/0	—	2/2	100.0
Across Diagnosis	200/215	93.0	221/247	89.4

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

In Table 23 the microbial eradication rate according to baseline diagnosis for both treatment groups is shown. The eradication rates for both drugs are similar for the 11 diagnoses listed.

Clinical reviewer's note: *The Evaluability Criteria for SSSI*

presented to the Division's Anti-Infective Advisory Committee in March 1997 specified that the following organisms would be considered in uncomplicated SSSI: Staphylococcus aureus and Streptococcus pyogenes. Therefore, the eradication rates for S. aureus and S. pyogenes according to baseline diagnosis for both treatment groups is very important. That information was extracted from the above table and is shown in Tables 24 and 25.

Statistical reviewer's note: *Cefdinir BID is therapeutically equivalent to cephalexin with regard to microbiologic eradication by pathogen and baseline diagnosis at the TOC visit, the 95% confidence interval being $_{215,247}$ (-0.0201, 0.0911) $_{93\%,89.4\%}$.*

TABLE 24. Microbiologic Eradication Rate for *S. aureus* and Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	33/37	89.2	32/33	97.0
Infected Traumatic/Surgical Wound	23/25	92.0	28/36	77.8
Paronychia	16/17	94.1	15/17	88.2
Cellulitis	10/10	100.0	14/14	100.0
Infected Dermatitis	16/17	94.1	14/15	93.3
Impetigo	13/16	81.3	9/14	64.3
Folliculitis	6/6	100.0	14/17	82.4
Furuncle	9/9	100.0	10/10	100.0
Carbuncle	3/3	100.0	3/3	100.0
Acutely Infected Ulcer	2/3	66.7	4/4	100.0
Infected Burn	0/0	0.0	2/2	100.0
Across Diagnosis	131/143	91.6	145/165	87.9

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

Clinical reviewer's note: *Of the 143 isolates of S. aureus from*

the cefdinir group, 118 were found as single pathogens and 25 were isolated from polymicrobial infections. Among the cephalexin patients with this organism, 133 of the isolates were found as single pathogens, while 32 occurred as part of a mixed infection. The overall eradication rate for the cefdinir group was 131/143 (91.6%) compared to 145/165 (87.9%) for the cephalexin patients.

Statistical reviewer's note: *Cefdinir BID is therapeutically equivalent to cephalexin with respect to microbiologic eradication at TOC of S. aureus as a baseline pathogen, the 95% Confidence Interval being* $_{143,165}$ *(-0.0367, 0.1112)* $_{91.6\%,87.9\%}$.

TABLE 25. Microbiologic Eradication Rate for *S. pyogenes* and Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID	Cephalexin
Abscess	0	1
Infected Traumatic/Surgical Wound	5	2
Paronychia	0	3
Cellulitis	5	3
Infected Dermatitis	1	1
Impetigo	3	0
Folliculitis	2	1
Furuncle	1	0
Across Diagnosis	17	11

There were 17 isolates of *S. pyogenes* among the evaluable cefdinir patients and 11 isolates among the cephalexin patients. All of them were eradicated from both treatment groups for a 100% eradication rate.

Clinical reviewer's note: *Of the 17 isolates of S. pyogenes from the cefdinir treatment group, 10 were found as single pathogens and 7 were isolated from polymicrobial infections. In the cephalexin treatment group, five of the 11 isolates were found as single pathogens, while 7 isolates were from mixed infections.*

TABLE 26. Microbiologic Eradication Rate by Patient (According to Their Baseline Cultures) at the Test-of-Cure Visit - Evaluable Patients

Baseline Pathogen	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
Staphylococcus aureus	109/118	92.4	119/133	89.5
Streptococcus agalactiae	3/3	100.0	6/6	100.0
Streptococcus pyogenes	10/10	100.0	5/5	100.0
Streptococcus Group G	1/1	100.0	1/1	100.0
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	2/2	100.0	6/6	100.0
Escherichia hermanii	1/1	100.0	0/0	—
Haemophilus parahaemolyticus	0/0	—	1/1	100.0
Haemophilus parainfluenzae	2/2	100.0	1/1	100.0
Klebsiella oxytoca	0/0	—	1/1	100.0
Klebsiella pneumoniae	1/1	100.0	2/3	66.7
Pasteurella multocida	1/1	100.0	0/0	—
Proteus mirabilis	4/4	100.0	5/6	83.3
Providencia rettgeri	0/0	—	1/1	100.0
Xanthomonas maltophilia	0/0	—	1/1	100.0
Multiple	27/31	87.1	30/37	81.1
Total	164/178	92.1	181/204	88.7

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

In Table 26 the microbial eradication rate by patient according to the microorganisms isolated at baseline is shown for the 178

evaluable cefdinir patients and the 204 evaluable cephalexin patients. In the cefdinir group, 164 of 178 (92.1%) of the patients had their baseline organisms eradicated, while 181 of 204 (88.7%) cephalexin patients had their baseline organisms eradicated.

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with regard to microbiologic eradication by patient at the TOC visit, the 95% confidence interval being* $_{178,204}$ *(-0.0298, 0.0981)* $_{92.1\%,88.7\%}$.

TABLE 27. Microbiologic Eradication Rate by Patient and Baseline Diagnosis at the Test-of-Cure Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir BID		Cephalexin	
	n/N	%	n/N	%
Abscess	40/44	90.9	42/44	95.5
Infected Traumatic/Surgical Wound	29/32	90.6	36/44	81.8
Paronychia	21/23	91.3	20/22	90.9
Infected Dermatitis	18/19	94.7	14/15	93.3
Cellulitis	17/17	100.0	17/17	100.0
Impetigo	15/18	83.3	11/17	64.7
Furuncle	10/10	100.0	12/12	100.0
Folliculitis	9/9	100.0	17/20	85.0
Carbuncle	3/3	100.0	6/6	100.0
Acutely Infected Ulcer	2/3	66.7	4/5	80.0
Infected Burn	0/0	—	2/2	100.0
Across Diagnosis	164/178	92.1	181/204	88.7

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

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with regard to microbiologic eradication by patient and baseline diagnosis at the TOC visit, the 95% confidence interval being* $_{178,204}$ *(-0.0298, 0.0981)* $_{92.1\%,88.7\%}$.

Clinical Reviewer's Analysis of Data

The applicant has requested the approval of an indication for the treatment of uncomplicated skin and skin structure infections caused by susceptible strains of *S. aureus, S. pyogenes, S. agalactiae,* and *K. pneumoniae.* Therefore, a closer examination of the data concerning these four organisms is necessary. The following table shows the microbiologic eradication rate for the requested pathogens from evaluable patients.

Table 28. Microbiologic eradication rate for requested pathogens from evaluable patients.

Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Staphylococcus aureus	131/143	91.6	145/165	87.9
Streptococcus agalactiae	13/13	100.0	16/18	88.9
Streptococcus pyogenes	17/17	100.0	11/11	100.0
Klebsiella pneumoniae	8/8	100.0	8/9	88.9
Total	169/181	93.4	180/203	88.7

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with regard to overall microbiologic eradication in evaluable patients [95% CI being* $_{181,203}$ *(-0.0149, 0.1089)* $_{93.4\%,88.7\%}$*], as well as in patients with S. aureus as a baseline pathogen, the 95% confidence interval being* $_{143,165}$ *(-0.0366, 0.1112)* $_{91.6\%,87.9\%}$*. It is to be noted that except*

for S. aureus on total eradication rates, the sample sizes are not adequate to ensure acceptable level of power to the statistical inferences obtained.

Safety

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

Adverse Events: Adverse events included any concurrent illness or symptom reported by the patient or noted by the investigator during the study. In addition, any new outbreak of an SSSI at a site other than that chosen at baseline was also reported as an adverse event. All adverse events that began during the study or that increased in intensity or frequency from baseline were considered treatment emergent signs and symptoms (TESS). Abnormal clinical laboratory values could also be designated as adverse events at the discretion of the investigator.

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

Adverse events were considered serious if they were fatal, immediately life-threatening, severely or permanently disabling, required or prolonged hospitalization, or were an intentional or accidental overdose, a congenital anomaly, or cancer. During the

medical review, other events could be identified as serious even if they did not meet the above definition. These other events could include:

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

There were 494 patients who received cefdinir (20 - QD and 474 - BID) and 478 patients who received cephalexin included in the safety analysis. One hundred ninety-three (39.1%) of the cefdinir patients and 144 (30.1%) of the cephalexin patients reported one or more adverse events. One hundred thirty-five (27.3%) of the adverse events reported by the cefdinir group and 79 (16.5%) of the adverse events reported by the cephalexin patients were considered to be drug associated events. The incidence of adverse events by body system is depicted in table 29.

TABLE 29. Summary of Adverse Events - All Patients Receiving Study Medication
[Number (%) of Patients]

	Cefdinir				Cephalexin	
	QD N = 20		BID N = 474		N = 478	
Adverse Events						
All Adverse Events	10	(50.0)	183	(38.6)	144	(30.1)
Associated[a] Adverse Events	8	(40.0)	127	(26.8)	79	(16.5)
Adverse Events by Age[b]						
All Adverse Events						
13 to <18 yr	0	(0.0)	5	(21.7)	11	(32.4)
18 to <65 yr	9	(50.0)	151	(39.7)	114	(30.5)
≥65 yr	1	(100.0)	27	(38.0)	19	(27.1)
Associated Adverse Events						
13 to <18 yr	0	(0.0)	5	(21.7)	5	(14.7)
18 to <65 yr	7	(38.9)	103	(27.1)	60	(16.0)
≥65 yr	1	(100.0)	19	(26.8)	14	(20.0)
Adverse Events by Gender[c]						
Male	7	(53.8)	113	(40.2)	79	(27.9)
Female	3	(42.9)	70	(36.3)	65	(33.3)
Adverse Events by Maximum Intensity[d]						
All Adverse Events						
Mild	7	(35.0)	128	(27.0)	103	(21.5)
Moderate	4	(20.0)	63	(13.3)	52	(10.9)
Severe	0	(0.0)	14	(3.0)	6	(1.3)
Associated Adverse Events						
Mild	5	(25.0)	87	(18.4)	53	(11.1)
Moderate	4	(20.0)	42	(8.9)	28	(5.9)
Severe	0	(0.0)	8	(1.7)	4	(0.8)
Serious Adverse Events	0	(0.0)	7	(1.5)	3	(0.6)
Deaths	0	(0.0)	1	(0.2)	0	(0.0)
Discontinuation of Treatment Due to Adverse Events						
All Adverse Events	3	(15.0)	28	(5.9)	17	(3.6)
Associated Adverse Events	2	(10.0)	20	(4.2)	13	(2.7)
Withdrawals After Treatment Due to Adverse Events						
All Adverse Events	0	(0.0)	1	(0.2)	2	(0.4)
Associated Adverse Events	0	(0.0)	0	(0.0)	0	(0.0)

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

TABLE 30. All and Associated[a] Adverse Events by Body System - Patients Receiving Study Medication [Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 20				Cefdinir BID N = 474				Cephalexin N = 478			
	All		Associated		All[b]		Associated		All		Associated	
BODY AS A WHOLE	1[c]	(5.0)	1	(5.0)	48[c]	(10.1)	15	(3.2)	67[c]	(14.0)	14[c]	(2.9)
Headache	1	(5.0)	1	(5.0)	23	(4.9)	10	(2.1)	26	(5.4)	4	(0.8)
Infection	0	(0.0)	0	(0.0)	5	(1.1)	0	(0.0)	5	(1.0)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	5	(1.1)	0	(0.0)	7	(1.5)	0	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	4	(0.8)	3	(0.6)	12	(2.5)	9	(1.9)
Asthenia	0	(0.0)	0	(0.0)	3	(0.6)	0	(0.0)	3	(0.6)	1	(0.2)
Flu Syndrome	1	(5.0)	0	(0.0)	2	(0.4)	1	(0.2)	3	(0.6)	0	(0.0)
Abscess	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	2	(0.4)	0	(0.0)
Accidental Injury	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	4	(0.8)	0	(0.0)
Allergic Reaction	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)
Back Pain	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	4	(0.8)	1	(0.2)
Chest Pain	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Face Edema	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Neck Pain	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Sudden Death	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Chills	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Fever	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Hernia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Intentional Injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Neck Rigidity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
CARDIOVASCULAR SYSTEM	0	(0.0)	0	(0.0)	3	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Vasodilatation	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Syncope	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
DIGESTIVE SYSTEM	8[c]	(40.0)	8[c]	(40.0)	112	(23.6)	100[c]	(21.1)	69[c]	(14.4)	58[c]	(12.1)
Diarrhea	7	(35.0)	7	(35.0)	82	(17.3)	78	(16.5)	40	(8.4)	36	(7.5)
Nausea	0	(0.0)	0	(0.0)	19	(4.0)	17	(3.6)	20	(4.2)	17	(3.6)
Constipation	0	(0.0)	0	(0.0)	4	(0.8)	3	(0.6)	0	(0.0)	0	(0.0)
Flatulence	1	(5.0)	1	(5.0)	4	(0.8)	3	(0.6)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	3	(0.6)	3	(0.6)	5	(1.0)	4	(0.8)
Abnormal Stools	0	(0.0)	0	(0.0)	2	(0.4)	1	(0.2)	0	(0.0)	0	(0.0)
Cheilitis	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)
Dry Mouth	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspepsia	2	(10.0)	2	(10.0)	1	(0.2)	1	(0.2)	6	(1.3)	4	(0.8)
Gastroenteritis	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal Disorder	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)
Melena	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)
Pseudomembranous Colitis	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)
Rectal Disorder	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.2)	0	(0.0)
Anorexia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 20		Cefdinir BID N = 474		Cephalexin N = 478	
	All	Associated	All[b]	Associated	All	Associated
Increased Appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Peptic Ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Tooth Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Lymphadenopathy	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphangitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1 (5.0)	0 (0.0)	4[c] (0.8)	3[c] (0.6)	3 (0.6)	2 (0.4)
ALT Increased	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
Alkaline Phosphatase Increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
AST Increased	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Weight Gain	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Hyperglycemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Peripheral Edema	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
NERVOUS SYSTEM	0 (0.0)	0 (0.0)	12 (2.5)	4 (0.8)	14[c] (2.9)	7 (1.5)
Dizziness	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	8 (1.7)	3 (0.6)
Insomnia	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Dreams	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.4)	0 (0.0)
Hyperkinesia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hypesthesia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Nervousness	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Somnolence	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
RESPIRATORY SYSTEM	0 (0.0)	0 (0.0)	6 (1.3)	1 (0.2)	9 (1.9)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cough Increased	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
Hypoxia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	4 (0.8)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
SKIN AND APPENDAGES	2 (10.0)	0 (0.0)	17 (3.6)	7[c] (1.5)	14[c] (2.9)	3[c] (0.6)
Rash	1 (5.0)	0 (0.0)	7 (1.5)	6 (1.3)	3 (0.6)	1 (0.2)
Pruritus	1 (5.0)	0 (0.0)	3 (0.6)	1 (0.2)	3 (0.6)	2 (0.4)
Dry Skin	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Furunculosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.6)	0 (0.0)
Pustular Rash	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Skin Disorder	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vesiculobullous Rash	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 20		Cefdinir BID N = 474		Cephalexin N = 478	
	All	Associated	All[b]	Associated	All	Associated
Contact Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Maculopapular Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Sweating	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
SPECIAL SENSES	0 (0.0)	0 (0.0)	5[c] (1.1)	0 (0.0)	2[c] (0.4)	0 (0.0)
Ear Disorder	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Disorder	0 (0.0)	0 (0.0)	2 0	(0.0)	0 (0.0)	0 (0.0)
Deafness	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Ear Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Otitis Media	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
UROGENITAL SYSTEM	0 (0.0)	0 (0.0)	18[c] (3.8)	15[c] (3.2)	18 (3.8)	11 (2.3)
Vaginal Moniliasis[d,e]	0 (0.0)	0 (0.0)	14 (7.3)	14 (7.3)	10 (5.1)	10 (5.1)
Urinary Frequency	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	2 (0.4)	0 (0.0)
Hematuria	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Menorrhagia[d]	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Vaginitis[d,e]	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (1.0)	1 (0.5)
Dysmenorrhea[d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Dysuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Urinary Tract Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

