V. UNCOMPLICATED SKIN OR SKIN STRUCTURE INFECTION

In support of this indication, the sponsor has submitted results from two phase 3 trials. The titles of the two trials are as follows.

> **CEF-97-009**:" Comparative Safety and Efficacy of Cefditoren Pivoxil and Cefuroxime Axetil in the Treatment of Patients with Uncomplicated Skin or Skin Structure Infection."
>
> **CEF-97-011**: "Comparative Safety and Efficacy of Cefditoren Pivoxil and Cefadroxil Monohydrate in the Treatment of Patients with Uncomplicated Skin or Skin Structure Infection."

STUDY CEF-97-009

INTRODUCTION

Study Objectives
To compare the safety and efficacy of orally administered cefditoren pivoxil 200 mg BID and 400 mg BID and cefuroxime axetil 250 mg BID in the treatment of patients with uncomplicated skin or skin structure infection.

Study Design
This was a Phase III, randomized, double-blind, active-controlled, parallel-group, multicenter study in outpatients with uncomplicated skin or skin structure infections. Approximately 70 investigators were to enroll 840 eligible patients. Patients who met the selection criteria were randomly assigned in a 1:1:1 ratio to receive either cefditoren pivoxil 200 mg BID (CDTR-PI 200 mg) for 10 days, cefditoren pivoxil 400 mg BID (CDTR-PI 400 mg) for 10 days, or cefuroxime axetil (CXM-AX) 250 mg BID for 10 days. Patients returned to the investigator's office for periodic microbiologic evaluation and assessment of the clinical signs and symptoms of infection.

METHODOLOGY

According to the sponsor, during Study Days 3 to 5, the investigator or study coordinator contacted the patient by telephone to assess the patient's status and determine whether an On-Therapy Visit was required. If a visit was not necessary, adverse event and treatment compliance data were obtained by telephone. If an On-Therapy Visit was conducted, the investigator assessed clinical signs and symptoms; obtained vital signs, a specimen for skin infection culture (if available), and blood and urine samples for laboratory tests; documented compliance by pill count and by questioning the patient; and recorded adverse events. Patients returned to the clinic within 48 hours after the last dose (Post-Therapy Visit) and 7 to 14 days after the last dose (Follow-Up Visit). At both posttreatment visits, physical examinations and vital signs measurements were performed, clinical signs and symptoms were assessed and a clinical response to therapy was assigned, a specimen for skin infection culture was obtained (if available), and adverse events were recorded. In addition, laboratory tests were performed and compliance was determined at the Post-Therapy Visit. The Test-of-Cure assessment was performed at the Follow-Up Visit.

Efficacy:

All efficacy analyses excluded patients whose diagnosis of skin or skin structure infection was insufficiently supported by clinical signs and symptoms. In addition, the microbiologic efficacy analysis excluded patients who did not have at least one causative skin pathogen isolated pretreatment. Target pathogens, organisms most frequently associated with skin infection, included *S. aureus* and *S. pyogenes.*

The primary efficacy endpoints used to summarize clinical and microbiologic outcomes at the Post-Therapy and Follow-Up Visits included:

- Clinical Cure Rate (percentage of patients who had a clinical response of "cure").
- Patient Microbiologic Cure Rate (percentage of patients for whom all pretreatment causative skin pathogens were eradicated).
- Pathogen Eradication Rate (percentage of pathogens that were eradicated for each pretreatment causative skin pathogen and combined over all pretreatment causative skin pathogens).

Clinical and microbiologic responses of CDTR-PI 200 mg BID and 400 mg BID were compared with those of CXM-AX 250 mg BID. The primary efficacy endpoints and the adverse event incidence rates were compared between each of the CDTR-PI treatment groups and the CXM-AX group as well as between the two CDTR-PI groups using Fisher's exact test. All statistical tests were two-tailed at the 0.05 level of significance. Binomial 95% confidence intervals, based on normal approximation for the binomial distribution, were calculated for the differences between each of the CDTR-PI groups and the CXM-AX group for the clinical cure rate and the patient microbiologic cure rate.

The primary efficacy endpoints of clinical cure rate, pathogen eradication rate, and patient microbiologic cure rate were summarized by treatment group and analyzed with Fisher's exact test to perform pairwise comparisons of the treatment groups at the Post-Therapy Visit and at the Follow-Up Visit.

Statistical Reviewer's Comments:
For primary efficacy endpoint, post-therapy is just as an assessment that the patient had failed at that point or not. Follow –up visit is the test-of-cure visit and the reviewer's evaluations were be based on the follow-up visit.

Clinical Response Definitions

At the Post-Therapy and Follow-Up Visits, the investigator compared the clinical signs and symptoms with those obtained at the Pre-Therapy Visit, using the following definitions per protocol. Microbiologic results were not considered when assigning the clinical response to therapy.

Clinical Cure	The pretreatment signs and symptoms of the infection resolved.
Clinical Improvement	The pretreatment signs and symptoms of the infection improved.
Clinical Failure	(Applicable for the Post-Therapy Visit only) The pretreatment signs and symptoms of the infection did not improve or worsened.
Clinical Relapse	(Applicable for the Follow-Up Visit only) The signs and symptoms of the infection improved at the Post-Therapy Visit and worsened or reappeared during the Follow-Up period.
Indeterminate	Clinical response to therapy could not be determined.

Microbiologic Response Definitions

Microbiologic response to therapy was assigned by TAP Holdings Inc. at the Post-Therapy and Follow-Up Visits based on the culture results. Response was assigned for each pathogen identified at pretreatment.

Eradication	Absence of the initial pathogen or the infection cleared to such an extent that no culturable material was available.
Persistence	(Applicable for the Post-Therapy Visit only) Presence of the initial pathogen.
Recurrence	(Applicable for the Follow-Up Visit only) Absence of the initial pathogen or the infection cleared to such an extent that no culturable material was available at the Post-Therapy Visit with reappearance of the same pathogen during the Follow-Up period.
Reinfection	Presence of a new pathogen.
Indeterminate	Microbiologic response to therapy could not be assigned.

Demographic and Baseline Variables

The quantitative demographic variables, age, height and weight, were analyzed for differences among the treatment groups using a one-way analysis of variance (ANOVA) with treatment group as the factor. The categorical demographic variables, gender and race, were analyzed for differences among the treatment using the chi-square test; the protocol-specified Fisher's exact test was not used due to the prohibitive computational time required for this test. The baseline characteristics of diagnosis, smoking status, and alcohol consumption were analyzed for differences among the treatment groups by a chi-square test. The baseline characteristics of infection status and clinical condition, and severity of pretreatment clinical

signs and symptoms were compared among the treatment groups using Cochran-Mantel-Haenszel methodology for ordered response variables.

These demographic and baseline characteristics were summarized for all patients and for patients who were clinically evaluable at the Follow-Up Visit.

Statistical Reviewer's Comments:

The Medical Officer concurs with the overall evaluability criteria defined and the outcome assessment classified by the sponsor.

For establishing equivalence, according to the Sponsor, the absolute value of the lower bound of the 95% confidence interval for the difference between two treatment groups in cure rates not exceed the clinically specified boundary. These boundaries vary depending on the cure rates observed in the study as follows:

If the observed cure rate for the better of two treatments is:	Then the lower bound of the confidence interval should not exceed:
>90%	10%
>80 and <90%	15%
<80%	20%

Statistical Reviewer's Comments:

The 1992 points to consider document has been phased out at the FDA and these boundaries are no longer used. The medical officer concurs with a delta of 15%, to establish equivalence for this indication

RESULTS

EFFICACY

A total of 857 patients were randomized in the study and received study drug. Patients were assigned to three treatment arms as follows: 291 patients took cefditoren pivoxil 200 mg BID (CDTR-PI 200 mg), 283 patients took cefditoren pivoxil 400 mg BID (CDTR-PI 400 mg), and 283 patients took cefuroxime axetil 250 mg BID (CXM-AX) as given in Table 5.1.

Statistical Reviewer's Comments:

The Sponsor's efficacy and other analyses were validated by the reviewer and the results are consistent. A re-analysis was completed by the sponsor in response to the items discussed during the teleconference held on August 25, 2000 with the agency and the results were assessed by the reviewer.

