Dalgin (#12791)						
Stamford, CT	5	4 (80)	5	3 (60)	5	5 (100)
Durden (#12998)						
Tallahassee, AL	8	6 (75)	8	5 (63)	8	5 (63)
Economou (#10079)						
Albuquerque, NM	0	-	0	-	1	1 (100)
Fisher (# 2855)						
Vancouver, WA	2	2 (100)	2	2 (100)	2	2 (100)
Fogarty (# 12973)						
Spartanburg, SC	7	6 (86)	8	7 (88)	7	7 (100)
Fried (#12999)						
Providence, RI	2	1 (50)	3	1 (33)	2	2 (100)
Gooch, III (#3218)						
Salt Lake City, UT	1	1 (100)	0	-	0	-
Gotfried (#4601)						
Phoenix, AZ	4	3 (75)	4	4 (100)	3	1 (33)
Handshoe (#12974)						
Charleston, SC	4	3 (75)	3	3 (100)	3	2 (67)
Hedrick (#6141)						
Bardstown, KY	4	4 (100)	4	4 (100)	4	3 (75)
Henry (#5516)						
Salt Lake City, UT	17	14 (82)	16	14 (88)	16	13 (81)
Hernandez (#13053)						
Tampa, FL	0	-	1	1 (100)	1	1 (100)
Interiano (#9629)						
Houston, TX	0	-	1	0 (0)	1	0 (0)
Keating (#13000)						
Scotland, PA	2	1 (50)	3	1 (33)	3	3 (100)
Kelsey (#13001)						
San Diego, CA	7	5 (71)	6	4 (67)	6	3 (50)
Kraus (#4617)						
Atlanta, GA	2	1 (50)	3	2 (67)	2	2 (100)
Lewin (#1939)						
Los Angeles, CA	3	2 (67)	2	0 (0)	3	3 (100)
Lieberman (#13002)						
Franklin, TN	0	-	1	0 (0)	0	-
Maggiacomo (#12528)						
Cranston, RI	5	2 (40)	4	4 (100)	5	5 (100)
Marinelli (#12070)						
Largo, FL	1	0 (0)	0	-	0	-
Mazzone (#12964)						
San Luis Obispo, CA	0	-	1	1 (100)	1	1 (100)
McAdoo (#12957)						
Milan, TN	9	6 (67)	8	6 (75)	8	7 (88)
McLaren (#13121)						
St. Louis, MO	0	-	1	1 (100)	0	-
Menendez (#3629)						
El Paso, TX	1	0 (0)	1	1 (100)	2	2 (100)
Miskin (#12804)						
West Palm Beach, FL	4	3 (75)	3	1 (33)	4	3 (75)
Morris (#11507)						
Tulsa, OK	1	0 (0)	2	2 (100)	1	1 (100)
Mullican (#9345)						
Evansville, IN	1	1 (100)	1	0 (0)	1	1 (100)
Newcomb (#13661)						
Tuscaloosa, AL	5	2 (40)	5	4 (80)	5	3 (60)

*O'Hearn (#13122)						
Portland, OR	1	1 (100)	0	-	1	1 (100)
Page (#12958)						
Tempe, AZ	7	6 (86)	6	5 (63)	6	2 (33)
Pierone (#13006)						
Vero Beach, FL	0	-	1	1 (100)	1	1 (100)
Rhudy (#12960)						
Salt Lake City, UT	10	7 (70)	11	8 (73)	10	8 (80)
Rice (#3490)						
Minneapolis, MN	1	1 (100)	2	1 (50)	1	1 (100)
Rosemore (#13007)						
Hueytown, AL	7	3 (43)	6	5 (83)	6	5 (83)
Simon (#9773)						
Austell, GA	6	5 (83)	6	4 (67)	6	4 (67)
Spitzer(#12959)						
Kalamazoo, MI	2	1 (50)	1	1 (100)	1	0 (0)
Thomas (#12976)						
Phoenix, AZ	1	1 (100)	1	0 (0)	2	1 (50)
Thompson (#13671)						
Buffalo, NY	1	1 (100)	1	1 (100)	1	1 (100)
Tonkens (#13672)						
Henderson, NV	1	1 (100)	0	-	0	-
Upchurch (#13008)						
Birmingham, AL	11	8 (73)	12	5 (42)	12	8 (67)
Verdegem (#13009)						
Covina, CA	0	-	0	-	1	1 (100)
Wallace (#12629)						
Paducah, KY	2	2 (100)	1	1 (100)	2	1 (50)
Weissberger (#13419)						
Atlantis, FL	0	-	0	-	1	1 (100)
Williams, II (#13039)						
Trenton, TN	4	2 (50)	5	3 (60)	5	4 (80)
Wong (#2848)						
Lafayette, LA	7	2 (79)	7	4 (57)	7	4 (57)
Zekert (#12541)						
St. Louis, MO	3	3 (100)	3	3 (100)	2	2 (100)
TOTAL	**203**	**148 (72.9)**	**208**	**146 (70.2)**	**207**	**163 (78.7)**
[redacted]						
DeAbate[redacted]						
Mathew[redacted]						
[redacted]						