[a] Possibly, probably, or definitely related to treatment
[b] All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir BI
[c] The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse eve
[d] Calculated for women who received study medication (cefdinir QD, N = 7; cefdinir BID, N = 193; cephalexin, N = 195).
[e] It is likely that vaginitis and vaginal moniliasis represent the same condition in women. Therefore, the total number of patients can be combine totals and percentages (calculated for women who received study medication) for cefdinir BID are 15 (7.8%) for all and associated events, and 12 (6.2%) and 11 (5.6%) for all and associated events, respectively.

All and Drug-Associated Adverse Events: Most adverse events among both cefdinir and cephalexin patients were related to the digestive system, body as a whole, or the urogenital system. Adverse events related to the digestive system were most often considered to be drug-associated by the investigator. Significantly more cefdinir BID-treated patients experienced adverse events ($p = 0.005$) and drug-associated adverse events ($p < 0.001$) than those treated with cephalexin according to the applicant.

The most frequently reported adverse events for patients treated with cefdinir BID included diarrhea (17%), vaginal moniliasis/vaginitis (8% of female patients), headache (5%), and nausea (4%). For patients treated with cephalexin, the most frequently reported adverse events included diarrhea (8%), vaginal moniliasis/vaginitis (6% of female patients), headache (5%), nausea (4%), and abdominal pain (3%). All other adverse events occurred in less than 2% of patients.

An analysis of diarrhea, the most common adverse event during the study, showed that significantly more patients treated with

cefdinir BID experienced diarrhea than patients treated with cephalexin (p <0.001 - applicant's analysis).

Deaths: There was one death in the study. It involved a 43 year-old white male who completed 10 days of cefdinir therapy for the treatment of a complicated infected trauma/surgical wound. He expired 14 days after completing therapy. The cause of death was due to alcoholic cardiomyopathy.

TABLE 31. Serious Adverse Events - Patients Receiving Study Medication

Treatment	Center	Patient Number	Age[a], Sex	Serious Adverse Event[b]	Intensity	Relationship to Study Medication[c]	Management of Study Drug	Outcome
Cefdinir BID								
	1	12	22, M	Pseudomembranous Colitis	Severe	Probably	Discontinued	Recovered
				Appendicitis (Gastrointestinal Disorder)	Moderate	Possibly	Discontinued	Recovered
	5	6	54, M	Reduced Tissue O_2 Concentration[d] (Hypoxia)	Severe	Definitely Not	Discontinued	Recovered/ Sequelae
		33	67, M	Chest Pain	Severe	Definitely Not	None	Recovered
	8	32	74, M	Eruption of Bullous Pemphigoid (Vesiculobullous Rash)	Moderate	Definitely Not	Discontinued	Recovered
		66	71, M	Fainting (Syncope)	Moderate	Definitely Not	None	Recovered
				Laceration of Scalp (Accidental Injury)	Moderate	Definitely Not	None	Recovered
	18	19	43, M	Sudden Death	Severe	Definitely Not	None	Died
	49	3	80, M	Severe Asthmatic Attack (Asthma)	Severe	Unlikely	Discontinued	Recovered
Cephalexin								
	5	8	50, M	Exacerbation of Infected Right Toe (Infection)	Moderate	Unlikely	Discontinued	Recovered
	6	62	47, M	Traumatic Blow to Head - Blunt Instrument (Intentional Injury)	Severe	Definitely Not	Discontinued	Recovered/ Sequelae
	19	11	48, M	Hear Loss, Right Ear (Deafness)	Moderate	Unlikely	None	Not Yet Recovered

[a] Age at baseline
[b] When the investigator term and COSTART term differ, the COSTART adverse event term appears in parentheses.
[c] As determined by the investigator
[d] At site of infection

Serious Adverse Events: There were seven cefdinir and three cephalexin patients who experienced serious adverse events, as shown in Table 31. Four of the cefdinir patients and two of the cephalexin patients withdrew from the study. One patient treated with BID cefdinir had pseudomembranous colitis which was probably related to therapy. A *C. difficile* toxin assay for this patient was negative. There did not appear to be any relationship between an adverse event and the study medication for the other nine patients.

Discontinued Patients: Table 32 is a summary of treatment discontinuations. It shows that three cefdinir QD patients, 33 cefdinir BID patients, and 27 cephalexin patients withdrew from the study due to adverse events. Diarrhea was the most frequent cause for discontinuation for both study groups.

Clinical Laboratory Values: Baseline values for each patient's clinical laboratory measurements were to be determined prior to the receipt of study medication. At the STFU visit, clinical laboratory tests were repeated and these values were compared to standard normal values and the patient's baseline values. If a significantly abnormal value was noted at STFU, laboratory tests were to be repeated until the abnormality resolved or a reason for the abnormality was determined.

Clinical laboratory values were reviewed by the sponsor to identify any changes that may have occurred during the study. Specifically, these included median changes from baseline, category shift changes, and markedly abnormal values.

Clinical Reviewer's note: *For patients treated with cefdinir BID and cephalexin, there were more decreases than increases in WBCs and PMNs which is consistent with a resolving infection. Also, more decreases than increases were observed for alkaline phosphatase, urine specific gravity, and urine ketones. The comparator drug had more markedly abnormal lab values than the study drug for eosinophils, glucose, ALT, and bicarbonate.*

TABLE 32. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Receiving Study Medication
[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 20		Cefdinir BID N = 474		Cephalexin N = 478	
BODY AS A WHOLE	1	(5.0)	6[a]	(1.3)	7	(1.5)
Flu Syndrome	1	(5.0)	2	(0.4)	0	(0.0)
Headache	0	(0.0)	2	(0.4)	0	(0.0)
Abdominal Pain	0	(0.0)	1	(0.2)	3	(0.6)
Allergic Reaction	0	(0.0)	1	(0.2)	0	(0.0)
Pain	0	(0.0)	1	(0.2)	0	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	1	(0.2)
Fever	0	(0.0)	0	(0.0)	1	(0.2)
Infection	0	(0.0)	0	(0.0)	1	(0.2)
Intentional Injury	0	(0.0)	0	(0.0)	1	(0.2)
DIGESTIVE SYSTEM	2	(10.0)	16[a]	(3.4)	13[a]	(2.7)
Diarrhea	1	(5.0)	11	(2.3)	7	(1.5)
Nausea	0	(0.0)	3	(0.6)	6	(1.3)
Vomiting	0	(0.0)	2	(0.4)	3	(0.6)
Gastrointestinal Disorder	0	(0.0)	1	(0.2)	0	(0.0)
Pseudomembranous Colitis	0	(0.0)	1	(0.2)	0	(0.0)
Dyspepsia	1	(5.0)	0	(0.0)	1	(0.2)
HEMIC AND LYMPHATIC SYSTEM	0	(0.0)	1	(0.2)	0	(0.0)
Lymphangitis	0	(0.0)	1	(0.2)	0	(0.0)
NERVOUS SYSTEM	0	(0.0)	2	(0.4)	3[a]	(0.6)
Abnormal Dreams	0	(0.0)	1	(0.2)	0	(0.0)
Insomnia	0	(0.0)	1	(0.2)	0	(0.0)
Anxiety	0	(0.0)	0	(0.0)	1	(0.2)
Dizziness	0	(0.0)	0	(0.0)	2	(0.4)
Somnolence	0	(0.0)	0	(0.0)	1	(0.2)
RESPIRATORY SYSTEM	0	(0.0)	2	(0.4)	1	(0.2)
Asthma	0	(0.0)	1	(0.2)	0	(0.0)
Hypoxia	0	(0.0)	1	(0.2)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	1	(0.2)
SKIN AND APPENDAGES	0	(0.0)	4[a]	(0.8)	1	(0.2)
Rash	0	(0.0)	2	(0.4)	0	(0.0)
Pruritus	0	(0.0)	1	(0.2)	1	(0.2)
Pustular Rash	0	(0.0)	1	(0.2)	0	(0.0)
Vesiculobullous Rash	0	(0.0)	1	(0.2)	0	(0.0)
UROGENITAL SYSTEM	0	(0.0)	1	(0.2)	2	(0.4)
Vaginal Moniliasis[b]	0	(0.0)	1	(0.5)	1	(0.5)
Urinary Tract Infection	0	(0.0)	0	(0.0)	1	(0.2)

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

b Calculated for women who received study medication (cefdinir QD, N = 7; cefdinir BID, N = 193; cephalexin, N = 195.)

Indication: Uncomplicated skin and skin structure infections

Title and Study Number: A phase 3, 10-day, investigator-blind, randomized, comparative, multicenter study of cefdinir (CI-983) versus cephalexin in the treatment of pediatric patients with uncomplicated skin and skin structure infections (protocol 983-13).

Objective: The objective of this study was to evaluate the efficacy and safety of cefdinir suspension (14 mg/kg/day as 7 mg/kg BID up to a maximum of 600 mg/day) versus cephalexin suspension (40 mg/kg/day as 10 mg/kg QID up to a maximum of 2000 mg/day) in the treatment of acute uncomplicated SSSIs in patients 6 months to 12 years of age.

Study Design: This was an investigator-blind, randomized, comparative, multicenter study with 2 parallel-treatment groups. Screening, dosing, follow-up visits, and the test-of-cure (TOC) visit window are illustrated in Figure 2. An on-therapy visit (Days 3 to 5) was part of the study design but is not illustrated in Figure 2 since it was not used in any efficacy evaluation.

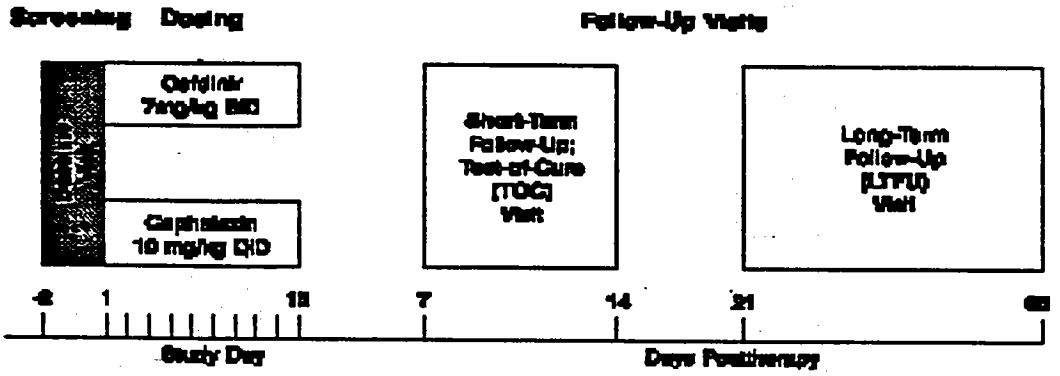

Figure 2. Protocol 983-13 Study Design

Protocol Overview

Population and Inclusion/Exclusion Criteria:

Population: Participants included boys and girls 6 months to 12 years of age. Girls who were postmenarchal had a negative pregnancy test at baseline.

Inclusion Criteria: Inclusion criteria were similar to that stated in the adult study (protocol 983-8) with the following exception. Pediatric patients were required to have one or more clinical signs and symptoms of SSSI for study entry. They could include pain/tenderness, erythema/warmth, swelling, induration/crusting, fluctuation, or drainage. The investigator performed the evaluation of signs and symptoms and classified them as absent, mild, moderate, or severe at each visit. In the adult study, two clinical signs/symptoms were required.

Exclusion Criteria: The patient exclusion criteria were identical to those found in the adult (capsule) study.

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

Confirmation of bacteriological etiology and in vitro susceptibility (or intermediate susceptibility) to study medication were required for a patient to be evaluable for efficacy analyses. If these conditions were not met, a patient could be discontinued from study medication and given appropriate therapy. The investigator could continue to treat patients who had a baseline pathogen that was resistant to 1 study medication and susceptible to the other if, in his or her judgement, they were exhibiting satisfactory clinical improvement.