Table 5.1. Disposition of Patients by Data Set			
	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CXM-AX 250 mg BID
All Patients:Randomized and Received Study Drug	291	283	283
Included in Clinically Evaluable Efficacy Analyses:			
Post-Therapy	257	254	258
Follow-Up	265	257	265
Excluded at Post-Therapy:	34	29	25
No clinical response assessed within visit window	22	15	17
Received less than 80% of study drug	3	6	3
Received less than 2 consecutive days of study drug	4	4	3
Lost to follow-up	3	0	1
Admission criteria not met	2	1	1
Received additional antimicrobials	0	3	0
Excluded at Follow-Up:	26	26	18
No clinical response assessed within visit window	14	11	9
Received less than 80% of study drug	2	6	2
Received less than 2 consecutive days of study drug	4	4	3
Lost to follow-up	3	0	1
Admission criteria not met	2	1	1
Received additional antimicrobials	1	4	2
Included in Microbiologically Evaluable Efficacy Analyses:			
Post-Therapy	131	137	119
Follow-Up	135	143	121
Excluded at Post-Therapy:	160	146	164
No causative skin pathogen isolated pretreatment	140	129	154
No culture obtained within visit window	9	11	6
Received less than 80% of study drug	2	3	2
Received less than 2 consecutive days of study drug	4	2	1
Lost to follow-up	3	0	1
Admission criteria not met	2	0	0
Received additional antimicrobials	0	1	0
Excluded at Follow-Up:	156	140	162
No causative skin pathogen isolated pretreatment	140	129	154
No culture obtained within visit window	6	6	5
Received less than 80% of study drug	1	2	0
Received less than 2 consecutive days of study drug	4	2	1
Lost to follow-up	3	0	1
Admission criteria not met	2	0	0
Received additional antimicrobials	0	1	1
Sponsor's Table			

Table 5.2 Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group: CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CXM-AX 250 mg BID	P-value[a]
Total Treated	291	283	283	
Gender				0.409
Female	138 (47%)	142 (50%)	150 (53%)	
Male	153 (53%)	141 (50%)	133 (47%)	
Race[b]				0.375
Caucasian	227 (78%)	234 (83%)	230 (81%)	
Black	42 (14%)	38 (13%)	35 (12%)	
Hispanic	15 (5%)	8 (3%)	14 (5%)	
Asian	4 (1%)	0 (0%)	1 (<1%)	
Other	3 (1%)	3 (1%)	3 (1%)	
Age (years)[c]				0.966
<45	181 (62%)	181 (64%)	175 (62%)	
45 - 65	83 (29%)	66 (23%)	76 (27%)	
>65	27 (9%)	36 (13%)	32 (11%)	
Mean (SD)	40.9 (17.3)	40.8 (17.9)	41.2 (18.0)	
Range	13-87	12-93	12-92	
Weight (pounds)[c]				0.683
<135	39 (13%)	49 (17%)	54 (19%)	
135 - 165	76 (26%)	77 (27%)	74 (26%)	
166 - 195	78 (27%)	63 (22%)	71 (25%)	
>195	94 (32%)	92 (33%)	82 (29%)	
Missing	4 (1%)	2 (1%)	2 (1%)	
Mean (SD)	181.1 (45.5)	181.5 (51.4)	178.1 (50.7)	
Range	95-341	99-388	95-430	
Height (inches)[c]	N=291	N=282	N=281	0.642
Mean (SD)	67.4 (4.1)	67.1 (4.2)	67.1 (4.1)	
Range	56-77	50-78	57-77	

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; SD = standard deviation

[a] P-values are from Chi-square test (two-tailed) for gender and race, and a one-way analysis of variance using treatment as the factor for age, weight, and height.

[b] P-value from Chi-square test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Statistical Reviewer's Comments:

There were no statistically significant differences among the treatment groups in gender, age, race, weight, or height in all patients. Demographic information among the all patients, 50% of the patients were females and 81% were Caucasian. Mean age of the study population was 40.9 years and age ranged from 12 to 93 years (Table 5.2).

Table 5.3 Summary of Pretreatment Signs and Symptoms (All Patients)

Sign/Symptom	Number of Patients by Treatment Group						P-value[a]
	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CXM-AX 250 mg BID		
Total Treated[b]	291		283		283		
Pain							0.711
Absent	34	(12%)	37	(13%)	36	(13%)	
Mild	107	(37%)	92	(33%)	91	(32%)	
Moderate	121	(42%)	115	(41%)	121	(43%)	
Severe	29	(10%)	39	(14%)	35	(12%)	
Tenderness							0.590
Absent	13	(4%)	12	(4%)	13	(5%)	
Mild	94	(32%)	91	(32%)	86	(30%)	
Moderate	147	(51%)	132	(47%)	135	(48%)	
Severe	37	(13%)	48	(17%)	49	(17%)	
Swelling							0.766
Absent	17	(6%)	16	(6%)	12	(4%)	
Mild	109	(37%)	107	(38%)	111	(39%)	
Moderate	136	(47%)	141	(50%)	133	(47%)	
Severe	29	(10%)	19	(7%)	27	(10%)	
Erythema	N=290						0.211
Absent	11	(4%)	8	(3%)	4	(1%)	
Mild	77	(27%)	87	(31%)	83	(29%)	
Moderate	169	(58%)	166	(59%)	158	(56%)	
Severe	33	(11%)	22	(8%)	38	(13%)	
Associated warmth							0.605
Absent	53	(18%)	42	(15%)	51	(18%)	
Mild	126	(43%)	136	(48%)	111	(39%)	
Moderate	98	(34%)	90	(32%)	101	(36%)	
Severe	14	(5%)	15	(5%)	20	(7%)	
Purulent drainage/discharge							0.167
Absent	89	(31%)	71	(25%)	97	(34%)	
Mild	119	(41%)	122	(43%)	109	(39%)	
Moderate	69	(24%)	79	(28%)	65	(23%)	
Severe	14	(5%)	11	(4%)	12	(4%)	
Induration							0.995
Absent	95	(33%)	94	(33%)	94	(33%)	
Mild	111	(38%)	104	(37%)	105	(37%)	
Moderate	75	(26%)	77	(27%)	73	(26%)	
Severe	10	(3%)	8	(3%)	11	(4%)	

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil

[a] P-values for comparison among treatment groups are from a Cochran-Mantel-Haenszel test.

[b] Unless otherwise specified, the number evaluated for a specific sign or symptom.

Table 5.3 Summary of Pretreatment Signs and Symptoms (continued)
(All Patients)

Sign/Symptom	Number of Patients by Treatment Group						P-value[a]
	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CXM-AX 250 mg BID		
Total Treated[b]	291		283		283		
Regional lymph node swelling			N=282				0.388
Absent	257	(88%)	245	(87%)	257	(91%)	
Mild	23	(8%)	23	(8%)	17	(6%)	
Moderate	11	(4%)	14	(5%)	8	(3%)	
Severe	0	(0%)	0	(0%)	1	(<1%)	
Regional lymph node tenderness			N=282				0.832
Absent	263	(90%)	249	(88%)	253	(89%)	
Mild	16	(5%)	19	(7%)	17	(6%)	
Moderate	10	(3%)	14	(5%)	9	(3%)	
Severe	2	(1%)	0	(0%)	4	(1%)	
Fever	N=290				N=282		0.095
Absent	289	(100%)	282	(100%)	277	(98%)	
Present	1	(<1%)	1	(<1%)	5	(2%)	

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
[a] P-values for comparison among treatment groups are from a Cochran-Mantel-Haenszel test.
[b] Unless otherwise specified, the number evaluated for a specific sign or symptom.

Statistical Reviewer's Comments:

Pretreatment signs and symptoms in all patients were similar among the three treatment groups, with no statistically significant differences. The most common signs and symptoms among all patients were erythema, tenderness, swelling, and pain (Table 5.3).

Table 5.4 Pretreatment Susceptibility Results for Causative Skin Pathogens

Causative Skin Pathogen	Cefditoren Susceptibility					Cefuroxime Susceptibility					TOTAL
	S	I	R	NA	U	S	I	R	NA	U	
S. aureus	223	8	21	0	0	223	17	12	0	0	252
S. pyogenes	30	0	0	0	0	0	0	0	30	0	30
P. magnus	0	0	0	38	33	0	0	0	38	33	71
E. faecalis	1	4	38	0	0	0	4	39	0	0	43
S. agalactiae	23	0	0	0	0	0	0	0	23	0	23
P. aeruginosa	0	0	21	0	0	0	0	21	0	0	21
P. asaccharolyticus	0	0	0	13	6	0	0	0	13	6	19
E. cloacae	16	1	0	0	0	1	14	2	0	0	17
E. coli	13	0	3	0	0	11	2	3	0	0	16
Bacteroides spp.	0	0	0	25	1	0	0	0	25	1	26

S = susceptible; I = intermediate; R = resistant;
NA = MIC available but no interpretation criteria available; U = no susceptibility data available
Susceptibility breakpoints:
Cefditoren: S = MIC ≤2 mcg/mL; I = 2 < MIC < 8 mcg/mL; R = MIC ≥8 mcg/mL
Cefuroxime: S = MIC ≤4 mcg/mL; I = 4 < MIC < 32 mcg/mL; R = MIC ≥32 mcg/mL
(*Haemophilus*): S = MIC ≤4 mcg/mL; I = MIC = 8 mcg/mL; R = MIC ≥16 mcg/mL
(*S. pneumoniae*): S = MIC ≤0.5 mcg/mL; I = 0.5 < MIC ≤1 mcg/mL; R = MIC > 1 mcg/mL
Sponsor's Table