@CDTR-PI = cefditoren pivoxil
+CXM-AX = cefuroxime axetil
! "Enrolled" patients are equivalent to ITT patients in this study
^ Clinically Evaluable at Follow-Up Visit as per Applicant ISE data set
*Dr. Greg Coodley replaced Dr. Mary O'Hearn on 7/May/98.

MO Comment: ***DSI has confirmed that the information from the DeAbate and Mathew sites should be considered unreliable and that its exclusion from analyses is appropriate. Further details regarding the Applicant's reasons for***

excluding these sites can be found in the NDA 21,222 Amendment 016 Volume 1 of 1, June 13, 2000 submission.

It is notable that 20 of the remaining sites were also used as study sites in the second AECB pivotal study. These 20 sites enrolled 405/618 (66%) patients in this study.

****

DATA PRESENTED, BY THE APPLICANT AND THE MO, FROM THIS POINT FORWARD WILL EXCLUDE PATIENTS FROM THE DEABATE AND MATHEW SITES

****

Of the 618 patients included in the Applicant's ITT analysis 457 (148 in the CDTR-PI 200 mg group, 146 in the CDTR-PI 400 mg group, and 163 in the CXM-AX group) patients were considered clinically evaluable at the Follow-Up visit. Of the 457 patients who were clinically evaluable, 28 patients were clinically "evaluable with variation" (22 had a mistimed visit and 6 had admission criteria not met). Of the 161 patients who were not evaluable, 132 patients (44, 53, and 35 in the CDTR-PI 200 mg, CDTR-PI 400 mg, and CXM-AX groups, respectively) did not have a causative respiratory pathogen isolated pretreatment, 8 patients did not have a clinical response assessed within the specified visit window, 8 patients received additional antimicrobials, 4 patients were lost to follow-up, 4 patients were misdiagnosed, 3 patients received less than 80% of the prescribed study drug, and 2 patients received less than 3 consecutive days of study drug.

Of the 618 patients included in the Applicant's ITT analysis 459 patients were considered microbiologically evaluable (149 in the CDTR-PI 200 mg group, 146 in the CDTR-PI 400 mg group, and 164 in the CXM-AX group). Of the 459 patients who were microbiologically evaluable, 155 patients were microbiologically "evaluable with variation" (143 with pre-therapy gram stain at central lab not adequate and 12 with missed timing of visit). Reasons for microbiologic unevaluability were the same as for clinical unevaluability with two exceptions: rather than 8 patients not having a clinical response assessment within the visit window, 7 patients did not have a culture obtained within the visit window and one less patient in the CDTR-PI 200 mg arm is listed as "received additional antimicrobials".

The disposition of patients according to the Applicant is presented in Table 6. (Table 11.1a., Volume 212 of 322, page 069)

Table 6. Disposition of Patients According to the Applicant

Table 11.1a. 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[a]	203	208	207
Included in Clinically Evaluable Efficacy Analyses:			
Post-Therapy	149	144	160
Follow-Up	148	146	163
Excluded at Post-Therapy:	54	64	47
No target pathogen isolated pretreatment	44	53	35
No clinical response assessed within visit window	5	7	8
Lost to follow-up	2	1	1
Misdiagnosis	0	3	1
Received less than 80% of study drug	1	0	2
Received less than 3 consecutive days of study drug	2	0	0
Excluded at Follow-Up:	55	62	44
No target pathogen isolated pretreatment	44	53	35
No clinical response assessed within visit window	2	3	3
Received additional antimicrobials	4	2	2
Lost to follow-up	2	1	1
Misdiagnosis	0	3	1
Received less than 80% of study drug	1	0	2
Received less than 3 consecutive days of study drug	2	0	0
Included in Microbiologically Evaluable Efficacy Analyses:			
Post-Therapy	148	144	160
Follow-Up	149	146	164
Excluded at Post-Therapy:	55	64	47
No target pathogen isolated pretreatment	44	53	35
No culture obtained within visit window	6	7	8
Lost to follow-up	2	1	1
Misdiagnosis	0	3	1
Received less than 80% of study drug	1	0	2
Received less than 3 consecutive days of study drug	2	0	0
Excluded at Follow-Up:	54	62	43
No target pathogen isolated pretreatment	44	53	35
No culture obtained within visit window	2	3	2
Received additional antimicrobials	3	2	2
Lost to follow-up	2	1	1
Misdiagnosis	0	3	1
Received less than 80% of study drug	1	0	2
Received less than 3 consecutive days of study drug	2	0	0

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
[a]All data from sites #4637 and #13004 were excluded; see Section 6.0.