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

Assessments of microbiologic and clinical response at the TOC visit, 7 to 14 days posttherapy, were used to evaluate the efficacy of cefdinir. A long-term follow-up (LTFU) visit, 21 to

35 days posttherapy, provided information on recurrence of infection.

Three efficacy measures were used in this study: microbiologic eradication rate by pathogen, microbiologic eradication rate by patient, and clinical cure rate by patient.

Endpoints Defined (Clinical and Microbiological)

The schedule of visits, examinations and evaluations for the patients in this study is shown in the following table, which was duplicated from the submission.

The visits, examinations, and collection of specimens were similar to those described in the adult (capsule) study.

TABLE 33. Schedule of Clinical Observations and Laboratory Measurements

Procedure/Observation	Baseline[a]	Day 1	Days 3-5	Day 10	Posttherapy Visits	
					7 to 14 Days	21 to 35 Days
Medical History	X					
Physical Examination[b]	X				X	
Clinical Evaluations (Signs and Symptoms)[b]	X		X		X	X
Skin Culture from Baseline Site of Infection and Susceptibility Testing[b]	X				X	X
Adverse Events		X			X	X
Clinical Laboratory Testing[b,c]	X				X	X[d]
Assessment of Clinical Efficacy[b]					X	X
Radiographic Evaluation[e]	X					
Dosing		X		X		

[a] Prior to treatment (within 48 hours)
[b] Performed whenever a patient was withdrawn
[c] Listed in protocol (Appendix A.2)
[d] Performed only if abnormalities were detected at the previous visit
[e] Only if indicated to rule out osteomyelitis

Microbiological endpoints: Assessments of microbiologic response at the TOC visit, 7 to 14 days posttherapy, were used to evaluate the efficacy of cefdinir. A long-term follow-up (LTFU) visit, 21 to 35 days posttherapy, provided information on recurrence of infection.

The pediatric protocol differs from the adult study in the test of cure determination. In the adult study, the TOC date occurs at the last visit which is between 12 to 16 days post-therapy. In the pediatric study, the TOC visit occurs at the short term follow-up visit which is between 7 to 14 days post-therapy. The

pediatric study has a long-term follow-up visit between 21 to 35 days post-therapy.

The criteria used for evaluation were identical to those found in the adult study.

Clinical endpoints: The criteria used for evaluation were identical to those found in the adult study.

Statistical Considerations

Sample Size: This double-blind, comparative study of cefdinir versus cephalexin was designed with a sample size of 120 evaluable patients per randomized treatment group for a total of 240 evaluable patients.

A microbiologic eradication rate of 85% across all randomized groups was assumed in the sample size calculations. Equivalence was to be assessed by comparing a two-tailed 95% confidence interval (CI) for the difference (cefdinir minus cephalexin) in microbiologic eradication rates to a set of predetermined, fixed criteria for equivalence. Sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and cephalexin microbiologic eradication rates at TOC, using this CI method.

The statistical analysis was performed as described previously in the adult study.

Study Results

Demographics, Evaluability

A total of 18 investigators enrolled 196 patients in the cefdinir group and 198 patients in the cephalexin group, for a total of 394 patients in the study. The following table shows the patient disposition, including the number of patients who were considered evaluable by each investigator.

TABLE 34. List of Investigators

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed[a]	Evaluable
2	C. Khurana	3	3	0
3	A. Iravani	30	30	17
4	J. Hedrick	51	50	34
5	W. Gooch	2	2	2
6	S. Wiederhold	28	23	15
7	S. Chartrand	24	24	19
8	J. McCarty	73	63	42
9	E. Rothstein	10	9	7
10	J. Haddad	3	1	0
11	R. Fiddes	75	63	34
12	S. McLinn	6	6	4
15	P. DiLorenzo	19	16	15
16	A. Phillips	6	2	2
17	R. Ford	13	12	8
18	J. Scott	21	19	16
19	S. Weakley	16	12	11
20	S. Davis	1	1	1
21	A. Herbert	13	7	4
	Total	394	343	231

[a] Completed treatment and test-of-cure visit

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

TABLE 35. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir N = 196		Cephalexin N = 198		Total N = 394	
Sex						
Male	110	(56.1)	107	(54.0)	217	(55.1)
Female	86	(43.9)	91	(46.0)	177	(44.9)
Race						
White	107	(54.6)	95	(48.0)	202	(51.3)
Black	24	(12.2)	27	(13.6)	51	(12.9)
Asian	0	(0.0)	2	(1.0)	2	(0.5)
Other[a]	65	(33.2)	74	(37.4)	139	(35.3)
Age, yr						
Median	5.5		5.2		5.3	
Range[b]	0.5-13.0		0.5-13.1		0.5-13.1	
Distribution						
<2[c]	29	(14.8)	30	(15.2)	59	(15.0)
2 to <6	79	(40.3)	88	(44.4)	167	(42.4)
6 to <13[d]	88	(44.9)	80	(40.4)	168	(42.6)
Baseline Diagnosis[e]						
Impetigo	109	(55.6)	117	(59.1)	226	(57.4)
Infected Dermatitis	20	(10.2)	15	(7.6)	35	(8.9)
Infected Traumatic/Surgical Wound	18	(9.2)	14	(7.1)	32	(8.1)
Cellulitis	16	(8.2)	13	(6.6)	29	(7.4)
Paronychia	9	(4.6)	14	(7.1)	23	(5.8)
Abscess	8	(4.1)	6	(3.0)	14	(3.6)
Folliculitis	7	(3.6)	4	(2.0)	11	(2.8)
Furuncle	4	(2.0)	7	(3.5)	11	(2.8)
Infected Burn	2	(1.0)	2	(1.0)	4	(1.0)
Acutely Infected Ulcer	0	(0.0)	1	(0.5)	1	(0.3)
Carbuncle	1	(0.5)	0	(0.0)	1	(0.3)
Other[f]	2	(1.0)	5	(2.5)	7	(1.8)

[a] Other = Hispanic, biracial, Native American, and Tongan.
[b] One cefdinir-treated patient's age of 12.97 years was rounded to 13 years for this table. One cephalexin-treated patient was >13 years old and considered a protocol variation
[c] Contains 1 cephalexin-treated patient approximately 5 days <6 months old.
[d] Contains 1 cephalexin-treated patient age 13 years, 1 month.
[e] Seventeen cefdinir-treated patients and 11 cephalexin-treated patients had conditions predisposing them to SSSIs. Section 5:1.4 contains information about patients with predisposing conditions.

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

Variable	Cefdinir N = 118		Cephalexin N = 113		Total N = 231	
Sex						
Male	63	(53.4)	53	(46.9)	116	(50.2)
Female	55	(46.6)	60	(53.1)	115	(49.8)
Race						
White	71	(60.2)	58	(51.3)	129	(55.8)
Black	10	(8.5)	15	(13.3)	25	(10.8)
Asian	0	(0.0)	1	(0.9)	1	(0.4)
Other[a]	37	(31.4)	39	(34.5)	76	(32.9)
Age, yr						
Median	5.3		5.3		5.3	
Range	0.5-12.7		0.9-13.1		0.5-13.1	
Distribution						
<2[b]	17	(14.4)	12	(10.6)	29	(12.6)
2 to <6	51	(43.2)	53	(46.9)	104	(45.0)
6 to <13[c]	50	(42.4)	48	(42.5)	98	(42.4)
Baseline Diagnosis						
Impetigo	74	(62.7)	76	(67.3)	150	(64.9)
Infected Dermatitis	15	(12.7)	6	(5.3)	21	(9.1)
Infected Traumatic/Surgical Wound	9	(7.6)	8	(7.1)	17	(7.4)
Cellulitis	7	(5.9)	5	(4.4)	12	(5.2)
Paronychia	3	(2.5)	7	(6.2)	10	(4.3)
Abscess	2	(1.7)	4	(3.5)	6	(2.6)
Folliculitis	3	(2.5)	1	(0.9)	4	(1.7)
Furuncle	1	(0.8)	3	(2.7)	4	(1.7)
Infected Burn	2	(1.7)	1	(0.9)	3	(1.3)
Carbuncle	1	(0.8)	0	(0.0)	1	(0.4)
Other[d]	1	(0.8)	2	(1.8)	3	(1.3)

[a] Other = Hispanic, Native American, biracial, and Tongan.
[b] Contains 1 cephalexin-treated patient approximately 5 days <6 months old.
[c] Contains 1 cephalexin-treated patient age 13 years, 1 month.
[d] Other = Infected blister, pyoderma, and secondarily infected chickenpox.

Clinical reviewer's note: *For all patients and evaluable patients, the study appears balanced with respect to gender, race, age, and baseline diagnoses.*

Statistical reviewer's note: *The two treatment arms are balanced with respect to baseline demographic variables - sex (p-value = 0.325), race (p-value = 0.374), and age (p-value = 0.664).*

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

TABLE 37. Patient Exposure to Study Medication - All Patients

Days on Study Medication	Cefdinir N = 196	Cephalexin N = 198
2	1	0
4	4	2
5	0	2
6	3	0
7	5	1
8	1	4
9	2	2
10	113	29
11	58	138
12	2	4
14	0	2
17	0	1
21	0	1
Median	10	11
Unknown	7	12

Clinical Reviewer's Note: *The median patient exposure to cefdinir was 10 days and 11 days for cephalexin. Among the cefdinir group, 171 (87%) 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:

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TABLE 38. Reasons Patients Were Not Evaluable at TOC or Disqualified at LTFU (Number of Patients)

	Cefdinir	Cephalexin
Randomized to Treatment	196	198
Reasons Patients Were Not Evaluable for TOC Analyses[a]		
Clinical Assessment Missed	8	12
Clinical Evaluation Out of Date Range[b]	25	34
Concurrent Antibacterial[b]	4	3
Culture[c] Out of Date Range[b]	21	32
Culture[c] Missed	13	14
Medication Not As Prescribed	24	17
No Proven Baseline Pathogen	28	22
Prior Antibacterial	4	3
Resistant Baseline Pathogen(s)	23	31
Total Not Evaluable	78	85
Patients Who Were Evaluable at TOC[d]	118	113
Reasons Patients Were Disqualified for LTFU Analyses		
Clinical Assessment Missed	7	7
Clinical Evaluation Out of Date Range[b]	4	7
Concurrent Antibacterial[b]	3	1
Culture[c] Out of Date Range[b]	4	7
Culture[c] Missed	6	7
Total Disqualified	14	15
Patients Who Were Qualified at LTFU	104	98

[a] Patients who had multiple reasons for being excluded from efficacy analyses were counted for each reason that was applied.
[b] Patients who had microbiologic and/or clinical assessments done early or who took a concurrent antibacterial because they were early failures were not removed from the evaluable analyses for these reasons.
[c] Baseline or TOC culture
[d] These patients were candidates for qualified analyses at LTFU.

Efficacy

Table 39 compares the number of patients randomized to treatment (i.e., the ITT population) to the number of patients in the other populations.

TABLE 39. Patients With Data Included in Efficacy Analyses
[Number (%) of Patients]

Patient Population	Cefdinir		Cephalexin	
ITT[a]	196	(100.0)	198	(100.0)
MITT[b]	161	(82.1)	165	(83.3)
Clinically Evaluable[c]	131	(66.8)	123	(62.1)
Evaluable[d]	118	(60.2)	113	(57.1)
Qualified[e]	104	(88.1)	98	(86.7)

[a] Patients in the ITT population were those randomized to treatment.

[b] Patients in the MITT population had the correct indication, received study medication, had at least 1 baseline pathogen, and had a follow-up culture

[c] Patients in the clinically evaluable population had the correct indication and at least 1 clinical sign or symptom; took study medication as prescribed; did not take nonstudy systemic or topical antibacterial therapy for other concurrent infections; and had their clinical evaluations performed within the range of days specified in the protocol. Patients were not excluded from this data set if they had no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the range of days specified in the protocol.

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

[e] Qualified patients were evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits (eg, qualified patients did not take concurrent systemic or topical antibacterial agents).

Clinical Results: As in the adult study, the primary measure of patient clinical response for efficacy analysis was a combination of investigator and sponsor assessments referred to as the combined investigator/sponsor clinical assessment. Table 40 shows the results of this reclassification for the patients who are both microbiologically and clinically evaluable.

TABLE 40. Investigator vs Combined Investigator/Sponsor Clinical Response Determination at the TOC Visit - Evaluable Patients

Investigator Determination	Combined Investigator/Sponsor Determination			
	Cefdinir N = 118		Cephalexin N = 113	
	Cure	Failure	Cure	Failure
Cure	116	0	106	0
Failure	0	2	0	7

Statistical reviewer's note: *The 95% CI for the difference between the cure rates for cefdinir and cephalexin was* $_{118,113}$ *(-0.0138, 0.1038)* $_{98.3\%,93.8\%}$, *showing therapeutic equivalence between the two treatment arms with respect to the clinical cure rate by evaluable patients.*

TABLE 41. Clinical Cure Rate[a] by Patient (According to Applicant's Proposed Baseline Pathogens) Across Baseline Diagnoses at the TOC Visit - Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
Enterococcus durans	1/1	100.0	0/0	–
Staphylococcus aureus	51/53	96.2	52/56	92.9
Staphylococcus Coagulase-Negative	1/1	100.0	0/0	–
Streptococcus pneumoniae	0/0	–	1/1	100.0
Streptococcus pyogenes	13/13	100.0	13/13	100.0
Streptococcus Group C	1/1	100.0	0/0	–
Gram-Negative				
Acinetobacter calcoaceticus var *lwoffi*	1/1	100.0	0/0	–
Enterobacter agglomerans	0/0	–	0/1	0.0
Haemophilus influenzae	2/2	100.0	0/0	–
Multiple	46/46	100.0	40/42	95.2
Total	116/118	98.3	106/113	93.8

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

In Table 41 the clinical cure rates for all microbiologically evaluable patients according to the baseline pathogen isolated is shown. For the 118 cefdinir patients, 116 (98.3%) patients were cured, while 106 of the 113 (93.8%) cephalexin patients were clinically cured.