Table 5.5 Pretreatment Susceptibility Results for *S. aureus* by Penicillinase Production, Oxacillin Resistance, and/or Penicillin Resistance

S. aureus Isolates	Cefditoren Susceptibility				Cefuroxime Susceptibility				TOTAL
	S	I	R	U	S	I	R	U	
Penicillinase-producing	198	8	21	0	198	17	12	0	227
Oxacillin-resistant	1	7	20	0	1	15	12	0	28
Penicillin-resistant	192	8	21	0	192	17	12	0	221

S = susceptible; I = intermediate; R = resistant;
NA = MIC available but no interpretation criteria available; U = no susceptibility data available
Susceptibility breakpoints:
Cefditoren: S = MIC ≤2 mcg/mL; I = 2 < MIC < 8 mcg/mL; R = MIC ≥8 mcg/mL
Cefuroxime: S = MIC ≤4 mcg/mL; I = 4 < MIC < 32 mcg/mL; R = MIC ≥32 mcg/mL
(*Haemophilus*): S = MIC ≤4 mcg/mL; I = MIC = 8 mcg/mL; R = MIC ≥16 mcg/mL
(*S. pneumoniae*): S = MIC ≤0.5 mcg/mL; I = 0.5 < MIC ≤1 mcg/mL; R = MIC > 1 mcg/mL
Sponsor's table

Statistical Reviewer's Comments:

Pretreatment susceptibility results for the causative skin pathogens as well as other identified isolates are presented in Table 5.4. Among the 857 patients enrolled in the study, the causative skin pathogens isolated pretreatment included S. aureus in 252 patients and S. pyogenes in 30 patients. Other commonly isolated pathogens included Peptostreptococcus magnus in 71 patients, Enterococcus faecalis in 43 patients, Streptococcus agalactiae in 23 patients, Pseudomonas aeruginosa in 21 patients, Peptostreptococcus asaccharolyticus in 19 patients, Enterobacter cloacae in 17 patients, and Escherichia coli in 16 patients.

Susceptibility results for S. aureus were also assessed by penicillinase production and oxacillin and/or penicillin resistance (Table 5.5). The 252 S. aureus isolates included 227 penicillinase-producing isolates, 28 oxacillin-resistant isolates, and 221 penicillin-resistant isolates.

Table 5.6 Clinical Response at the Follow-Up Visit (Evaluable Patients)

Clinical Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Cure	223/265	(84%)	216/257	(84%)	234/265	(88%)
Failure	42/265	(16%)	41/257	(16%)	31/265	(12%)

Comparison of Cure Rates	95% CI for Difference in Cure Rate[a]
CDTR-PI 200 mg vs CXM-AX	[-10.0, 1.7]
CDTR-PI 400 mg vs CXM-AX	[-10.2, 1.7]
CDTR-PI 200 mg vs CDTR-PI 400 mg	[-6.2, 6.4]

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Clinical cure rates at the Follow-Up Visit were; CDTR-PI 200 mg (84%), CDTR-PI 400 mg (84%), and CXM-AX (88%) treatment groups (Table 5.6). The 95% CI for clinical cure rates demonstrated that each cefditoren pivoxil group was equivalent to the cefuroxime axetil group, using a delta of 15%.

The Sponsor's statistical analysis plan was not designed for multiple comparisons. For all the analyses in this study, testing the equivalence of treatment difference should be assessed based on a two-tailed 97.5% confidence interval of the difference in clinical cure rates and the width of the 97.5% CI would be larger compared to a two-tailed 95% CI for clinical cure rates.

Table 5.7 Clinical Response at the Follow-Up Visit (Intent-to-Treat Patients)

Clinical Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Cure	227/291	(78%)	221/283	(78%)	236/283	(83%)
Failure	64/291	(22%)	62/283	(22%)	47/283	(17%)
Comparison of Cure Rates			**95% CI for Difference in Cure Rate[a]**			
CDTR-PI 200 mg vs CXM-AX			[-11.8, 1.1]			
CDTR-PI 400 mg vs CXM-AX			[-11.8, 1.2]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-6.9, 6.7]			

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Clinical cure rates among the intent-to-treat subjects at the Follow-Up Visit were 78% in the CDTR-PI 200 mg group, 78% in the CDTR-PI 400 mg group, and 83% in the CXM-AX group (Table 5.7). Both the regimen , CDTR-PI 200 mg and CDTR-PI 400 mg are equivalent to the comparator CXM-AX 250 mg if we consider a delta of 15%.

Table 5.8 Microbiologic Response at the Follow-Up Visit (Evaluable Patients)

Microbiologic Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Cure	110/135	(81%)	121/143	(85%)	103/121	(85%)
Mixed[a]	1/135	(1%)	2/143	(1%)	5/121	(4%)
Failure	24/135	(18%)	20/143	(14%)	13/121	(11%)
Comparison of Cure Rates			**95% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-12.8, 5.5]			
CDTR-PI 400 mg vs CXM-AX			[-9.2, 8.2]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-12.0, 5.7]			

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[a] Eradication of some but not all of the pretreatment causative skin pathogens.
[b] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Microbiologic cure rates at the Follow-Up Visit were 81% in the CDTR-PI 200 mg group, 85% in the CDTR-PI 400 mg group, and 85% in the CXM-AX group (Table 5.8). The 95% CI for microbiologic cure rates demonstrated that CDTR-PI 200 mg was equivalent to the comparator, cefuroxime axetil group and CDTR-PI 400 mg group was equivalent to the cefuroxime axetil group, if we consider a delta of 15%.

As before, testing the equivalence of treatment difference should be assessed based on a two-tailed 97.5% confidence interval for the difference in microbiological cure rates.

Table 5.9 Microbiologic Response at the Follow-Up Visit (ITT Patients)

Microbiologic Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Cure	112/151	(74%)	124/154	(81%)	104/129	(81%)
Mixed[a]	1/151	(1%)	2/154	(1%)	5/129	(4%)
Failure	38/151	(25%)	28/154	(18%)	20/129	(16%)

Comparison of Cure Rates	95% CI for Difference in Cure Rate[b]
CDTR-PI 200 mg vs CXM-AX	[-16.2, 3.3]
CDTR-PI 400 mg vs CXM-AX	[-9.4, 9.2]
CDTR-PI 200 mg vs CDTR-PI 400 mg	[-15.7, 3.0]

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[a] Eradication of some but not all of the pretreatment causative skin pathogens.
[b] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Microbiologic cure rates among the ITT patients at the Follow-Up Visit were 74% in the CDTR-PI 200 mg group, 81% in the CDTR-PI 400 mg group, and 81% in the CXM-AX group (Table 5.9). The cure rate for the cefditoren 200 mg has dropped compared to the evaluable patients and the 95% CI for microbiologic cure rates demonstrated that CDTR-PI 200 mg was not equivalent to cefuroxime axetil 250 mg group even if we consider a delta of 15% and CDTR-PI 400 mg group was equivalent to the comparator using a delta of 15%. As stated before, the equivalence should be assessed using a 97.5% CI, adjusting for the multiple comparisons.

Re-Analysis:

The re-analysis was completed by the sponsor in response to the items discussed during the teleconference held August 25, 2000. This request concerned the patients enrolled in the USSI clinical studies. There were two issues raised. The first issue concerns patients who were evaluated as clinical improvements at the follow-up visit. There were instances where these evaluations were overridden by TAP to either a clinical cure or failure. It was requested that these patients be reevaluated based on their signs and symptoms as follows:

1. If a patient had three or more signs and symptoms present at the follow up visit, the patient is considered a failure.

2. If a patient had two or fewer signs and symptoms present at the follow up visit, the patient is considered a clinical cure.

The second issue raised for the USSI studies involved patients with skin pathogens present at the Pre-therapy, who were considered clinical failures or relapses at the follow-up visit but were considered microbiological cures. It was requested that these patients be considered microbiological failures and it was agreed that the re-analysis would incorporate the re-evaluations for both of the above issues.

Statistical Reviewer's comments:

The Sponsor's re-analysis results, in response to the items discussed during the teleconference held on August 25, 2000 with the agency, were assessed by the reviewer. For all the analyses in this study, testing the equivalence of treatment difference should be assessed based on a two-tailed 97.5% confidence interval of the difference in clinical or microbiological cure rates as appropriate.

Table 5.6a

CLINICAL RESPONSE AT THE FOLLOW-UP VISIT
EVALUABLE PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL
OVERRIDING INVESTIGATOR ASSESSED CLINICAL
IMPROVEMENTS BASED ON SIGNS AND SYMPTOMS

	CEFDITOREN PIVOXIL 200 MG BID	CEFDITOREN PIVOXIL 400 MG BID	CEFUROXIME AXETIL 250 MG BID
CLINICAL RESPONSE			
CURE	82% (212/265)	78% (201/257)	84% (223/265)
FAILURE	20% (53/265)	22% (56/257)	16% (42/265)

CURE	95% CI FOR DIFFERENCE&
CDTR-PI 200 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-10.7, 2.4)
CDTR-P1 400 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-12.6, 0.8)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-5.2, 8.8)

Statistical Reviewer's Comments:

Based on the re-analysis, clinical cure rates among the evaluable patients at the Follow-Up Visit were; CDTR-PI 200 mg (82%), CDTR-PI 400 mg (78%), and CXM-AX (84%) treatment groups (Table 5.6a). The 95% CI for clinical cure rates demonstrated that CDTR-PI 400 mg group was equivalent to the cefuroxime axetil group and CDTR-PI 200 mg demonstrated equivalence to the comparator, if we consider a delta of 15%. Assessment based on a 97.5% CI would be appropriate to demonstrate equivalence for this regimen.

Table 5.7a

CLINICAL RESPONSE AT THE FOLLOW-UP VISIT
INTENT-TO-TREAT PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL
OVERRIDING INVESTIGATOR ASSESSED CLINICAL
IMPROVEMENTS BASED ON SIGNS AND SYMPTOMS

	CEFDITOREN PIVOXIL ====== 200 MG BID ======	CEFDITOREN PIVOXIL ====== 400 MG BID ======	CEFUROXIME AXETIL ====== 500 MG BID ======
CLINICAL RESPONSE			
CURE	74% (215/291)	73% (206/283)	80% (225/283)
FAILURE	26% (76/291)	27% (77/283)	20% (58/283)

CURE	95% CI FOR ====DIFFERENCE&====
CDTR-PI 200 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-12.5, 1.3)
CDTR-P1 400 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-13.7, 0.3)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-6.1, 8.3)

Statistical Reviewer's Comments:

Based on the re-analysis, clinical cure rates among the ITT patients at the Follow-Up Visit were; CDTR-PI 200 mg (74%), CDTR-PI 400 mg (73%), and CXM-AX (80%) treatment groups (Table 5.7a). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg or CDTR-PI 400 mg group compared to the cefuroxime axetil group, considering a delta of 15%.

Table 5.8a

MICROBIOLOGIC RESPONSE AT THE FOLLOW-UP VISIT
EVALUABLE PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL

	CEFDITOREN PIVOXIL ====== 200 MG BID ======	CEFDITOREN PIVOXIL ====== 400 MG BID ======	CEFUROXIME AXETIL ====== 250 MG BID ======
MICROBIOLOGIC RESPONSE			
CURE	76% (103/135)	79% (113/143)	81% (98/121)
MIXED	1% (1/135)	1% (2/143)	4% (5/121)
FAILURE	23% (31/135)	20% (28/143)	15% (18/121)

CURE	95% CI FOR ====DIFFERENCE====
CDTR-PI 200 MG VS CEFUROXIME AXETIL 250 MG	(-14.7, 5.3)
CDTR-P1 400 MG VS CEFUROXIME AXETIL 250 MG	(-11.6, 7.7)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-12.5, 7.1)

Statistical Reviewer's Comments:
Based on the re-analysis, microbiologic cure rates among the evaluable patients at the Follow-Up Visit were; CDTR-PI 200 mg (76%), CDTR-PI 400 mg (79%), and CXM-AX (81%) treatment groups (Table 5.8a). The 95% CI for microbiological cure rates demonstrated equivalence of CDTR-PI 200 mg and CDTR-PI 400 mg group compared to the cefuroxime axetil group,using a delta of 15%.

Table 5.9a

MICROBIOLOGIC RESPONSE AT THE FOLLOW-UP VISIT
INTENT-TO-TREAT PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL

	CEFDITOREN PIVOXIL 200 MG BID	CEFDITOREN PIVOXIL 400 MG BID	CEFUROXIME AXETIL 250 MG BID
MICROBIOLOGIC RESPONSE			
CURE	69% (104/151)	75% (116/154)	76% (98/129)
MIXED	1% (1/151)	1% (2/154)	4% (5/129)
FAILURE	30% (46/151)	23% (36/154)	20% (26/129)

CURE	95% CI FOR ====DIFFERENCE====
CDTR-PI 200 MG VS CEFUROXIME AXETIL 250 MG	(-17.5, 3.3)
CDTR-P1 400 MG VS CEFUROXIME AXETIL 250 MG	(-10.7, 9.4)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-16.5, 3.6)

Statistical Reviewer's Comments:
Based on the re-analysis, for ITT population, the microbiologic cure rates at the Follow-Up Visit were; CDTR-PI 200 mg (69%), CDTR-PI 400 mg (75%), and CXM-AX (76%) treatment groups (Table 5.9a). The 95% CI for microbiological cure rates failed to demonstrate equivalence of CDTR-PI 200 mg compared to the cefuroxime axetil group. The CDTR-PI 400 mg demonstrated equivalence to the comparator using a delta of 15%. Also the two cefditoren pivoxil regimens (200mg and 400 mg) were not equivalent.

SAFETY

All patients who received at least one dose of study drug (N=857) were included in the safety analyses.

Table 5.10 Summary of Common[a] Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI 200 mg BID (N=291)					CDTR-PI 400 mg BID (N=283)					CXM-AX 250 mg BID (N=283)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c@†]				96	(33%)				128	(45%)				99	(35%)
BODY AS A WHOLE				35	(12%)				41	(14%)				36	(13%)
Abdominal pain	1	1	0	2	(1%)	2	4	1	7	(2%)	1	2	1	4	(1%)
Asthenia	2	1	0	3	(1%)	4	1	0	5	(2%)	0	0	0	0	(0%)
Headache	11	4	1	16	(5%)	4	5	2	11	(4%)	8	3	3	14	(5%)
Infection	2	2	0	4	(1%)	4	2	2	8	(3%)	2	2	0	4	(1%)
DIGESTIVE SYSTEM[@†]				57	(20%)				91	(32%)				46	(16%)
Diarrhea[@†#]	26	9	3	38	(13%)	44	11	3	58	(20%)	13	4	2	19	(7%)
Dyspepsia	2	2	1	5	(2%)	2	2	1	5	(2%)	4	3	1	8	(3%)
Flatulence[@]	1	0	0	1	(<1%)	6	2	0	8	(3%)	2	0	0	2	(1%)
Nausea[@†]	11	2	1	14	(5%)	19	6	3	28	(10%)	6	7	0	13	(5%)
Vomiting	1	1	0	2	(1%)	6	1	1	8	(3%)	2	1	0	3	(1%)
SKIN AND APPENDAGES				13	(4%)				10	(4%)				11	(4%)
Pruritus	4	2	1	7	(2%)	2	0	0	2	(1%)	1	2	0	3	(1%)
UROGENITAL				(N=138)					(N=142)					(N=151)	
SYSTEM (female)[d]				4	(3%)				7	(5%)				7	(5%)
Vaginal Moniliasis[d]	1	0	0	1	(1%)	3	2	0	5	(4%)	3	2	0	5	(3%)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; Mod = moderate; Sev = severe

[a] Adverse events occurring in ≥2% of patients in any treatment group.

[b] Table summarizes the most severe occurrence of each COSTART term from each patient.

[c] Number of patients with one or more adverse events.

[d] Gender-specific adverse event; percentage given is of females only.

[@] Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CDTR-PI 400 mg groups ($p \leq 0.05$).

† Statistically significant difference in incidence rate between the CDTR-PI 400 mg and CXM-AX groups ($p \leq 0.05$).

Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CXM-AX groups ($p \leq 0.05$).

Sponsor's Table

Table 5.11 Action Taken for Patients Who Experienced Diarrhea by Intensity of Diarrhea

	CDTR-PI 200 mg				CDTR-PI 400 mg				CXM-AX 250 mg			
	Severity[a]				Severity[a]				Severity[a]			
Adverse Event of Diarrhea	Mild	Mod	Sev	Total	Mild	Mod	Sev	Total	Mild	Mod	Sev	Total
Intensity of Diarrhea	26	9	3	38	44	11	3	58	13	4	2	19
Action Taken:												
Study drug discontinued	1	0	2	3	2	2	2	6	0	0	1	1
Other medication prescribed	3	4	0	7	4	2	1	7	1	1	0	2
No action taken	22	5	1	28	38	7	0	45	12	3	1	16

[a] Table summarizes the most severe occurrence of each COSTART term from each patient.
Sponsor's Table

Statistical Reviewer's Comments:

The incidences of all adverse events and treatment-related adverse events were 33% and 22%, respectively, in the CDTR-PI 200 mg group, 45% and 33%, respectively, in the CDTR-PI 400 mg group, and 35% and 23%, respectively, in the CXM-AX group during the treatment (table 5.10). The differences between the two cefditoren pivoxil groups (p=0.003) and between the CDTR-PI 400 mg and CXM-AX groups (p≤0.016) in the incidence of all adverse events and treatment-related adverse events were statistically significant.