Clinical reviewer's note: *As in the adult study, the data presented in Table 41 are based on the assignment of one organism as the primary pathogen for each evaluable patient. Actually, 72 cefdinir patients and 71 cephalexin patients had a single pathogen present, while 46 cefdinir patients and 42 cephalexin patients had multiple organisms present in their infections.*

Statistical reviewer's note: *The 95% CI for the difference between the cure rates for cefdinir and cephalexin was* $_{118,113}$ *(-0.0138, 0.1038)* $_{98.3\%,93.8\%}$, *showing therapeutic equivalence between the two treatment arms with respect to the clinical cure rate by patients.*

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TABLE 42. Clinical Cure Rate[a] by Baseline Diagnosis at the TOC Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Impetigo	72/74	97.3	73/76	96.1
Infected Dermatitis	15/15	100.0	5/6	83.3
Infected Traumatic/Surgical Wound	9/9	100.0	8/8	100.0
Cellulitis	7/7	100.0	4/5	80.0
Paronychia	3/3	100.0	6/7	85.7
Abscess	2/2	100.0	4/4	100.0
Folliculitis	3/3	100.0	1/1	100.0
Furuncle	1/1	100.0	3/3	100.0
Infected Burn	2/2	100.0	1/1	100.0
Carbuncle	1/1	100.0	0/0	–
Other	1/1	100.0	½	50.0
Across Diagnosis	116/118	98.3	106/113	93.8

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

Statistical reviewer's note: *The 95% CI for the difference between the cure rates for cefdinir and cephalexin was $_{118,113}$ (-0.0138, 0.1038) $_{98.3\%,93.8\%}$, showing therapeutic equivalence between the two treatment arms with respect to the clinical cure rate by baseline diagnosis.*

TABLE 43 Microbiologic vs Clinical Response Rates at the TOC Visit - Evaluable Patients
[Number (%) of Patients]

Microbiologic Response	Clinical Response[a]	
	Cure	Failure
Cefdinir, N = 118		
Patients With Eradication	116 (98.3)	1 (0.8)
Patients With Persistence	0 (0.0)	1 (0.8)
Cephalexin, N = 113		
Patients With Eradication	105 (92.9)	4 (3.5)
Patients With Persistence	1 (0.9)	3 (2.7)

[a] Based on combined investigator/sponsor clinical assessments

Clinical reviewer's note: *There were two clinical failures among the 118 evaluable cefdinir patients. One patient was an 8 year-old boy with impetigo due to S. aureus. The organism was eradicated; however, his clinical signs/symptoms persisted. He experienced four adverse events, including diarrhea, headache, pharyngitis, and lymphadenopathy.*

The second patient was a 22 month-old boy with impetigo due to S. aureus which persisted. The patient had clinical signs/symptoms along with S. aureus at the TOC visit. He also experienced vomiting and diarrhea but was able to complete therapy.

Among the 113 cephalexin patients, four were clinical failures with eradication of the pathogen and three patients were clinical failures with a persistent pathogen.

Clinically Evaluable Patients: In the clinically evaluable patient population, 126 of 131 (96%) patients in the cefdinir treatment group and 114 of 123 (93%) in the cephalexin treatment group were cured at TOC.

Superinfections: Three cefdinir patients and five cephalexin patients had superinfections due to other pathogens. The following table shows the organisms responsible for these infections.

TABLE 44. Patients With Superinfections - All Patients (Number of Patients)

Pathogen	Cefdinir N = 196	Cephalexin N = 198
Gram-Positive[a]		
Enterococcus faecalis	1	0
Staphylococcus aureus	1	1
Gram-Negative[a]		
Acinetobacter calcoaceticus var *lwoffi*	0	1
Enterobacter cloacae	1	1
Multiple	0	2
Total	3	5

[a] Pathogens appearing as sole superinfecting pathogens

Microbiologic Efficacy

TABLE 45. Microbiologic Eradication Rate by Baseline Pathogen at the TOC Visit - Pathogens From Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
Enterococcus durans	1/1	100.0	0/0	–
Enterococcus faecalis	0/0	–	1/1	100.0
Enterococcus hirae	1/1	100.0	0/0	–
Staphylococcus aureus	96/97	99.0	95/98	96.9
Staphylococcus Coagulase-Negative	1/1	100.0	0/0	–
Streptococcus agalactiae	4/4	100.0	6/6	100.0
Streptococcus pneumoniae	2/2	100.0	1/1	100.0
Streptococcus pyogenes	42/42	100.0	41/42	97.6
Streptococcus Group C	1/1	100.0	0/0	–
Gram-Negative				
Acinetobacter calcoaceticus var *lwoffi*	2/2	100.0	1/1	100.0
Enterobacter agglomerans	5/5	100.0	5/5	100.0
Enterobacter cloacae	2/2	100.0	0/0	–
Escherichia coli	1/1	100.0	1/1	100.0
Haemophilus influenzae	2/2	100.0	0/0	–
Klebsiella oxytoca	1/1	100.0	0/0	–
Klebsiella pneumoniae	3/3	100.0	0/0	–
Moraxella sp	1/1	100.0	1/1	100.0
Total	165/166	99.4	152/156	97.4

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

Table 45 shows the pathogen eradication rates for the 118 evaluable cefdinir patients and the 113 evaluable cephalexin patients. In the cefdinir group, 165 of 166 (99.4%) pathogens were eradicated at the test of cure visit, while in the comparator group, 152 of 156 (97.4%) pathogens were eradicated.

Statistical reviewer's note: *The 95% CI for the difference in the eradication rates between cefdinir and cephalexin was* $_{166,156}$ *(-0.0141, 0.0533)* $_{99.4\%,97.4\%}$, *noting that cefdinir is*

therapeutically equivalent to cephalexin in this respect.

TABLE 46. Microbiologic Eradication Rate by Baseline Diagnosis at the TOC Visit - Isolates From Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Impetigo	103/104	99.0	103/106	97.2
Infected Dermatitis	23/23	100.0	8/8	100.0
Infected Traumatic/Surgical Wound	13/13	100.0	10/10	100.0
Paronychia	6/6	100.0	10/11	90.9
Cellulitis	8/8	100.0	6/6	100.0
Abscess	2/2	100.0	4/4	100.0
Folliculitis	3/3	100.0	2/2	100.0
Furuncle	1/1	100.0	4/4	100.0
Infected Burn	3/3	100.0	1/1	100.0
Carbuncle	1/1	100.0	0/0	--
Other	2/2	100.0	4/4	100.0
Across Diagnosis	165/166	99.4	152/156	97.4

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

Table 46 shows the results of microbial eradication according to pathogen isolated and baseline diagnosis for both treatment groups. The eradication rates are similar for both drugs across the 10 diagnoses listed. The numbers of patients in each diagnostic category are similar for the two treatment groups except for patients with infected dermatitis. There were 23 patients in the cefdinir group and only eight in the cephalexin group with this diagnosis.

Statistical reviewer's note: *The 95% CI for the difference in the eradication rates between cefdinir and cephalexin was* $_{166,156}$ *(-0.0141, 0.0533)* $_{99.4\%,97.4\%}$*, noting that cefdinir is therapeutically equivalent to cephalexin in this respect.*

TABLE 47. Microbiologic Eradication Rate by Patient (According to Applicant's Proposed Baseline Pathogens) at the TOC Visit - Evaluable Patients

Baseline Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Gram-Positive				
Enterococcus durans	1/1	100.0	0/0	–
Staphylococcus aureus	52/53	98.1	53/56	94.6
Staphylococcus Coagulase-Negative	1/1	100.0	0/0	–
Streptococcus pneumoniae	0/0	–	1/1	100.0
Streptococcus pyogenes	13/13	100.0	13/13	100.0
Streptococcus Group C	1/1	100.0	0/0	–
Gram-Negative				
Acinetobacter calcoaceticus var *lwoffi*	1/1	100.0	0/0	–
Enterobacter agglomerans	0/0	–	1/1	100.0
Haemophilus influenzae	2/2	100.0	0/0	–
Multiple	46/46	100.0	41/42	97.6
Total	117/118	99.2	109/113	96.5

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

In Table 47 the microbial eradication rates by patient according to baseline pathogens isolated are shown for the 118 evaluable cefdinir patients and the 113 cephalexin patients. In the cefdinir group, 117 of 118 (99.2%) patients had their baseline pathogens eradicated, while 109 of 113 (96.5%) of the cephalexin patients had their baseline pathogens eradicated.

Clinical reviewer's note: *Note the lack of any cases that list Streptococcus agalactiae and Klebsiella pneumoniae as primary, baseline pathogens.*

Statistical reviewer's note: *The 95% CI for the difference in the eradication rates between the two drugs was* $_{118,113}$ *(-0.0196, 0.0734)* $_{99.2\%,96.5\%}$*, noting that cefdinir is therapeutically equivalent to cephalexin with respect to the microbiologic eradication rate by patient.*

TABLE 48. Microbiologic Eradication Rate by Baseline Diagnosis at the TOC Visit - Evaluable Patients

Baseline Diagnosis	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Impetigo	73/74	98.6	73/76	96.1
Infected Dermatitis	15/15	100.0	6/6	100.0
Infected Traumatic/Surgical Wound	9/9	100.0	8/8	100.0
Cellulitis	7/7	100.0	5/5	100.0
Paronychia	3/3	100.0	6/7	85.7
Abscess	2/2	100.0	4/4	100.0
Folliculitis	3/3	100.0	1/1	100.0
Furuncle	1/1	100.0	3/3	100.0
Infected Burn	2/2	100.0	1/1	100.0
Carbuncle	1/1	100.0	0/0	–
Other	1/1	100.0	2/2	100.0
Across Diagnosis	117/118	99.2	109/113	96.5

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

Table 48 shows the same eradication data according to baseline diagnosis.

Statistical reviewer's note: *The 95% CI is identical to that found in the previous table.*

Clinical Reviewer's Analysis of Data

Exclusion of Centers under investigation: During the review of the data submitted on December 30, 1996, the Division of Anti-Infective Drug Products was notified that some investigators in the pediatric study were under investigation by FDA's Division of Scientific Investigation. As a result of ongoing investigations, the applicant was contacted and requested to re-analyze the data excluding those centers. On May 6, 1997, the applicant submitted an amendment containing the requested information. The following tables are based on an examination of that data which excludes those centers currently under investigation.

On May 30, 1997, the applicant submitted revised tables based on

the exclusion of data from two centers currently under investigation. Those tables are attached as Appendices A through P.

The applicant has requested the approval of an indication for the treatment of uncomplicated skin and skin structure infections in pediatric patients caused by susceptible strains of *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *K. pneumoniae*. As with the adult study, a closer examination of the data concerning these four organisms is necessary. The analysis of the clinical data presented by the applicant grouped these four organisms together with regard to the various baseline diagnoses. In the following tables, the clinical cure rates for each pathogen from the microbiologically evaluable patients according to diagnosis is presented.

Clinical Efficacy

Table 49. Clinical cure rates - Evaluable pediatric patients with *S. aureus* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 75		Cephalexin n = 77	
	Cure	Failure	Cure	Failure
Impetigo	51	2	53	2
Abscess	1	0	3	0
Paronychia	3	0	5	0
Infected Dermatitis	9	0	3	0
Infected Wound	2	0	5	0
Cellulitis	3	0	1	1
Folliculitis	1	0	0	0
Furuncle	1	0	2	0
Infected Burn	1	0	0	0
Other - Pyoderma	0	0	1	0
Infected Chickenpox	0	0	0	1
Infected Blister	1	0	0	0
Total	73	2	73	4

In Table 49 the clinical cure rates, according to baseline diagnosis, for the 75 pediatric cefdinir patients and the 77 cephalexin patients with S. *aureus* as a baseline pathogen are shown. One cefdinir patient had two different strains of *S.*

aureus present, one beta-lactamase positive and one negative. There were 73 cefdinir patients (97.3%) and 73 cephalexin patients (94.8%) who were cured.

Clinical reviewer's note: *The numbers of patients in both treatment groups for each of the diagnostic categories were similar with the exception of patients with infected dermatitis and infected wounds.*

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to overall clinical cure rates based on the diagnosis excluding centers under investigation, the 95% confidence interval being* $_{75,77}$ *(-0.0494, 0.0999)* $_{97.3\%,94.8\%}$.

Table 50. Clinical cure rates - Evaluable pediatric patients with *S. pyogenes* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 34		Cephalexin n = 33	
	Cure	Failure	Cure	Failure
Impetigo	26	0	18	1
Abscess	0	0	1	0
Paronychia	1	0	3	0
Infected Dermatitis	5	0	3	0
Infected Wound	1	0	2	0
Cellulitis	0	0	2	0
Infected Burn	1	0	1	0
Other - Infected Chickenpox	0	0	0	1
Pyoderma	0	0	1	0
Total	34	0	31	2

Among the 34 cefdinir patients with S. pyogenes as a baseline pathogen, all were cured for a 100% cure rate. For the 33 cephalexin patients, there were 31 cures and two failures for a 93.9% cure rate.

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to clinical cure rates in patients with S. pyogenes, the 95% CI being* $_{34,33}$ *(-0.0506, 0.1718)* $_{100\%,93.9\%}$.

Table 51. Clinical cure rates - Evaluable pediatric patients with *S. agalactiae* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 4		Cephalexin n = 6	
	Cure	Failure	Cure	Failure
Impetigo	3	0	5	0
Paronychia	0	0	1	0
Infected Dermatitis	1	0	0	0
Total	4	0	6	0

All four cefdinir patients and all six cephalexin patients were cures for a 100% cure rate for both treatment groups.

Table 52. Clinical cure rates - Evaluable pediatric patients with *K. pneumoniae* according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 3		Cephalexin n = 0	
	Cure	Failure	Cure	Failure
Impetigo	2	0	0	0
Infected Dermatitis	1	0	0	0
Total	3	0	0	0

There were no failures among the three cefdinir patients with *K. pneumoniae* as a baseline pathogen. All of the patients had a polymicrobial infection. Two of the patients had S. *aureus* present and one patient had *E. cloacae* present, along with the *K. pneumoniae*.