The most frequently occurring treatment-related adverse event in all three treatment groups was diarrhea. In the CDTR-PI 200 mg, CDTR-PI 400 mg, and CXM-AX groups, treatment-related diarrhea was reported by 13%, 18%, and 7% of patients, respectively. In addition, treatment-related nausea was reported by 8% of the patients in the CDTR-PI 400 mg group. Statistically significant differences were observed between the two cefditoren groups in the incidence of flatulence, with a higher incidence in the CDTR-PI 400 mg group (3% vs. <1%); between the CDTR-PI 400 mg and CXM-AX groups in the incidence of nausea, with a higher incidence in the CDTR-PI 400 mg group (8% vs. 4%); and between each cefditoren group and the CXM-AX group in the incidence of diarrhea, with higher incidences in the CDTR-PI 200 mg (13% vs. 7%) and CDTR-PI 400 mg (18% vs. 7%) groups.

Table 5.12 Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI 200 mg BID (N=291)					CDTR-PI 400 mg BID (N=283)					CXM-AX 250 mg BID (N=283)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c@†]				64	(22%)				94	(33%)				64	(23%)
BODY AS A WHOLE				15	(5%)				22	(8%)				13	(5%)
Abdominal Pain	1	1	0	2	(1%)	2	4	1	7	(2%)	1	2	0	3	(1%)
Headache	5	3	1	9	(3%)	3	5	1	9	(3%)	2	1	2	5	(2%)
DIGESTIVE SYSTEM[@†]				51	(18%)				79	(28%)				42	(15%)
Diarrhea†#	25	9	3	37	(13%)	40	9	3	52	(18%)	13	4	2	19	(7%)
Dyspepsia	2	2	1	5	(2%)	2	2	1	5	(2%)	4	3	1	8	(3%)
Flatulence[@]	1	0	0	0	(<1%)	6	2	0	8	(3%)	2	0	0	2	(1%)
Nausea†	11	1	1	13	(4%)	15	5	3	23	(8%)	3	7	0	10	(4%)
SKIN AND APPENDAGES				6	(2%)				2	(1%)				4	(1%)
Pruritus	3	2	1	6	(2%)	1	0	0	1	(<1%)	0	1	0	1	(<1%)
UROGENITAL SYSTEM (female)[d]				(N=138)					(N=142)					(N=151)	
				2	(1%)				6	(4%)				6	(4%)
Vaginal Moniliasis[d]	1	0	0	1	(1%)	3	2	0	5	(4%)	3	2	0	5	(3%)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; Mod = moderate; Sev = severe

[a] Adverse events occurring in ≥2% of patients in any treatment group.
[b] Table summarizes the most severe occurrence of each COSTART term from each patient.
[c] Number of patients with one or more adverse events.
[d] Gender-specific adverse event; percentage given is of females only.
[@] Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CDTR-PI 400 mg groups ($p \leq 0.05$).
[†] Statistically significant difference in incidence rate between the CDTR-PI 400 mg and CXM-AX groups ($p \leq 0.05$).
[#] Statistically significant difference in incidence rate between the CDTR-PI 200 mg and CXM-AX groups ($p \leq 0.05$).
Sponsor's Table

Statistical Reviewer's Comments:

Sixty-four (22%) patients in the CDTR-PI 200 mg group, 94 (33%) patients in the CDTR-PI 400 mg group, and 64 (23%) patients in the CXM-AX group reported at least one adverse event during treatment that was considered by the investigator to be possibly, probably, or definitely treatment-related (Table 5.12). The differences in the incidence of treatment-related adverse events were statistically significant between the two CDTR-PI groups (p=0.003) and between the CDTR-PI 400 mg and CXM-AX groups (p=0.006). The most frequently occurring treatment-related adverse events were diarrhea (13%) in the CDTR-PI 200 mg group; diarrhea (18%) and nausea (8%) in the CDTR-PI 400 mg group; and diarrhea (7%) in the CXM-AX group.

Statistically significant differences were observed between the CDTR-PI 200 mg and CXM-AX groups (p=0.017) and between the CDTR-PI 400 mg and CXM-AX groups (p<0.001) in the incidence of diarrhea. Statistically significant differences were also observed between the CDTR-PI 200 mg and CDTR-PI 400 mg groups for flatulence (<1% and 3%, respectively, p=0.019); between the CDTR-PI 400 mg and CXM-AX groups for nausea (8% and 4%, respectively, p=0.030).

STUDY: CEF-97-011

INTRODUCTION

Study Objectives
To compare the safety and efficacy of orally administered cefditoren pivoxil 200 mg BID and 400 mg BID and cefadroxil monohydrate 500 mg BID in the treatment of patients with uncomplicated skin or skin structure infection

Study Design
This was a Phase III, randomized, double-blind, active-controlled, parallel-group, multicenter study in outpatients with uncomplicated skin or skin structure infections. Approximately 70 investigators were to enroll 840 eligible patients. Patients who met the selection criteria were randomly assigned in a 1:1:1 ratio to receive either cefditoren pivoxil 200 mg BID (CDTR-PI 200 mg) for 10 days, cefditoren pivoxil 400 mg BID (CDTR-PI 400 mg) for 10 days, or cefadroxil monohydrate 500 mg (CFDX-MN) BID for 10 days. Patients returned to the investigator's office for periodic microbiologic evaluation and assessment of the clinical signs and symptoms of infection.

METHODOLOGY

Clinical and microbiologic responses of CDTR-PI 200 mg BID and 400 mg BID were compared with those of CFDX-MN 500 mg BID. The primary efficacy endpoints and the adverse event incidence rates were compared between each of the CDTR-PI treatment groups and the CFDX-MN group as well as between the two CDTR-PI groups using Fisher's exact test. All statistical tests were two-tailed at the 0.05 level of significance. Binomial 95% confidence intervals, based on normal approximation for the binomial distribution, were calculated for the differences between each of the CDTR-PI groups and the CFDX-MN group for the clinical cure rate and the patient microbiologic cure rate.

Statistical Reviewer's Comments:

The Medical Officer concurs with the overall evaluability criteria defined and the outcome assessment classified by the sponsor. The efficacy evaluation (clinical and microbiological) and all the definitions are the same as in the previous study (CEF-97-009).

For establishing equivalence, according to the Sponsor, the absolute value of the lower bound of the 95% confidence interval for the difference between two treatment groups in cure rates not exceed the clinically specified boundary. These boundaries vary depending on the cure rates observed in the study as follows:

If the observed cure rate for the better of two treatments is:	Then the lower bound of the confidence interval should not exceed:
>90%	10%
>80 and <90%	15%
<80%	20%

Statistical Reviewer's Comments:

The 1992 points to consider document has been phased out at the FDA and these boundaries are no longer used. The medical officer concurs with a delta of 10%, to establish equivalence for this indication

RESULTS

EFFICACY

Of the 828 patients included in the analysis, 765 (258 in the CDTR-PI 200 mg group, 259 in the CDTR-PI 400 mg group, and 248 in the CFDX-MN group) patients were clinically evaluable and 63 (20 in the CDTR-PI 200 mg group, 18 in the CDTR-PI 400 mg group, and 25 in the CFDX-MN group) were excluded from the clinically evaluable efficacy analyses at the Follow-Up Visit as given in Table 6.1.

Statistical Reviewer's Comments:

The Sponsor's efficacy and other analyses were validated by the reviewer and the results are consistent. A re-analysis was completed by the sponsor in response to the items discussed during the teleconference held on August 25, 2000 with the agency and the results were assessed by the reviewer.

APPEARS THIS WAY
ON ORIGINAL

Table 6.1 Disposition of Patients by Data Set

	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CFDX-MN 500 mg BID
All Patients: Randomized and Received Study Drug[a]	278	277	273
Included in Clinically Evaluable Efficacy Analyses:			
Post-Therapy	252	248	244
Follow-Up	258	259	248
Excluded at Post-Therapy:	26	29	29
No clinical response assessed within visit window	15	18	15
Received less than 80% of study drug	3	3	6
Admission criteria not met	3	2	4
Received less than 2 consecutive days of study drug	2	3	1
Lost to follow-up	1	3	1
Pretherapy assessment performed too early	1	0	0
Previously enrolled in a cefditoren study with same indication	0	0	1
Received additional antimicrobials	0	0	1
Received another antimicrobial agent pretreatment	1	0	0
Excluded at Follow-Up:	20	18	25
No clinical response assessed with visit window	6	4	7
Received additional antimicrobials	4	3	5
Received less than 80% of study drug	2	2	6
Admission criteria not met	3	2	4
Received less than 2 consecutive days of study drug	2	3	1
Lost to follow-up	1	3	1
Misdiagnosis	0	1	0
Pretherapy assessment performed too early	1	0	0
Previously enrolled in a cefditoren study with same indication	0	0	1
Received another antimicrobial agent pretreatment	1	0	0
Included in Microbiologically Evaluable Efficacy Analyses:			
Post-Therapy	121	124	115
Follow-Up	120	127	116
Excluded at Post-Therapy:	157	153	158
No causative skin pathogen isolated pretreatment	147	140	141
No culture obtained within visit window	4	7	11
Admission criteria not met	1	1	2
Received less than 80% of study drug	2	1	2
Lost to follow-up	1	2	0
Culture results could not be confirmed	1	1	0
Received less than 2 consecutive days of study drug	0	1	1
Pretherapy assessment performed too early	1	0	0
Received additional antimicrobials	0	0	1
Excluded at Follow-Up:	158	150	157
No causative skin pathogen isolated pretreatment	147	140	141
No culture obtained within visit window	4	4	7
Received additional antimicrobials	2	1	4
Admission criteria not met	1	1	2
Received less than 80% of study drug	1	0	2
Lost to follow-up	1	2	0
Culture results could not be confirmed	1	1	0
Received less than 2 consecutive days of study drug	0	1	1
Pretherapy assessment performed too early	1	0	0

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
Sponsor's Table

Statistical Reviewer's comments:

A total of 858 patients were randomized in the study and received study drug; 30 patients were excluded (investigative site #13057) and the remaining 828 patients were included in the analysis. Patients were assigned to three treatment arms as follows: 278 patients took cefditoren pivoxil 200 mg BID (CDTR-PI 200 mg), 277 patients took cefditoren pivoxil 400 mg BID (CDTR-PI 400 mg), and 273 patients took cefadroxil monohydrate (CFDX-MN) 500 mg BID (Table 6.1).

Table 6.2 Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group			P-value[a]
	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CFDX-MN 500 mg BID	
Total Treated	278	277	273	
Gender				0.848
Female	138 (50%)	133 (48%)	129 (47%)	
Male	140 (50%)	144 (52%)	144 (53%)	
Race[b]				0.218
Caucasian	224 (81%)	221 (80%)	217 (79%)	
Hispanic	28 (10%)	37 (13%)	27 (10%)	
Black	20 (7%)	10 (4%)	19 (7%)	
Asian	4 (1%)	2 (1%)	4 (1%)	
Other	2 (1%)	7 (3%)	6 (2%)	
Age (years)[c]				0.268
<45	168 (60%)	178 (64%)	175 (64%)	
45 - 65	75 (27%)	72 (26%)	71 (26%)	
>65	35 (13%)	27 (10%)	27 (10%)	
Mean (SD)	42.6 (16.7)	40.7 (16.5)	40.6 (16.8)	
Range	12 - 95	12 - 85	13 - 93	
Weight (pounds)[c]	N=277	N=277	N=271	0.644
<135	40 (14%)	37 (13%)	35 (13%)	
135 - 165	76 (27%)	73 (26%)	84 (31%)	
166 - 195	80 (29%)	85 (31%)	71 (26%)	
>195	81 (29%)	82 (30%)	81 (30%)	
Missing	1 (<1%)	0 (0%)	2 (1%)	
Mean (SD)	180.1 (43.6)	181.2 (49.7)	177.7 (42.0)	
Range	110 - 340	85 - 401	85 - 355	
Height (inches)[c]	N=277	N=277	N=270	0.705
Mean (SD)	67.1 (4.0)	67.1 (4.3)	67.3 (4.2)	
Range	53 - 78	50 - 79	54 - 79	

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; SD = standard deviation

[a] P-values are from Chi-square test (two-tailed) for gender and race, and a one-way analysis of variance using treatment as the factor for age, weight, and height.

[b] P-value from Chi-square test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Statistical Reviewer's comments:

There were no statistically significant differences among the treatment groups in gender, age, race, weight, or height in all patients. Among the all patients, fifty-two percent (52%) of the

patients were males and 80% were Caucasian. Mean age of the study population was 41.3 years and age ranged from 12 to 95 years (Table 6.2). Evaluable patients at the follow up had a similar demographic profile.

Table 6.3 Summary of Diagnoses and Baseline Characteristics (All Patients)

	Number of Patients by Treatment Group			
Diagnoses and Baseline Characteristics	**CDTR-PI 200 mg BID**	**CDTR-PI 400 mg BID**	**CFDX-MN 500 mg BID**	**P-value[a]**
Total Treated	278	277	273	
Diagnosis				0.481
Cellulitis	70 (25%)	60 (22%)	73 (27%)	
Wound infection	70 (25%)	64 (23%)	68 (25%)	
Folliculitis	34 (12%)	42 (15%)	31 (11%)	
Simple abscess	37 (13%)	28 (10%)	39 (14%)	
Infected sebaceous cyst	23 (8%)	32 (12%)	26 (10%)	
Impetigo	27 (10%)	25 (9%)	22 (8%)	
Furunculosis	6 (2%)	17 (6%)	10 (4%)	
Other (erysipelas, carbunculosis, etc.)	11 (4%)	9 (3%)	4 (1%)	
Infection Status				0.418
Mild	79 (28%)	79 (29%)	87 (32%)	
Moderate	185 (67%)	184 (66%)	177 (65%)	
Severe	14 (5%)	14 (5%)	9 (3%)	
Clinical Condition				0.262
Good	204 (73%)	217 (78%)	216 (79%)	
Fair	73 (26%)	58 (21%)	56 (21%)	
Poor	1 (<1%)	2 (1%)	1 (<1%)	
Smoking Status				0.118
Non-smoker	136 (49%)	160 (58%)	158 (58%)	
Smoker	98 (35%)	85 (31%)	87 (32%)	
Ex-smoker	44 (16%)	32 (12%)	28 (10%)	
Alcohol Use				0.755
Non-drinker	121 (44%)	125 (45%)	125 (46%)	
Drinker	138 (50%)	140 (51%)	134 (49%)	
Ex-drinker	19 (7%)	12 (4%)	14 (5%)	

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate.

[a] P-values are from Chi-square test for diagnosis, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status and clinical condition.

Sponsor's Table

Statistical Reviewer's Comments:

The most common diagnoses were cellulitis (25% of patients), wound infection (24%), folliculitis (13%), and simple abscess (13%). The majority of patients had a moderate infection (66%) and were considered to be in good clinical condition (77%). No statistically significant differences were observed.

Table 6.4 Pretreatment Susceptibility Results for Causative Skin Pathogens

Causative Skin Pathogen	Cefditoren Susceptibility					Cefadroxil Susceptibility[a]					TOTAL
	S	I	R	NA	U	S	I	R	NA	U	
S. aureus	261	2	10	0	0	269	2	2	0	0	273
S. pyogenes	23	0	0	0	0	0	0	0	23	0	23
P. magnus	0	0	0	19	25	0	0	0	18	26	44
P. asaccharolyticus	0	0	0	12	8	0	0	0	12	8	20
E. faecalis	2	5	13	0	0	1	0	19	0	0	20
P. aeruginosa	0	0	18	0	0	0	0	18	0	0	18
S. agalactiae	17	0	0	0	0	0	0	0	17	0	17
Bacteroides spp.	0	0	0	17	5	0	0	0	17	5	22
Enterobacter spp.	15	0	1	0	0	1	1	14	0	0	16

S = susceptible; I = intermediate; R = resistant; U = unknown; N/A = not applicable

[a] There currently are no breakpoints for cefadroxil; therefore breakpoints for cephalothin were used.

Susceptibility breakpoints:

Cefditoren: S = MIC ≤2 mcg/mL; I = 2 < MIC < 8 mcg/mL; R = MIC ≥8 mcg/mL

Cephalothin: S = MIC ≤8 mcg/mL; I = MIC = 16 mcg/mL; R = MIC ≥32 mcg/mL

Sponsor's Table

Table 6.5 Pretreatment Susceptibility Results for *S. aureus* by Penicillinase Production, Oxacillin Resistance, and/or Penicillin Resistance

S. aureus Isolates	Cefditoren Susceptibility				Cefadroxil Susceptibility[a]					TOTAL
	S	I	R	U	S	I	R	U	NA	
Penicillinase-producing	222	2	9	0	230	1	2	0	0	233
Oxacillin-resistant	3	2	10	0	11	2	2	0	0	15
Penicillin-resistant	220	2	10	0	228	2	2	0	0	232

S = susceptible; I = intermediate; R = resistant; U = unknown; N/A = not applicable

[a] There currently are no breakpoints for cefadroxil; therefore breakpoints for cephalothin were used.

Susceptibility breakpoints:

Cefditoren: S = MIC ≤2 mcg/mL; I = 2 < MIC < 8 mcg/mL; R = MIC ≥8 mcg/mL

Cephalothin: S = MIC ≤8 mcg/mL; I = MIC = 16 mcg/mL; R = MIC ≥32 mcg/mL

Statistical Reviewer's Comments:

Pretreatment susceptibility results for the causative skin pathogens as well as other identified isolates are presented in Table 6.4. Among the 828 patients enrolled in the study, the causative skin pathogens isolated pretreatment included S. aureus in 273 patients and S. pyogenes in 23 patients; other commonly isolated pathogens included Peptostreptococcus magnus in 44 patients, Peptostreptococcus asaccharolyticus and Enterococcus faecalis in 20 patients each, Pseudomonas aeruginosa in 18 patients, and Streptococcus agalactiae in 17 patients. In addition, Bacteroides spp. were isolated in 22 patients and Enterobacter spp. were isolated in 16 patients.