Statistical reviewer's note: *The sample sizes are too inadequate to perform confidence interval analysis on the data in Tables 51 or 52.*

Table 53. Clinical cure rates - Summary of Evaluable pediatric patients with requested organisms according to diagnosis excluding centers under investigation.

Baseline Diagnosis	Cefdinir n = 116		Cephalexin n = 116	
	Cure	Failure	Cure	Failure
Impetigo	82	2	76	3
Abscess	1	0	4	0
Paronychia	4	0	9	0
Infected Dermatitis	16	0	6	0
Infected Wound	3	0	7	0
Cellulitis	3	0	3	1
olliculitis	1	0	0	0
Furuncle	1	0	2	0
Infected Burn	2	0	1	0
Other - Pyoderma	0	0	2	0
Infected Chickenpox	0	0	0	2
Infected Blister	1	0	0	0
Total	114	2	110	6

There were 116 evaluable cefdinir patients and 116 evaluable cephalexin patients with the requested organisms as shown in Table 53. There were 114 cefdinir patients (98.3%) and 110 cephalexin patients (94.8%) who were cured. The overall numbers of patients in both treatment groups were similar with the exception of patients with infected dermatitis and infected wounds.

Statistical reviewer's note: *Cefdinir is therapeutically equivalent to cephalexin with respect to the clinical cure rates in evaluable patients with the requested organisms (excluding the centers under investigation), the 95% CI being* $_{116,116}$ *(-0.0208, 0.0898)* $_{98.2\%,94.8\%}$.

Microbiologic Efficacy

Table 54. Microbiologic eradication rates for requested pathogens from evaluable pediatric patients excluding centers under investigation.

Pathogen	Cefdinir		Cephalexin	
	n/N	%	n/N	%
Staphylococcus aureus	75/76	98.7	75/77	97.4
Streptococcus agalactiae	4/4	100.0	6/6	100.0
Streptococcus pyogenes	34/34	100.0	32/33	97.0
Klebsiella pneumoniae	3/3	100.0	0/0	0.0
Total	116/117	99.1	113/116	97.4

Statistical reviewer's note: Cefdinir is therapeutically equivalent in pediatric patients with regards to microbiologic eradication of S. aureus [95% CI = $_{76,77}$ (-0.0441, 0.0696) $_{98.7\%,97.4\%}$], S. pyogenes [95% CI = $_{34,33}$ (-0.0580, 0.1186) $_{100\%,96.9\%}$], and overall microbiologic eradication rate [95% CI = $_{117,116}$ (-0.0246, 0.0592) $_{99.1\%,97.4\%}$. The sample sizes were inadequate for S. agalactiae and K. pneumoniae to ensure an acceptable level of power to obtain confidence intervals.

Safety

The safety of cefdinir and cephalexin was assessed as described previously in protocol 983-8 using adverse event data, and the results from physical examinations and clinical laboratory tests.

Adverse Events as reported by the applicant: Two hundred eighty-nine patients were included in the safety analysis. Sixty-six of the 142 (46.5%) cefdinir patients and 45 of the 147 (30.6%) cephalexin patients reported one or more adverse events. There were 25 (17.6%) drug-associated adverse events among the cefdinir patients and 16 (10.9%) reported by the patients in the cephalexin group.

TABLE 55. Summary of Adverse Events - All Patients Excluding Centers Under Investigation. [Number (%) of Patients]

(Page 1 of 2)

	Cefdinir N = 142	Cephalexin N = 147
Adverse Events During Study		
All Adverse Events	66 (46.5)	45 (30.6)
Associated[a] Adverse Events	25 (17.6)	16 (10.9)
Adverse Events During Treatment		
All Adverse Events	30 (21.1)	21 (14.3)
Adverse Events by Sex[b]		
All Adverse Events		
Male	35 (46.1)	22 (28.9)
Female	31 (47.0)	23 (32.4)
Associated Adverse Events		
Male	13 (17.1)	7 (9.2)
Female	12 (18.2)	9 (12.7)
Adverse Events by Race[c]		
All Adverse Events		
White	44 (50.0)	22 (27.5)
Black	8 (40.0)	5 (20.8)
Asian	0 (0.0)	0 (0.0)
Other	14 (41.2)	18 (42.9)
Associated Adverse Events		
White	13 (14.8)	5 (6.3)
Black	5 (25.0)	3 (12.5)
Asian	0 (0.0)	0 (0.0)
Other	7 (20.6)	8 (19.0)
Adverse Events by Age[d]		
All Adverse Events		
<2 yr[e]	17 (85.0)	11 (52.4)
2 to <6 yr	27 (42.2)	24 (32.9)
6 to <13 yr[f]	22 (31.4)	10 (15.6)
Associated Adverse Events		
<2 yr[e]	6 (30.0)	8 (38.1)
2 to <6 yr	10 (15.6)	6 (8.2)
6 to <13 yr[f]	9 (12.9)	2 (3.1)

a Considered by the investigator to be possibly, probably, or definitely related to study medication.

b Percentages based on total numbers of males or females in a treatment group

c Percentages based on total numbers of patients of each race in a treatment group

d Percentages = Number of patients in specified age range experiencing ≥ 1 adverse event/total number of patients in specified age range.

e Includes 1 cephalexin-treated patient approximately 5 days <6 months old

f Includes 1 cephalexin-treated patient age 13 years, 1 month

**TABLE 55. Summary of Adverse Events -
All Patients Excluding Centers Under Investigation.
[Number (%) of Patients]
(Page 2 of 2)**

	Cefdinir N = 142		Cephalexin N = 147	
Adverse Events by Maximum Intensity[s]				
All Adverse Events				
Mild	47	(33.1)	32	(21.8)
Moderate	30	(21.1)	16	(10.9)
Severe	2	(1.4)	1	(0.7)
Associated Adverse Events				
Mild	17	(12.0)	12	(8.2)
Moderate	10	(7.0)	5	(3.4)
Severe	0	(0.0)	0	(0.0)
Serious Adverse Events	0	(0.0)	0	(0.0)
Deaths	0	(0.0)	0	(0.0)
Discontinuation of Treatment Due to Adverse Events				
All Adverse Events	2	(1.4)	0	(0.0)
Associated Adverse Events	1	(0.7)	0	(0.0)
Withdrawals After Treatment Due to Adverse Events				
All Adverse Events	9	(6.3)	2	(1.4)
Associated Adverse Events	0	(0.0)	0	(0.0)

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

Patients who received cefdinir reported a significantly higher number of adverse events (n=66, 46.5%) than those patients who received cephalexin (n=45, 30.6%). The difference between the two treatment groups in drug-associated adverse events was not as great (17.6% versus 10.9%).

TABLE 56. All and Associated[a] Adverse Events by Body System - Patients Receiving Study Medication Excluding Centers Under Investigation.
[Number (%) of Patients]
(Page 1 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir[b] N = 142				Cephalexin N = 147			
	All		Associated		All		Associated	
BODY AS A WHOLE	21[c]	(14.8)	2	(1.4)	18[c]	(12.2)	0	(0.0)
Infection	13	(9.2)	0	(0.0)	13	(8.8)	0	(0.0)
Headache	4	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Fever	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Accidental Injury	2	(1.4)	0	(0.0)	3	(2.0)	0	(0.0)
Asthenia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
DIGESTIVE SYSTEM	19[c]	(13.4)	16[c]	(11.3)	13	(8.8)	10	(6.8)
Diarrhea	15	(10.6)	15	(10.6)	10	(6.8)	9	(6.1)
Gastroenteritis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Vomiting	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Dyspepsia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Constipation	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
HEMIC AND LYMPHATIC SYSTEM	5	(3.5)	4	(2.8)	0	(0.0)	0	(0.0)
Leukopenia	4	(2.8)	4	(2.8)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1	(0.7)	0	(0.0)	1	(0.7)	1	(0.7)
Alkaline Phosphatase Increased	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood Urea Nitrogen Increased	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
NERVOUS SYSTEM	3[c]	(2.1)	1	(0.7)	2	(1.4)	0	(0.0)
Nervousness	2	(1.4)	1	(0.7)	0	(0.0)	0	(0.0)
Incoordination	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vestibular Disorder	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Insomnia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
RESPIRATORY SYSTEM	16[c]	(11.3)	0	(0.0)	10[c]	(6.8)	0	(0.0)
Rhinitis	5	(3.5)	0	(0.0)	3	(2.0)	0	(0.0)
Cough Increased	5	(3.5)	0	(0.0)	2	(1.4)	0	(0.0)
Pharyngitis	5	(3.5)	0	(0.0)	3	(2.0)	0	(0.0)
Bronchitis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Lung Disorder	2	(1.4)	0	(0.0)	2	(1.4)	0	(0.0)
Sinusitis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Asthma	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)

[a] Possibly, probably, or definitely related to treatment
[b] All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.
[c] The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

TABLE 56. All and Associated[a] Adverse Events by Body System - Patients Receiving Study Medication Excluding Centers Under Investigation.
[Number (%) of Patients]
(Page 2 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir[b] N=142				Cephalexin N=147			
	All		Associated		All		Associated	
SKIN AND APPENDAGES	19[c]	(13.4)	4[c]	(2.8)	16	(10.9)	6	(4.1)
Rash	7	(4.9)	2	(1.4)	6	(4.1)	3	(2.0)
Eczema	3	(2.1)	0	(0.0)	2	(1.4)	0	(0.0)
Pustular Rash	3	(2.1)	0	(0.0)	2	(1.4)	1	(0.7)
Contact Dermatitis	2	(1.4)	1	(0.7)	2	(1.4)	0	(0.0)
Cutaneous Moniliasis	2	(1.4)	2	(1.4)	2	(1.4)	2	(1.4)
Nail Disorder	2	(1.4)	0	(0.0)	0	(0.0)	1	(0.7)
Fungal Dermatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Furunculosis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes Simplex	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vesiculobullous Rash	1	(0.7)	0	(0.0)	0	(0.0)	1	(0.7)
Acne	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dry Skin	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
SPECIAL SENSES	9	(6.3)	0	(0.0)	2	(1.4)	0	(0.0)
Otitis Media	4	(2.8)	0	(0.0)	2	(1.4)	0	(0.0)
Conjunctivitis	3	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Disorder	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Pain	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
UROGENITAL SYSTEM	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Hematuria	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Urine Abnormality	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

[a] Possibly, probably, or definitely related to treatment
[b] All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.
[c] The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Clinical reviewer's note: *As found in the adult study, diarrhea was the most frequently reported adverse event with 15 cases among the cefdinir patients and 10 cases reported by the cephalexin patients. Infection was the second most frequently reported adverse event with 10 cases reported for both treatment groups.*

Deaths: There were no deaths during the study.

Serious Adverse Events: There were no serious adverse events reported during the study.

TABLE 57. Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - Patients Receiving Study Medication Excluding Centers Under Investigation.

[Number (%) of Patients]

BODY SYSTEM/ Adverse Event	Cefdinir N=142		Cephalexin N = 147	
BODY AS A WHOLE	1	(0.7)	2	(1.4)
Accidental Injury	1	(0.7)	1	(0.7)
Infection	0	(0.0)	0	(0.0)
DIGESTIVE SYSTEM	0[a]	(0.0)	0	(0.0)
Diarrhea	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)
RESPIRATORY SYSTEM	3	(2.1)	0	(0.0)
Sinusitis	2	(1.4)	0	(0.0)
Bronchitis	1	(0.7)	0	(0.0)
SKIN AND APPENDAGES	2	(1.4)	0	(0.0)
Pustular Rash	1	(0.7)	0	(0.0)
Rash	1	(0.7)	0	(0.0)
SPECIAL SENSES	6	(4.2)	1	(0.7)
Otitis Media	4	(2.8)	1	(0.7)
Conjunctivitis	2	(1.4)	0	(0.0)

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

There were two cefdinir patients (1.4%) and no cephalexin patients who discontinued the study medication due to adverse events. One of the cefdinir patients had an adverse event considered drug-associated (rash). Nine cefdinir patients (6.3%) and three cephalexin patients (2.0%) withdrew from the study after completing their respective treatments.

Clinical Laboratory Measurements: No remarkable changes were noted in the median differences between baseline and final laboratory values for both groups of patients receiving study medication. Most laboratory values remained within the same category (i.e., above, within or below normal values) at the final visit when compared with baseline values. For both patient groups, there were more decreases in white cell counts than

increases, which is consistent with a resolving infection. The most frequent markedly abnormal laboratory values were increased eosinophil counts (higher frequency with cephalexin), and increased values for lactate dehydrogenase, alkaline phosphatase (higher frequency with cefdinir), phosphorus, and urine pH.

Clinical and Statistical Reviewers' Conclusions Regarding NDA 50-739, Protocol 983-8, and NDA 50-749, Protocol 983-13.

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

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

In the adult study, there were 178 evaluable patients with 215 pathogens in the cefdinir treatment group and 204 evaluable patients with 247 pathogens in the cephalexin treatment group. The eradication rate for all pathogens in the cefdinir group was 200/215 (93.0%) compared to 221/247 (89.5%) for all pathogens in the cephalexin treatment group. The clinical cure rates for cefdinir and cephalexin were 148/178 (83.1%) and 163/204 (79.9%), respectively. The 95% CI showed them to be equivalent.

In the FDA clinical reviewer's analysis of the data, the results were evaluated according to the specific organisms requested and the baseline diagnoses. There was a total of 181 evaluable cefdinir patients and 203 evaluable cephalexin patients with skin and skin structure infections caused by the four organisms

requested. The overall clinical cure rates for cefdinir and 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, 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, which excluded centers under investigation, 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 the adult and pediatric studies, patients who received cefdinir had more adverse events than those patients in the cephalexin treatment group. In the adult study, 193 (39.1%) of the 494 cefdinir patients and 144 (30.1%) of the 478 cephalexin patients reported one or more adverse events. There were 135 (27.3%) drug-associated adverse events among the cefdinir patients and 79 (16.5%) among the patients who received cephalexin.