Susceptibility results for S. aureus were also assessed by penicillinase production and oxacillin and/or penicillin resistance (Table 6.5). The 273 S. aureus isolates included 233 penicillinase-producing isolates, 15 oxacillin-resistant isolates, and 232 penicillin-resistant isolates.

Table 6.6 Clinical Response at the Follow-Up Visit (Evaluable Patients)

Clinical Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	220/258	(85%)	211/259	(81%)	211/248	(85%)
Failure	38/258	(15%)	48/259	(19%)	37/248	(15%)

Comparison of Cure Rates	95% CI for Difference in Cure Rate[a]
CDTR-PI 200 mg vs CFDX-MN	[-6.0, 6.4]
CDTR-PI 400 mg vs CFDX-MN	[-10.1, 2.9]
CDTR-PI 200 mg vs CDTR-PI 400 mg	[-2.6, 10.2]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Clinical cure rates at the Follow-Up Visit were similar in the CDTR-PI 200 mg (85%), CDTR-PI 400 mg (81%), and CFDX-MN (85%) treatment groups (Table 6.6). The 95% CI for clinical cure rates demonstrated that each cefditoren pivoxil group was equivalent to the cefadroxil monohydrate group and that the two cefditoren pivoxil regimens were equivalent, using a delta of 15%.

The Sponsor's statistical analysis plan was not designed for multiple comparisons. For all the analyses in this study, testing the equivalence of treatment difference should be assessed based on a two-tailed 97.5% confidence interval of the difference in cure rates.

Table 6.7 Clinical Response at the Follow-Up Visit (Intent-to-Treat Patients)

Clinical Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	231/277	(83%)	218/277	(79%)	223/273	(82%)
Failure	47/278	(17%)	59/277	(21%)	50/273	(18%)

Comparison of Cure Rates	95% CI for Difference in Cure Rate[a]
CDTR-PI 200 mg vs CFDX-MN	[-5.0, 7.8]
CDTR-PI 400 mg vs CFDX-MN	[-9.6, 3.7]
CDTR-PI 200 mg vs CDTR-PI 400 mg	[-2.1, 10.9]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's comments:

Results in intent-to-treat patients were generally similar to those in evaluable patients. Clinical cure rates at the Follow-Up Visit were 83% in the CDTR-PI 200 mg group, 79% in the CDTR-PI 400 mg group, and 82% in the CFDX-MN group (Table 6.7). The 95% CI for clinical cure rates demonstrated that each cefditoren pivoxil group (200 mg and 400 mg) was equivalent to the cefadroxil monohydrate group and that the two cefditoren pivoxil regimens were equivalent using a delta of 15%.

Table 6.8 Microbiologic Response at the Follow-Up Visit (Evaluable Patients)

Microbiologic Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	101/120	(84%)	101/127	(80%)	90/116	(78%)
Mixed[a]	0/120	(0%)	2/127	(2%)	2/116	(2%)
Failure	19/120	(16%)	24/127	(19%)	24/116	(21%)

Comparison of Cure Rates	95% CI for Difference in Cure Rate[b]
CDTR-PI 200 mg vs CFDX-MN	[-3.4, 16.6]
CDTR-PI 400 mg vs CFDX-MN	[-8.4, 12.3]
CDTR-PI 200 mg vs CDTR-PI 400 mg	[-4.9, 14.2]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[a] Eradication of some but not all of the pretreatment causative skin pathogens.
[b] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Microbiologic cure rates among the evaluable population at the Follow-Up Visit were similar in the CDTR-PI 200 mg (84%), CDTR-PI 400 mg (80%), and CFDX-MN (78%) treatment groups (Table 6.8). The 95% CI for microbiologic cure rates demonstrated that each cefditoren pivoxil group was equivalent to the cefadroxil monohydrate group and that the two cefditoren pivoxil regimens were equivalent, using a delta of 15%.

Table 6.9 Microbiologic Response at the Follow-Up Visit (Intent-to-Treat Patients)

Microbiologic Response	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CFDX-MN 500 mg BID n/N (%)	
Cure	105/130	(81%)	102/136	(75%)	97/132	(73%)
Mixed[a]	0/130	(0%)	2/136	(1%)	3/132	(2%)
Failure	25/130	(19%)	32/136	(24%)	32/132	(24%)

Comparison of Cure Rates	95% CI for Difference in Cure Rate[b]
CDTR-PI 200 mg vs CFDX-MN	[-2.8, 17.4]
CDTR-PI 400 mg vs CFDX-MN	[-9.0, 12.0]
CDTR-PI 200 mg vs CDTR-PI 400 mg	[-4.2, 15.7]

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients

[a] Eradication of some but not all of the pretreatment causative skin pathogens.

[b] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Results in intent-to-treat patients were similar to those in evaluable patients. Microbiologic cure rates at the Follow-Up Visit were 81% in the CDTR-PI 200 mg group, 75% in the CDTR-PI 400 mg group, and 73% in the CFDX-MN group (Table 6.9). The 95% CI for microbiologic cure rates demonstrated that each cefditoren pivoxil group was equivalent to the cefadroxil monohydrate group and that the two cefditoren pivoxil regimens were equivalent considering a delta of 15%.

In the above Table 6.9, the total number of patients in the intent-to-treat population at follow up for CDTR-PI 200 mg group should be 131 patients and 137 patients for CDTR-PI 400 mg group.

Re-analysis

Statistical Reviewer's comments:

The Sponsor's re-analysis results, in response to the items discussed during the teleconference held on August 25, 2000 with the agency, were assessed by the reviewer. For all the analyses in this study, testing the equivalence of treatment difference should be assessed based on a two-tailed 97.5% confidence interval of the difference in clinical or microbiological cure rates.

Table 6.6a **CLINICAL RESPONSE AT THE FOLLOW-UP VISIT**
EVALUABLE PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL
OVERRIDING INVESTIGATOR ASSESSED CLINICAL CURES AND IMPROVEMENTS BASED ON SIGNS AND SYMPTOMS

	CEFDITOREN PIVOXIL ====== 200 MG BID ======	CEFDITOREN PIVOXIL ====== 400 MG BID ======	CEFADROXIL MONOHYDRATE ====== 500 MG BID ======
CLINICAL RESPONSE			
CURE	79% (205/258)	75% (193/259)	79% (195/248)
FAILURE	21% (53/258)	25% (66/259)	21% (53/248)

CURE	95% CI FOR DIFFERENCE====
CDTR-PI 200 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-6.3, 7.9)
CDTR-P1 400 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-11.5, 3.2)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-2.3, 12.2)

Statistical Reviewer's Comments:

Based on the re-analysis, the clinical cure rates of the evaluable patients at the Follow-Up Visit were similar in the CDTR-PI 200 mg (79%), CDTR-PI 400 mg (75%), and CFDX-MN (79%) treatment groups (Table 6.6a). The 95% CI for clinical cure rates demonstrated that CDTR-PI 200 and CDTR-PI 400 mg demonstrated equivalence to the cefadroxil monohydrate group, using a 15% delta.

Table 6.7a

CLINICAL RESPONSE AT THE FOLLOW-UP VISIT
INTENT-TO-TREAT PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL
OVERRIDING INVESTIGATOR ASSESSED CLINICAL CURES AND IMPROVEMENTS BASED ON SIGNS AND SYMPTOMS

	CEFDITOREN PIVOXIL 200 MG BID	CEFDITOREN PIVOXIL 400 MG BID	CEFADROXIL MONOHYDRATE 500 MG BID
CLINICAL RESPONSE			
CURE	77% (215/278)	72% (199/277)	76% (207/273)
FAILURE	23% (63/278)	28% (78/277)	24% (66/273)

CURE	95% CI FOR DIFFERENCE&
CDTR-PI 200 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-5.6, 8.6)
CDTR-P1 400 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-11.3, 3.4)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-1.7, 12.7)

Statistical Reviewer's Comments:

Based on the re-analysis, the clinical cure rates at the Follow-Up Visit were very low; in the CDTR-PI 200 mg (77%), CDTR-PI 400 mg (72%), and CFDX-MN (76%) treatment groups (Table 6.7a). The 95% CI for clinical cure rates demonstrated that CDTR-PI 200 and CDTR-PI 400 mg demonstrated equivalence compared to the cefadroxil monohydrate group using a delta of 15%.