In the pediatric study with the data excluding centers under investigation, 66 of the 142 (46.5%) cefdinir patients and 45 of the 147 (30.6%) cephalexin patients reported one or more adverse events. There were 25 (17.6%) drug-associated adverse events among the cefdinir patients and 16 (10.9%) reported by the patients in the cephalexin group.

In both studies, diarrhea was the most frequently reported adverse event among the cefdinir patients. There were 78 reports (16.5%) of diarrhea in the adult study and 15 cases (10.6%) reported in the pediatric study. Other frequently reported adverse events included nausea with 17 reports (3.6%) and moniliasis with 14 reports (7.3%) in the adult study. Infection with 13 cases (9.2%) was the second most frequently reported adverse event, following diarrhea, in the pediatric study.

Discussion: The Division of Anti-Infective Drug Products has traditionally divided skin and skin structure infections (SSSI) into two broad categories: uncomplicated SSSI and complicated SSSI (Points to Consider Document, Skin and Skin Structure

Infection Guidelines presented at the Anti-Infective Advisory Committee Meeting, March 5-7, 1997). The uncomplicated category consists of superficial skin infections, e.g., impetigo, simple abscesses, while the complicated category refers to infections involving deeper soft tissue or ones that require surgical intervention.

The pathogens responsible for the various types of SSSI in both categories also differ. For uncomplicated SSSI, the two most commonly seen pathogens are *S. aureus* and *S. pyogenes*. Traditionally, those two organisms are the only ones included as pathogens for this indication. Other organisms are not universally accepted by academia as pathogens in this indication; most are considered as colonizers or contaminants.

One of the ways to identify a true pathogen from a possible contaminant or colonizer is to examine the frequency in which the organism is isolated in a pure culture. In the case of *S. aureus*, this organism is very often isolated from uncomplicated SSSI as a single pathogen. On the other hand, *K. pneumoniae* is most often part of a mixed or polymicrobial infection. For example, in the applicant's two studies, 11 cases of *K. pneumoniae* were reported, with 10 cases involving other species. There was only one case involving a patient with paronychia where the *K. pneumoniae* appeared as a single pathogen. A similar situation exists with *S. agalactiae* where it was commonly isolated as part of a polymicrobial infection, rather than a primary, baseline pathogen.

Labeling: The applicant has submitted sufficient data to show that cefdinir is safe and effective in the treatment of uncomplicated skin and skin structure infections in both an adult and pediatric population. Data from both clinical trials show the drug to be effective in the eradication of various types of skin and skin structure infections caused by *S. aureus* and *S. pyogenes*, when used as directed. The data regarding *S.*

agalactiae and *K. pneumoniae* are insufficient because of the much smaller number of cases involving these organisms, their occurrence primarily in polymicrobial infections, and their questionable role at this time as pathogens or contaminants in these infections.

Therefore, the proposed indications should be revised to read as follows: "Uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*".

In the Pediatric Use subsection under PRECAUTIONS, the following statement, based on the age of the participants, should be added: "Safety and effectiveness in children below the age of 6 months have not been established."

With regard to the ADVERSE REACTIONS section of the labeling, diarrhea should be listed as an adverse event related to cefdinir therapy in both formulations. Nausea, headache and moniliasis should be listed as adverse events in the labeling for the capsule formulation.

The proposed dosage should be: 300 mg q12h for 10 days for the capsule formulation and 7 mg/kg q12h for 10 days for the oral suspension.

APPEARS THIS WAY
ON ORIGINAL

Recommendation: It is recommended that cefdinir capsules and cefdinir suspension be approved for the treatment of uncomplicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*. Additional statements to the labeling should be added as described under Labeling.

/S/

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/S/

James Blank, Ph.D.

/S/

Daphne Lin, Ph.D.

/S/ 12/18/98

Janice Soreth, M.D.

cc: Orig. NDA
HFD-340
HFD-520
HFD-520/MO/Soreth
ClinRev/Blank
Pharm/Osterberg
Chem/Pagay
Micro/Sheldon
PM/Duvall-Miller
HFD-725/Dr. Chakravarty
Dr. Lin
Dr. Huque
Chron.
HFD-344/Dr. Thomas
WP 6.1; 50-739; 5-28-97;9-26-97;11-5-97

Concurrence only:
HFD-520/ActDivDir/GChikami 12/20/98
HFD-520/SMO/JSoreth 12/18/98

Appendix A

TABLE 1. List of Investigators without Sites 3 and 11

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed[a]	Evaluable
2	C. Khurana	3	3	0
4	J. Hedrick	51	50	34
5	W. Gooch	2	2	2
6	S. Wiederhold	28	23	15
7	S. Chartrand	24	24	19
8	J. McCarty	73	63	42
9	E. Rothstein	10	9	7
10	J. Haddad	3	1	0
12	S. McLinn	6	6	4
15	P. DiLorenzo	19	16	15
16	A. Phillips	6	2	2
17	R. Ford	13	12	8
18	J. Scott	21	19	16
19	S. Weakley	16	12	11
20	S. Davis	1	1	1
21	A. Herbert	13	7	4
	Total	289	250	180

[a] Completed treatment and test-of-cure visit

Appendix B
Table 8

Summary of Patient Characteristics
Patients Who Received Study Medication

		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparators	Cephalexin
Total	Patients	142	142	147	147
Sex					
Male	N	76	76	76	76
	Percent	53.5	53.5	51.7	51.7
Female	N	66	66	71	71
	Percent	46.5	46.5	48.3	48.3
Race					
White	N	88	88	80	80
	Percent	62.0	62.0	54.4	54.4
Black	N	20	20	24	24
	Percent	14.1	14.1	16.3	16.3
Asian	N	0	0	1	1
	Percent	0	0	0.7	0.7
Other	N	1	1	6	6
	Percent	0.7	0.7	4.1	4.1
Hispanic	N	33	33	36	36
	Percent	23.2	23.2	24.5	24.5

Appendix B
Table 8

Summary of Patient Characteristics
Patients Who Received Study Medication

		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparators	Cephalexin
Age (Years)					
< 2	N	19	19	21	21
	Percent	13.4	13.4	14.3	14.3
2 to < 6	N	54	54	64	64
	Percent	38.0	38.0	43.5	43.5
6 to < 13	N	69	69	62	62
	Percent	48.6	48.6	42.2	42.2
Age Range	Max	13	13	13	13
	Min	1	1	0	0

Appendix

Table 9

Summary of Patient Characteristics

Microbiologically-Clinically Evaluable Patients

		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparators	Cephalexin
Total	Patients	90	90	90	90
Sex					
Male	N	46	46	41	41
	Percent	51.1	51.1	45.6	45.6
Female	N	44	44	49	49
	Percent	48.9	48.9	54.4	54.4
Race					
White	N	61	61	52	52
	Percent	67.8	67.8	57.8	57.8
Black	N	8	8	14	14
	Percent	8.9	8.9	15.6	15.6
Asian	N	0	0	1	
	Percent	0	0	1.1	1.1
Other	N	1	1	3	3
	Percent	1.1	1.1	3.3	3.3
Hispanic	N	20	20	20	20
	Percent	22.2	22.2	22.2	22.2

Appendix C

Summary of Patient Characteristics
Microbiologically-Clinically Evaluable Patients

Age (Years)		Number (%) of Patients			
		All Cefdinir	Cefdinir 7 mg/kg BID	All Comparators	Cephalexin
< 2	N	11	11	10	10
< 2	Percent	12.2	12.2	11.1	11.1
2 to < 6	N	37	37	38	38
	Percent	41.1	41.1	42.2	42.2
6 to < 13	N	42	42	42	42
	Percent	46.7	46.7	46.7	46.7
Age Range	Max	13	13	13	13
	Min	1	1	1	1

Appendix D
Table 11

Distribution of Baseline Pathogens by Susceptibility to Treatment-
Pathogens from All Patients with Baseline Pathogens

Pathogen			Cefdinir			Cephalexin		
			S	I	R	S	I	R
		Total	N	N	N	N	N	N
Gram Positive	Bacil sp	1	0	0	1	0	0	1
	E faecal	17	3	6	8	1	0	16
	E faeciu	1	0	0	1	0	0	1
	E hirae	2	1	0	1	1	0	1
	S agalac	16	16	0	0	15	1	0
	S aureus	216	216	0	0	215	0	1
	S pneumo	3	3	0	0	3	0	0
	S pyogen	89	89	0	0	89	0	0
	Strep C	1	1	0	0	1	0	0
	Strep D	1	0	0	1	0	0	1
	Strep F	1	1	0	0	1	0	0
	Total	348	330	6	12	326	1	21
Gram Negative	A anit	7	0	0	7	1	0	6
	A lwoffi	2	0	0	2	0	0	2
	Cdc NOS	1	0	0	1	0	0	1
	E aeroge	1	1	0	0	0	0	1
	E agglom	5	5	0	0	4	1	0
	E cloaca	4	4	0	0	3	0	1

-S=Susceptible, I=Moderately Susceptible or Intermediate,
R=Resistant, U=Unknown

Appendix D

**Distribution of Baseline Pathogens by Susceptibility to Treatment-
Pathogens from All Patients with Baseline Pathogens**

Pathogen			Cefdinir			Cephalexin		
			S	I	R	S	I	R
		Total	N	N	N	N	N	N
Gram Negative	E coli	2	2	0	0	2	0	0
	K oxytoc	2	2	0	0	2	0	0
	K pneumo	4	4	0	0	3	1	0
	Morax sp	2	2	0	0	2	0	0
	P aerugi	4	0	0	4	0	0	4
	Pa multo	1	1	0	0	1	0	0
	S marces	1	0	0	1	0	0	1
	Total	36	21	0	15	18	2	16
Total	Pathogens	384	351	6	27	344	3	37

-S=Susceptible, I=Moderately Susceptible or Intermediate,
R=Resistant, U=Unknown

Appendix E

Summary of Patient Exposure to Study Medication
All Patients

Days on Study Medication	Number (%) of Patients							
	All Cefdinir		Cefdinir 7 mg/kg BID		All Comparators		Cephalexin	
	N	%	N	%	N	%	N	%
2	1	0.7	1	0.7	0	0	0	0
4	3	2.1	3	2.1	2	1.4	2	1.4
5	0	0	0	0	2	1.4	2	1.4
6	3	2.1	3	2.1	0	0	0	0
7	5	3.5	5	3.5	0	0	0	0
8	1	0.7	1	0.7	4	2.7	4	2.7
9	2	1.4	2	1.4	2	1.4	2	1.4
10	75	52.8	75	52.8	24	16.3	24	16.3
11	46	32.4	46	32.4	98	66.7	98	66.7
12	2	1.4	2	1.4	4	2.7	4	2.7
14	0	0	0	0	2	1.4	2	1.4
17	0	0	0	0	1	0.7	1	0.7
21	0	0	0	0	1	0.7	1	0.7
Unknown	4	2.8	4	2.8	7	4.8	7	4.8
Total	142	100.0	142	100.0	147	100.0	147	100.0

Appendix F
Table 14

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

		Number (%) of Patients					
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID		Total	
		N	%	N	%	N	%
Exclusions from Clinical Analyses	*** Total ***	47	33.1	51	34.7	98	33.9
	Clin asmt missed	5	3.5	7	4.8	12	4.2
	Clin out of range	19	13.4	22	15.0	41	14.2
	Concurrent antibac	4	2.8	3	2.0	7	2.4
	Med not as prescrb	19	13.4	11	7.5	30	10.4
	Prior antibact	4	2.8	3	2.0	7	2.4
	Resistant pathogns	14	9.9	23	15.6	37	12.8
Additional Exclusions from Microbiological Analyses	*** Total ***	5	3.5	6	4.1	11	3.8
	Cult out of range	16	11.3	20	13.6	36	12.5
	Culture missed	7	4.9	9	6.1	16	5.5
	No proven pathogn	18	12.7	14	9.5	32	11.1
Total	*** TOTAL ***	52	36.6	57	38.8	109	37.7

Appendix F

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

Disqualification	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
*** Total ***	13	14.4	9	10.0
Clin asmt missed	7	7.8	6	6.7
Clin out of range	3	3.3	2	2.2
Concurrent antibac	3	3.3	1	1.1
Cult out of range	3	3.3	2	2.2
Culture missed	6	6.7	6	6.7

Appendix
Table 16

Summary of Microbiologic Response Rates by Pathogen (According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Pathogens from Microbiologically-Clinically Evaluable Patients

Pathogen		Number (%) of Pathogens															
		All Cefdinir				Cefdinir 7 mg/kg BID				All Comparators				Cephalexin			
		Eradication		Persistence		Eradication		Persistence		Eradication		Persistence		Eradication		Persistence	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gram Positive	E faecal	0	0	0	0	0	0	0	0	1	100.0	0	0	1	100.0	0	0
	E hirae	1	100.0	0	0	1	100.0	0	0	0	0	0	0	0	0	0	0
	S agalac	4	100.0	0	0	4	100.0	0	0	6	100.0	0	0	6	100.0	0	0
	S aureus	75	98.7	1	1.3	75	98.7	1	1.3	75	97.4	2	2.6	75	97.4	2	2.6
	S pneumo	2	100.0	0	0	2	100.0	0	0	1	100.0	0	0	1	100.0	0	0
	S pyogen	34	100.0	0	0	34	100.0	0	0	32	97.0	1	3.0	32	97.0	1	3.0
	Strep C	1	100.0	0	0	1	100.0	0	0	0	0	0	0	0	0	0	0
Gram Negative	E agglom	3	100.0	0	0	3	100.0	0	0	2	100.0	0	0	2	100.0	0	0
	E cloaca	2	100.0	0	0	2	100.0	0	0	0	0	0	0	0	0	0	0
	E coli	0	0	0	0	0	0	0	0	1	100.0	0	0	1	100.0	0	0
	K oxytoc	1	100.0	0	0	1	100.0	0	0	0	0	0	0	0	0	0	0
	K pneumo	3	100.0	0	0	3	100.0	0	0	0	0	0	0	0	0	0	0
	Morax sp	1	100.0	0	0	1	100.0	0	0	1	100.0	0	0	1	100.0	0	0
Total	Pathogens	127	99.2	1	0.8	127	99.2	1	0.8	119	97.5	3	2.5	119	97.5	3	2.5

Appendix H
Table 18

Summary of Microbiologic Response Rates by Pathogen (By Baseline Diagnosis)

Test-of-Cure Visit
Pathogens from Microbiologically-Clinically Evaluable Patients

Diagnosis at Baseline = Abscess

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S aureus	1	100.0	3	100.0
	S pyogen	0	0	1	100.0
Total	Pathogens	1	100.0	4	100.0

Diagnosis at Baseline = Infected burn

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S aureus	1	100.0	0	0
	S pyogen	1	100.0	1	100.0
Total	Pathogens	2	100.0	1	100.0

Appendix H

Diagnosis at Baseline = Cellulitis

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S aureus	3	100.0	2	100.0
	S pyogen	0	0	2	100.0
Gram Negative	E cloaca	1	100.0	0	0
Total	Pathogens	4	100.0	4	100.0

Diagnosis at Baseline = Infected dermatitis

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S agalac	1	100.0	0	0
	S aureus	9	100.0	3	100.0
	S pyogen	5	100.0	3	100.0
Gram Negative	E agglom	1	100.0	1	100.0
	E coli	0	0	1	100.0
	K pneumo	1	100.0	0	0
Total	Pathogens	17	100.0	8	100.0

Appendix H

Diagnosis at Baseline = Folliculitis

Pathogen		Number (%) of Pathogens	
		Cefdinir 7 mg/kg BID	
		Eradication	
		N	%
Gram Positive	S aureus	1	100.0
Total	Pathogens	1	100.0

Diagnosis at Baseline = Furuncle

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S aureus	1	100.0	2	100.0
Total	Pathogens	1	100.0	2	100.0

Appendix H

Diagnosis at Baseline = Impetigo

Pathogen		Number (%) of Pathogens							
		Cefdinir 7 mg/kg BID				Cephalexin 10 mg/kg QID			
		Eradication		Persistence		Eradication		Persistence	
		N	%	N	%	N	%	N	%
Gram Positive	E faecal	0	0	0	0	1	100.0	0	0
	E hirae	1	100.0	0	0	0	0	0	0
	S agalac	3	100.0	0	0	5	100.0	0	0
	S aureus	52	98.1	1	1.9	53	96.4	2	3.6
	S pneumo	2	100.0	0	0	1	100.0	0	0
	S pyogen	26	100.0	0	0	18	94.7	1	5.3
Gram Negative	E agglom	0	0	0	0	1	100.0	0	0
	E cloaca	1	100.0	0	0	0	0	0	0
	K oxytoc	1	100.0	0	0	0	0	0	0
	K pneumo	2	100.0	0	0	0	0	0	0
	Morax sp	1	100.0	0	0	1	100.0	0	0
Total	Pathogens	89	98.9	1	1.1	80	96.4	3	3.6

Appendix H

Diagnosis at Baseline = Paronychia

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S agalac	0	0	1	100.0
	S aureus	3	100.0	5	100.0
	S pyogen	1	100.0	3	100.0
Gram Negative	E agglom	2	100.0	0	0
Total	Pathogens	6	100.0	9	100.0

Diagnosis at Baseline = Infected traum/surg wound

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S aureus	2	100.0	5	100.0
	S pyogen	1	100.0	2	100.0
	Strep C	1	100.0	0	0
Total	Pathogens	4	100.0	7	100.0

Appendix H

Diagnosis at Baseline = Other

Pathogen		Number (%) of Pathogens			
		Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
		Eradication		Eradication	
		N	%	N	%
Gram Positive	S aureus	2	100.0	2	100.0
	S pyogen	0	0	2	100.0
Total	Pathogens	2	100.0	4	100.0

Table 9

Summary of Microbiologic Eradication Rates by Patient (According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		All Cefdinir			Cefdinir 7 mg/kg BID			All Comparators		
		Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%	Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%	Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%
Gram Positive	S aureus	42	41	97.6	42	41	97.6	46	44	95.7
	S pneumo	0	0	0	0	0	0	1	1	100.0
	S pyogen	11	11	100.0	11	11	100.0	11	11	100.0
	Strep C	1	1	100.0	1	1	100.0	0	0	0
Gram Negative	E agglom	0	0	0	0	0	0	1	1	100.0
Multiple	E faecal + S aureus + S pyogen	0	0	0	0	0	0	1	1	100.0
	E hirae + S aureus	1	1	100.0	1	1	100.0	0	0	0
	S agalac + S aureus	3	3	100.0	3	3	100.0	6	6	100.0
	S agalac + S aureus + S pyogen	1	1	100.0	1	1	100.0	0	0	0
	S aureus + S aureus (1)	1	1	100.0	1	1	100.0	0	0	0
	S aureus + S pneumo	2	2	100.0	2	2	100.0	0	0	0
	S aureus + S pyogen	20	20	100.0	20	20	100.0	21	20	95.2

Append. I

Summary of Microbiologic Eradication Rates by Patient (According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Indication: Uncomplicated Skin and Skin Structure Infections

Baseline Pathogen(s)		All Cefdinir			Cefdinir 7 mg/kg BID			All Comparators		
		Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%	Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%	Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%
Multiple	S aureus + E agglom	0	0	0	0	0	0	1	1	100.0
	S aureus + E agglom + E agglom (1)	1	1	100.0	1	1	100.0	0	0	0
	S aureus + E cloaca	1	1	100.0	1	1	100.0	0	0	0
	S aureus + E coli	0	0	0	0	0	0	1	1	100.0
	S aureus + K oxytoc	1	1	100.0	1	1	100.0	0	0	0
	S aureus + K pneumo	2	2	100.0	2	2	100.0	0	0	0
	S aureus + Morax sp	0	0	0	0	0	0	1	1	100.0
	S pyogen + E agglom	1	1	100.0	1	1	100.0	0	0	0
	S pyogen + Morax sp	1	1	100.0	1	1	100.0	0	0	0
	E cloaca + K pneumo	1	1	100.0	1	1	100.0	0	0	0
Total	Patients	90	89	98.9	90	89	98.9	90	87	96.7

Summary of Microbiologic Eradication Rates by Patient (According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		Cephalexin		
		Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%
Gram Positive	S aureus	46	44	95.7
	S pneumo	1	1	100.0
	S pyogen	11	11	100.0
	Strep C	0	0	0
Gram Negative	E agglom	1	1	100.0
Multiple	E faecal + S aureus + S pyogen	1	1	100.0
	E hirae + S aureus	0	0	0
	S agalac + S aureus	6	6	100.0
	S agalac + S aureus + S pyogen	0	0	0
	S aureus + S aureus (1)	0	0	0
	S aureus + S pneumo	0	0	0
	S aureus + S pyogen	21	20	95.2

Appendix I

Summary of Microbiologic Eradication Rates by Patient
(According to Baseline Pathogen) by Indication
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		Cephalexin		
		Number of Pts w/ Pathogen(s) at Baseline	Number with Eradication at TOC Visit	%
Multiple	S aureus + E agglom	1	1	100.0
	S aureus + E agglom + E agglom (1)	0	0	0
	S aureus + E cloaca	0	0	0
	S aureus + E coli	1	1	100.0
	S aureus + K oxytoc	0	0	0
	S aureus + K pneumo	0	0	0
	S aureus + Morax sp	1	1	100.0
	S pyogen + E agglom	0	0	0
	S pyogen + Morax sp	0	0	0
	E cloaca + K pneumo	0	0	0
Total	Patients	90	87	96.7

Appendix J
Table 20

Summary of Microbiologic Response Rates by Patient (By Baseline Diagnosis)
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Diagnosis at Baseline = Abscess

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	1	100.0	4	100.0
Total	1	100.0	4	100.0

Diagnosis at Baseline = Infected burn

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	1	100.0	1	100.0
Total	1	100.0	1	100.0

Diagnosis at Baseline = Cellulitis

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	3	100.0	3	100.0
Total	3	100.0	3	100.0

Appendix J

Diagnosis at Baseline = Infected dermatitis

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	11	100.0	6	100.0
Total	11	100.0	6	100.0

Diagnosis at Baseline = Folliculitis

Microbiologic Response	Number (%) of Patients	
	Cefdinir 7 mg/kg BID	
	N	%
Patients w/ eradication	1	100.0
Total	1	100.0

Diagnosis at Baseline = Furuncle

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	1	100.0	2	100.0
Total	1	100.0	2	100.0

Appendix J

Diagnosis at Baseline = Impetigo

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	63	98.4	58	95.1
Patients w/ persistence	1	1.6	3	4.9
Total	64	100.0	61	100.0

Diagnosis at Baseline = Paronychia

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	3	100.0	5	100.0
Total	3	100.0	5	100.0

Diagnosis at Baseline = Infected traum/surg wound

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	4	100.0	6	100.0
Total	4	100.0	6	100.0

Diagnosis at Baseline = Other

Microbiologic Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Patients w/ eradication	1	100.0	2	100.0
Total	1	100.0	2	100.0

Appendix K

Table 22

Summary of Clinical Response Rate by Pathogen (Across All Diagnoses)
Combined Investigator/Sponsor Determination
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Baseline Pathogen(s)		Number (%) of Patients							
		Cefdinir 7 mg/kg BID				Cephalexin 10 mg/kg QID			
		Cure		Failure		Cure		Failure	
		N	%	N	%	N	%	N	%
Gram Positive	S aureus	40	95.2	2	4.8	44	95.7	2	4.3
	S pneumo	0	0	0	0	1	100.0	0	0
	S pyogen	11	100.0	0	0	11	100.0	0	0
	Strep C	1	100.0	0	0	0	0	0	0
Gram Negative	E agglom	0	0	0	0	0	0	1	100.0
Multiple	E faecal + S aureus + S pyogen	0	0	0	0	1	100.0	0	0
	E hirae + S aureus	1	100.0	0	0	0	0	0	0
	S agalac + S aureus	3	100.0	0	0	6	100.0	0	0
	S agalac + S aureus + S pyogen	1	100.0	0	0	0	0	0	0
	S aureus + S aureus (1)	1	100.0	0	0	0	0	0	0
	S aureus + S pneumo	2	100.0	0	0	0	0	0	0

Appendix K

Baseline Pathogen(s)		Number (%) of Patients							
		Cefdinir 7 mg/kg BID				Cephalexin 10 mg/kg QID			
		Cure		Failure		Cure		Failure	
		N	%	N	%	N	%	N	%
Multiple	S aureus + S pyogen	20	100.0	0	0	19	90.5	2	9.5
	S aureus + E agglom	0	0	0	0	1	100.0	0	0
	S aureus + E agglom + E agglom (1)	1	100.0	0	0	0	0	0	0
	S aureus + E cloaca	1	100.0	0	0	0	0	0	0
	S aureus + E coli	0	0	0	0	1	100.0	0	0
	S aureus + K oxytoc	1	100.0	0	0	0	0	0	0
	S aureus + K pneumo	2	100.0	0	0	0	0	0	0
	S aureus + Morax sp	0	0	0	0	1	100.0	0	0
	S pyogen + E agglom	1	100.0	0	0	0	0	0	0
	S pyogen + Morax sp	1	100.0	0	0	0	0	0	0

Appendix K

Baseline Pathogen(s)		Number (%) of Patients							
		Cefdinir 7 mg/kg BID				Cephalexin 10 mg/kg QID			
		Cure		Failure		Cure		Failure	
		N	%	N	%	N	%	N	%
Multiple	E cloaca + K pneumo	1	100.0	0	0	0	0	0	0
Total Patients		88	97.8	2	2.2	85	94.4	5	5.6

Appendix L

Table 23

Summary of Clinical Response Rates by Patient (By Baseline Diagnosis)
Combined Investigator/Sponsor Determination
Test-of-Cure Visit
Microbiologically-Clinically Evaluable Patients

Diagnosis at Baseline = Abscess

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	1	100.0	4	100.0
Total	1	100.0	4	100.0

Diagnosis at Baseline = Infected burn

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	1	100.0	1	100.0
Total	1	100.0	1	100.0

Diagnosis at Baseline = Cellulitis

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	3	100.0	2	66.7
Failure	0	0	1	33.3
Total	3	100.0	3	100.0

Diagnosis at Baseline = Infected dermatitis

Appendix L

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	11	100.0	5	83.3
Failure	0	0	1	16.7
Total	11	100.0	6	100.0

Diagnosis at Baseline = Folliculitis

Clinical Response	Number (%) of Patients	
	Cefdinir 7 mg/kg BID	
	N	%
Cure	1	100.0
Total	1	100.0

Diagnosis at Baseline = Furuncle

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	1	100.0	2	100.0
Total	1	100.0	2	100.0

Diagnosis at Baseline = Impetigo

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	62	96.9	59	96.7
Failure	2	3.1	2	3.3
Total	64	100.0	61	100.0

Appendix L

Diagnosis at Baseline = Paronychia

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	3	100.0	5	100.0
Total	3	100.0	5	100.0

Diagnosis at Baseline = Infected traum/surg wound

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	4	100.0	6	100.0
Total	4	100.0	6	100.0

Diagnosis at Baseline = Other

Clinical Response	Number (%) of Patients			
	Cefdinir 7 mg/kg BID		Cephalexin 10 mg/kg QID	
	N	%	N	%
Cure	1	100.0	1	50.0
Failure	0	0	1	50.0
Total	1	100.0	2	100.0