Table 6.8a

MICROBIOLOGIC RESPONSE AT THE FOLLOW-UP VISIT
EVALUABLE PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL

	CEFDITOREN PIVOXIL ====== 200 MG BID ======	CEFDITOREN PIVOXIL ====== 400 MG BID ======	CEFADROXIL MONOHYDRATE ====== 500 MG BID ======
MICROBIOLOGIC RESPONSE			
CURE	73% (88/120)	73% (93/127)	72% (84/116)
MIXED	0% (0/120)	2% (2/127)	2% (2/116)
FAILURE	27% (32/120)	25% (32/127)	26% (30/116)

CURE	95% CI FOR ====DIFFERENCE====
CDTR-PI 200 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-10.4, 12.3)
CDTR-P1 400 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-10.4, 12.0)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-10.9, 11.1)

Statistical Reviewer's Comments

Based on the re-analysis, the microbiological cure rates among the evaluable patients at the Follow-Up Visit were similar; in the CDTR-PI 200 mg (73%), CDTR-PI 400 mg (73%), and CFDX-MN (72%) treatment groups (Table 6.8a). The 95% CI for microbiological cure rates demonstrated that CDTR-PI 200 mg and CDTR-PI 400 mg demonstrated equivalence compared to the comparator, using a delta 15%.

Table 6.9a

MICROBIOLOGIC RESPONSE AT THE FOLLOW-UP VISIT
INTENT-TO-TREAT PATIENTS
APPLYING FDA CRITERIA FROM 8/25 CONFERENCE CALL

	CEFDITOREN PIVOXIL ====== 200 MG BID ======	CEFDITOREN PIVOXIL ====== 400 MG BID ======	CEFADROXIL MONOHYDRATE ====== 500 MG BID ======
MICROBIOLOGIC RESPONSE			
CURE	70% (91/130)	69% (94/136)	69% (91/132)
MIXED	0% (0/130)	1% (2/136)	2% (3/132)
FAILURE	30% (39/130)	29% (40/136)	29% (38/132)

CURE	95% CI FOR ====DIFFERENCE====
CDTR-PI 200 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-10.1, 12.2)
CDTR-P1 400 MG VS CEFADROXIL MONOHYDRATE 500 MG	(-10.9, 11.3)
CDTR-PI 200 MG VS CDTR-PI 400 MG	(-10.2, 11.9)

Statistical Reviewer's Comments

Based on the re-analysis, the microbiological cure rates among the ITT patients at the Follow-Up Visit, similar results based on evaluable patients were obtained. The cure rates in each of these groups were; in the CDTR-PI 200 mg (70%), CDTR-PI 400 mg (69%), and CFDX-MN (69%) treatment groups (Table 6.9a). The 95% CI for microbiological cure rates demonstrated that CDTR-PI 200 mg and CDTR-PI 400 mg demonstrated equivalence compared to the comparator, using a delta 15%

SAFETY

All patients who received at least one dose of study drug (N=828) were included in the safety analyses.

Table 6.10 Summary of Common[a] Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI 200 mg BID (N=278)					CDTR-PI 400 mg BID (N=277)					CFDX-MN 500 mg BID (N=273)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				125	45%				124	45%				100	37%
BODY AS A WHOLE				44	16%				47	17%				41	15%
Headache	9	6	1	16	6%	7	6	1	14	5%	9	6	1	16	6%
Abdominal pain	6	4	1	11	4%	6	3	1	10	4%	5	0	2	7	3%
Infection	4	4	1	9	3%	6	1	0	7	3%	5	2	0	7	3%
Asthenia	0	1	1	2	1%	3	2	1	6	2%	3	1	0	4	1%
DIGESTIVE SYSTEM[#]				66	24%				82	30%				47	17%
Diarrhea[$#]	23	19	2	44	16%	41	13	4	58	21%	15	4	2	21	8%
Nausea	13	3	0	16	6%	12	1	1	14	5%	12	8	0	20	7%
Dyspepsia	4	2	0	6	2%	3	1	1	5	2%	3	5	1	9	3%
RESPIRATORY SYSTEM				10	4%				7	3%				10	4%
Rhinitis	1	2	0	3	1%	3	2	0	5	2%	1	1	0	2	1%
SKIN AND APPENDAGES				11	4%				8	3%				7	3%
Rash	1.	3	1	5	2%	2	0	0	2	1%	1	1	0	2	1%
Pruritus	1	2	0	3	1%	4	1	0	5	2%	1	2	0	3	1%
UROGENITAL SYSTEM (female)[d]				(N=138) 8	6%				(N=133) 5	4%				(N=129) 6	5%
Vaginal Moniliasis[d]	1	3	0	4	3%	2	2	1	5	4%	3	1	0	4	3%
Vaginitis[d]	1	3	0	4	3%	0	0	0	0	0%	0	1	0	1	1%

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; Mod = moderate; Sev = severe

[$] Statistically significant difference in incidence rate between CDTR-PI 200 mg and CFDX-MN, p≤0.01.

[#] Statistically significant difference in incidence rate between CDTR-PI 400 mg and CFDX-MN, p≤0.001.

[a] Adverse events occurring in ≥2% of patients in any treatment group.

[b] Table summarizes the most severe occurrence of each COSTART term from each patient.

[c] Number of patients with one or more adverse events.

[d] Gender-specific adverse event; percentage given is of females only.

Sponsor's Table

Table 6.11 Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI 200 mg BID (N=278)					CDTR-PI 400 mg BID (N=277)					CFDX-MN 500 mg BID (N=273)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c#]				88	32%				95	34%				69	25%
BODY AS A WHOLE				24	9%				25	9%				20	7%
Headache	7	4	0	11	4%	6	6	1	13	5%	5	5	1	11	4%
Abdominal pain	6	4	1	11	4%	5	3	1	9	3%	4	0	1	5	2%
DIGESTIVE SYSTEM[#]				61	22%				76	27%				43	16%
Diarrhea[$#]	23	19	2	44	16%	40	12	3	55	20%	15	4	2	21	8%
Nausea	11	3	0	14	5%	12	1	1	14	5%	10	8	0	18	7%
Dyspepsia	4	2	0	6	2%	3	1	1	5	2%	3	4	1	8	3%
UROGENITAL SYSTEM (female)[d]				(N=138) 7	5%				(N=133) 5	4%				(N=129) 5	4%
Vaginal Moniliasis[d]	1	3	0	4	3%	2	2	1	5	4%	3	1	0	4	3%
Vaginitis[d]	1	2	0	3	2%	0	0	0	0	0%	0	1	0	1	1%

CDTR-PI = cefditoren pivoxil; CFDX-MN = cefadroxil monohydrate; Mod = moderate; Sev = severe

[$] Statistically significant difference in incidence rate between CDTR-PI 200 mg and CFDX-MN, $p \leq 0.01$.

[#] Statistically significant difference in incidence rate between CDTR-PI 400 mg and CFDX-MN, $p \leq 0.05$.

[a] Adverse events occurring in ≥2% of patients in any treatment group.

[b] Table summarizes the most severe occurrence of each COSTART term from each patient.

[c] Number of patients with one or more adverse events.

[d] Gender-specific adverse event; percentage given is of females only.

Statistical Reviewer's Comments:

During treatment, the incidences of all adverse events and treatment-related adverse events were 45% and 32%, respectively, in the CDTR-PI 200 mg group, 45% and 34%, respectively, in the CDTR-PI 400 mg group, and 37% and 25%, respectively, in the CFDX-MN group (Table 6.10 and 6.11). A statistically significant difference was observed between the CDTR-PI 400 mg group and the CFDX-MN group in the incidence of treatment-related adverse events (p=0.025). The most frequently occurring treatment-related adverse events in all three treatment groups were diarrhea and nausea. In the CDTR-PI 200 mg, CDTR-PI 400 mg, and CFDX-MN groups, diarrhea was reported by 16%, 20%, and 8%, respectively, and nausea was reported by 5%, 5%, and 7%, respectively. In addition, 5% of patients in the CDTR-PI 400 mg group reported headache. A statistically significant difference was observed between each CDTR-PI group and the CFDX-MN group in the incidence of diarrhea (p≤0.004).

OVERALL SUMMARY AND CONCLUSIONS

The sponsor has designed these studies for the statistical comparison of the cefditoren 400 mg treatment group to the cefuroxime axetil 250 mg BID treatment group in study CEF-97-009 and cefadroxil monohydrate 500 mg BID treatment group in study CEF-97-011. Although the Applicant stated that the primary comparison for efficacy would be between the cefditoren pivoxil 400 mg and the comparator arm, the Applicant has made multiple comparisons between all the three treatment arms. An appropriate statistical adjustment should be used for the multiple comparisons to control the overall type-I error rate. A two-tailed 97.5% CI (maintaining the overall significance level at 0.05) of the difference in response rates with respect to the efficacy variables should be used for evaluation.

Based on the re-analysis results, in study CEF-97-009, among CDTR-PI 200 mg and CDTR-PI 400 mg group demonstrated equivalence to its comparator cefuroxime axetil 250 mg BID, if we consider using a delta of 15%.

In study, CEF-97-011, CDTR-PI 200 mg and CDTR-400 mg BID group demonstrated equivalence to cefedroxil monohydrate 500 mg BID, if we consider using a delta of 15%.

The re-analysis using the medical officer's assessment of clinical cures and improvements dropped the cure rates low for both the studies.

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