Appendix M

Table 33

Summary of All Adverse Events
Patients Who Received Study Medication - cefdinir

	All Cefdinir N=142		Cefdinir 7 mg/kg BID N=142	
	N	%	N	%
Number of Patients Reporting AE	66	46.5	66	46.5
Number of Patients Reporting Mild AE	46	32.4	46	32.4
Number of Patients Reporting Moderate AE	30	21.1	30	21.1
Number of Patients Reporting Severe AE	2	1.4	2	1.4
Number of Patients < 2 Years Old Reporting AE	17	89.5	17	89.5
Number of Patients 2 to < 6 Years Old Reporting AE	27	50.0	27	50.0
Number of Patients 6 to < 13 Years Old Reporting AE	22	31.9	22	31.9
Number of Male Patients Reporting AE	35	46.1	35	46.1
Number of Female Patients Reporting AE	31	47.0	31	47.0
Number of Premenarchal Females Reporting AE	31	47.0	31	47.0
Number of Whites Reporting AE	44	50.0	44	50.0
Number of Blacks Reporting AE	8	40.0	8	40.0
Number of Hispanics Reporting AE	13	39.4	13	39.4
Number of Other Races Reporting AE	1	100.0	1	100.0
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	2	1.4	2	1.4
Number of Patients Withdrawn from Study Due to AE~	9	6.3	9	6.3

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Number of Patients with Renal Impairment Reporting AE	1	100.0	1	100.0
Number of Patients without Renal Impairment Reporting AE	65	46.1	65	46.1
Number of Patients without Hepatic Impairment Reporting AE	66	46.5	66	46.5

Summary of All Adverse Events
Patients Who Received Study Medication - cepthalexin

	All Comparators N=147		Cephalexin N=147	
	N	%	N	%
Number of Patients Reporting AE	45	30.6	45	30.6
Number of Patients Reporting Mild AE	32	21.8	32	21.8
Number of Patients Reporting Moderate AE	16	10.9	16	10.9
Number of Patients Reporting Severe AE	1	0.7	1	0.7
Number of Patients < 2 Years Old Reporting AE	11	52.4	11	52.4
Number of Patients 2 to < 6 Years Old Reporting AE	24	37.5	24	37.5
Number of Patients 6 to < 13 Years Old Reporting AE	10	16.1	10	16.1
Number of Male Patients Reporting AE	22	28.9	22	28.9
Number of Female Patients Reporting AE	23	32.4	23	32.4
Number of Premenarchal Females Reporting AE	23	32.4	23	32.4
Number of Whites Reporting AE	22	27.5	22	27.5
Number of Blacks Reporting AE	5	20.8	5	20.8

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Number of Hispanics Reporting AE	14	38.9	14	38.9
Number of Other Races Reporting AE	4	66.7	4	66.7
Number of Patients Withdrawn from Study Due to AE~	2	1.4	2	1.4
Number of Patients without Renal Impairment Reporting AE	45	30.6	45	30.6
Number of Patients without Hepatic Impairment Reporting AE	45	30.6	45	30.6

Summary of Associated Adverse Events
Patients Who Received Study Medication - cefdinir

	All Cefdinir N=142		Cefdinir 7 mg/kg BID N=142	
	N	%	N	%
Number of Patients Reporting AE	25	17.6	25	17.6
Number of Patients Reporting Mild AE	17	12.0	17	12.0
Number of Patients Reporting Moderate AE	10	7.0	10	7.0
Number of Patients < 2 Years Old Reporting AE	6	31.6	6	31.6
Number of Patients 2 to < 6 Years Old Reporting AE	10	18.5	10	18.5
Number of Patients 6 to < 13 Years Old Reporting AE	9	13.0	9	13.0
Number of Male Patients Reporting AE	13	17.1	13	17.1
Number of Female Patients Reporting AE	12	18.2	12	18.2
Number of Premenarchal Females Reporting AE	12	18.2	12	18.2
Number of Whites Reporting AE	13	14.8	13	14.8

Number of Blacks Reporting AE	5	25.0	5	25.0
Number of Hispanics Reporting AE	7	21.2	7	21.2
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	1	0.7	1	0.7
Number of Patients with Renal Impairment Reporting AE	1	100.0	1	100.0
Number of Patients without Renal Impairment Reporting AE	24	17.0	24	17.0
Number of Patients without Hepatic Impairment Reporting AE	25	17.6	25	17.6

Summary of Associated Adverse Events
Patients Who Received Study Medication - cephalexin

	All Comparators in N=147		Cephalexin N=147	
	N	%	N	%
Number of Patients Reporting AE	16	10.9	16	10.9
Number of Patients Reporting Mild AE	12	8.2	12	8.2
Number of Patients Reporting Moderate AE	5	3.4	5	3.4
Number of Patients < 2 Years Old Reporting AE	8	38.1	8	38.1
Number of Patients 2 to < 6 Years Old Reporting AE	6	9.4	6	9.4
Number of Patients 6 to < 13 Years Old Reporting AE	2	3.2	2	3.2
Number of Male Patients Reporting AE	7	9.2	7	9.2

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Number of Female Patients Reporting AE	9	12.7	9	12.7
Number of Premenarchal Females Reporting AE	9	12.7	9	12.7
Number of Whites Reporting AE	5	6.3	5	6.3
Number of Blacks Reporting AE	3	12.5	3	12.5
Number of Hispanics Reporting AE	7	19.4	7	19.4
Number of Other Races Reporting AE	1	16.7	1	16.7
Number of Patients without Renal Impairment Reporting AE	16	10.9	16	10.9
Number of Patients without Hepatic Impairment Reporting AE	16	10.9	16	10.9

Appendix N

TABLE 34. All and Associated[a] Adverse Events by Body System - Patients Receiving Study Medication Without Sites 3 and 11
[Number (%) of Patients]
(Page 1 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir[b] N = 142				Cephalexin N = 147			
	All		Associated		All		Associated	
BODY AS A WHOLE	20[c]	(14.1)	2	(1.4)	18	(12.2)	0	(0.0)
Infection	12	(8.5)	0	(0.0)	13	(8.8)	0	(0.0)
Headache	4	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)
Accidental Injury	2	(1.4)	0	(0.0)	3	(2.0)	0	(0.0)
Fever	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Asthenia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
DIGESTIVE SYSTEM	19	(13.4)	16	(11.3)	13	(8.8)	10	(6.8)
Diarrhea	15	(10.6)	15	(10.6)	10	(6.8)	9	(6.1)
Gastroenteritis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Vomiting	2	(1.4)	1	(0.7)	1	(0.7)	0	(0.0)
Dyspepsia	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)
Constipation	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
HEMIC AND LYMPHATIC SYSTEM	5	(3.5)	4	(2.8)	0	(0.0)	0	(0.0)
Leukopenia	4	(2.8)	4	(2.8)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL DISORDERS	1	(0.7)	0	(0.0)	1	(0.7)	1	(0.7)
Alkaline Phosphatase Increased	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood Urea Nitrogen Increased	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)
NERVOUS SYSTEM	3	(2.1)	1	(0.7)	2	(1.4)	0	(0.0)
Nervousness	2	(1.4)	1	(0.7)	0	(0.0)	0	(0.0)
Incoordination	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vestibular Disorder	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Insomnia	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
RESPIRATORY SYSTEM	16	(11.3)	0	(0.0)	10	(6.8)	0	(0.0)
Rhinitis	5	(3.5)	0	(0.0)	3	(2.0)	0	(0.0)
Cough Increased	4	(2.8)	0	(0.0)	2	(1.4)	0	(0.0)
Pharyngitis	4	(2.8)	0	(0.0)	3	(2.0)	0	(0.0)
Lung Disorder	2	(1.4)	0	(0.0)	2	(1.4)	0	(0.0)
Sinusitis	2	(1.4)	0	(0.0)	1	(0.7)	0	(0.0)
Asthma	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Bronchitis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Possibly, probably, or definitely related to treatment
[b] All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.
[c] The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Appendix N

TABLE 34. All and Associated[a] Adverse Events by Body System - Patients Receiving Study Medication Without Sites 3 and 11
[Number (%) of Patients]
(Page 2 of 2)

BODY SYSTEM/ Adverse Event	Cefdinir[b] N = 142				Cephalexin N = 147			
	All		Associated		All		Associated	
SKIN AND APPENDAGES	20	(14.1)	4	(2.8)	16	(10.9)	6	(4.1)
Rash	7	(4.9)	2	(1.4)	6	(4.1)	3	(2.0)
Eczema	3	(2.1)	0	(0.0)	2	(1.4)	0	(0.0)
Pustular Rash	3	(2.1)	0	(0.0)	2	(1.4)	1	(0.7)
Contact Dermatitis	2	(1.4)	1	(0.7)	2	(1.4)	0	(0.0)
Cutaneous Moniliasis	2	(1.4)	2	(1.4)	2	(1.4)	2	(1.4)
Nail Disorder	2	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)
Fungal Dermatitis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Furunculosis	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes Simplex	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Vesiculobullous Rash	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Acne	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
Dry Skin	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)
SPECIAL SENSES	9	(6.3)	0	(0.0)	2	(1.4)	0	(0.0)
Otitis Media	4	(2.8)	0	(0.0)	2	(1.4)	0	(0.0)
Conjunctivitis	3	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Disorder	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Ear Pain	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
UROGENITAL SYSTEM	1	(0.7)	0	(0.0)	1	(0.7)	0	(0.0)
Hematuria	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Urine Abnormality	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)

[a] Possibly, probably, or definitely related to treatment
[b] All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir treatment.
[c] The total number for each body system may be less than the number of patients in that body system because a patient can have ≥ 1 adverse event per system.

Appendix O''

Table 38

Summary of Treatment Discontinuations Due to Adverse Events
Patients Who Received Study Medication - Cefdinir

Body System / Costart Term		Number (%) of Patients			
		All Cefdinir N=142		Cefdinir 7 mg/kg BID N=142	
		N	%	N	%
Respiratory system	*** TOTAL ***	1	0.7	1	0.7
	Bronchitis	1	0.7	1	0.7
Skin and appendages	*** TOTAL ***	1	0.7	1	0.7
	Rash	1	0.7	1	0.7

Appendix O

Listing of Withdrawals from Study due to Adverse Events

Treatment Group:Cefdinir 7 mg/kg BID
Protocol 983-013-

Center	Patient Number	Sex	Age	Adverse Event*	Relationship to Study Medication	Study Day of Last Dose	Start Day of Adverse Event	Adverse Event Outcome
4	18	M	1.04	*NEW IMPETIGINOUS LESION (Pustular rash)	Def. Not	10	22	Not yet recovered
	24	M	1.29	*BILATERAL OTITIS MEDIA (Otitis media)	Unlikely	10	15	Recovered
				*SINUSITIS	Unlikely		15	Recovered
	27	M	8	*SINUSITIS	Def. Not	10	19	Unknown
	36	F	1.54	*CONJUNCTIVITIS	Unlikely	10	20	Not yet recovered
	44	F	2	*BILATERAL OTITIS MEDIA (Otitis media)	Def. Not	10	17	Recovered
8	59	M	10	*BURNED RIGHT FOOT WITH IRON (Accidental injury)	Def. Not	11	15	Unknown
	64	M	2	*RT. CONJUNCTIVITIS (Conjunctivitis)	Def. Not	11	8	Recovered
9	2	M	4	*HIVEY RASH (Rash)	Probably	2	2	Recovered
	8	F	1.83	*RIGHT OTITIS MEDIA (Otitis media)	Def. Not	11	22	Not yet recovered
	9	M	10	*LEFT OTITIS MEDIA (Otitis media)	Def. Not	10	13	Recovered
18	3	M	4	*BRONCHITIS	Def. Not	9	9	Not yet recovered

*When the investigator term and COSTART term differ, the COSTART adverse event appears in parentheses.
*Treatment Emergent Sign or Symptom - First occurrence

Appendix O

Listing of Withdrawals from Study due to Adverse Events

Treatment Group:Cephalexin
Protocol 983-013-

Center	Patient Number	Sex	Age	Adverse Event*	Relationship to Study Medication	Study Day of Last Dose	Start Day of Adverse Event	Adverse Event Outcome
7	1	F	7	*RT OTITIS MEDIA (Otitis media)	Def. Not	11	19	Recovered
12	6	M	9	*BURN RIGHT HAND (Accidental injury)	Def. Not	11	23	Recovered

*When the investigator term and COSTART term differ, the COSTART adverse event appears in parentheses.
*Treatment Emergent Sign or Symptom - First occurrence

Appendix P

TABLE 42. Summary of Markedly Abnormal Laboratory Values More Abnormal at TOC Than at Baseline Without Sites 3 and 11[a]

[Number (%) of Patients]

Parameter	Direction of Change	Cefdinir N = 142		Cephalexin N = 147	
Hematology					
Hemoglobin[b]	Decrease	1	(0.7)	0	(0.0)
Hematocrit	Decrease	0	(0.0)	1	(0.7)
White Blood Cells	Decrease	3	(2.1)	0	(0.0)
Lymphocytes	Increase	1	(0.7)	2	(1.4)
Eosinophils[b]	Increase	2	(1.4)	6	(4.1)
Platelets	Decrease	1	(0.7)	0	(0.0)
Blood Chemistry					
Alkaline Phosphatase	Increase	6	(4.2)	2	(1.4)
Lactate Dehydrogenase[b]	Increase	2	(1.4)	3	(2.0)
AST[b]	Increase	0	(0.0)	1	(0.7)
ALT	Increase	0	(0.0)	1	(0.7)
Potassium[b]	Increase	0	(0.0)	3	(2.0)
Calcium	Decrease	0	(0.0)	1	(0.7)
Phosphorus	Increase	3	(2.1)	2	(1.4)
	Decrease	1	(0.7)	3	(2.0)
Bicarbonate[b]	Increase	0	(0.0)	1	(0.7)
	Decrease	0	(0.0)	1	(0.7)
Urinalysis					
Protein	Increase	1	(0.7)	1	(0.7)
pH[b]	Increase	6	(4.2)	4	(2.7)
Any Parameter[c]		24	(16.9)	27	(18.4)

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

[b] Four patients had no baseline values for comparison, but are included in this summary. Of these, 1 was a cefdinir-treated patient (Patient 33, Center 8, for eosinophils) and 3 were cephalexin-treated (Patient 12, Center 4, for bicarbonate, AST, potassium, and lactate dehydrogenase; Patient 30, Center 4, for urine pH; and Patient 55, Center 8, for eosinophils).

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