MO Comment: ***Six of the eight patients who received additional antimicrobials received them for infections related to the upper respiratory tract (1 with otitis media, 1 with noncultured pharyngitis, and 4 with sinusitis). Signs and symptoms of pharyngitis and sinusitis may be similar to those found in AECB. Therefore, unless these patients showed improvement or clearance of all signs and symptoms used to document their episode of AECB at the Follow-UP visit, they will be considered evaluable failures in MO analyses.***

There were two more microbiologically evaluable patients than there were clinically evaluable patients (one in the CDTR-PI 200 mg group and one in the CXM-AX group) in the Applicant's Follow-Up analyses. Since the Applicant requires a patient to be clinically evaluable to be microbiologically evaluable, these two patients should not have been microbiologically evaluable and will not be considered evaluable in the MO analyses.

The Applicant's "all patient" data set is more correctly defined as the ITT data set since it included all patients enrolled who took at least one dose of study drug. The "ITT" data set is more correctly defined as the MITT data set since it also required that patients have at least one "causative respiratory pathogen" on the pretreatment sputum sample. Patients included in the Applicant's "ITT" data set were calculated from the Applicant's ISE data base by excluding patients who had negative pretreatment sputum cultures and these results are included in Table 7.

The MO has required that that the pretreatment culture have a protocol defined "causative respiratory pathogen" (per protocol target respiratory pathogens for this study were H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, S. pneumoniae, and S. pyogenes). The MO has also required that the gram stain at the central lab to be "good," and that the patient had at least two signs or symptoms consistent with AECB to include a patient in the MITT population. These requirements have resulted in a smaller MITT population and lower overall evaluability rate in the MO's analyses, as is seen in Table 7. Of note, the MO's evaluability rates of 40-49% are more consistent with the evaluability rate of 50% predicted by the Applicant in their determination of sample size calculation, than the evaluability rates of 70-79% in the Applicant's analyses.

Table 7. Disposition of Patients According to the MO Compared to the Applicant

	@CDTR-PI 200 mg			@CDTR-PI 400 mg			+CXM-AX 250 mg		
	Enrolled	MITT	*Eval (%)	Enrolled	MITT	*Eval (%)	Enrolled	MITT	*Eval (%)
TAP	203	159	148 (73%)	208	155	146 (70%)	207	172	163 (79%)
MO	203	96	87 (43%)	208	95	83 (40%)	207	112	102 (49%)

@CDTR-PI = cefditoren pivoxil
+CXM-AX = cefuroxime axetil
*Clinically evaluable at Test-of-Cure visit (see review text for TAP and MO criteria)

The reason for the higher evaluability rate for patients in the CXM arm in both the Applicant's and MO's analyses is not clear.

3.2.1.4.2 Demographics

3.2.1.4.2.1 General Demographics

The Applicant found no statistically significant differences between treatment groups for the demographic variables of gender, age, race, weight, or height for all patients or for clinically evaluable patients. In the clinically evaluable population, fourty-four percent of the patients were males and 90% of the patients were Caucasian. The mean age of the clinically evaluable study population was 50.8 years and the median age 51 years (range from 13 to 85 years). A summary of demographic information for all patients by treatment group is presented in Table 8. (Table 11.2a., Volume 212 of 322, page 066-066) and for clinically evaluable patients by treatment group in Table 9. (modified from Table 14.1-3.2, Volume 212 of 322, pages 295-296).

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Table 8. Demographic Information for All Patients According to the Applicant

Table 11.2a. 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	203	208	207	
Gender				0.638
Female	115 (57%)	113 (54%)	122 (59%)	
Male	88 (43%)	95 (46%)	85 (41%)	
Race[b]				0.982
Caucasian	183 (90%)	188 (90%)	185 (89%)	
Black	11 (5%)	10 (5%)	14 (7%)	
Hispanic	6 (3%)	7 (3%)	5 (2%)	
Asian	1 (<1%)	2 (1%)	2 (1%)	
Other	2 (1%)	1 (<1%)	1 (<1%)	
Age (years)[c]				0.468
<45	64 (32%)	79 (38%)	71 (34%)	
45 - 65	92 (45%)	81 (39%)	87 (42%)	
>65	47 (23%)	48 (23%)	49 (24%)	
Mean (SD)	52.1 (16.6)	50.3 (17.2)	52.1 (17.1)	
Range	14 - 90	13 - 87	15 - 86	
Weight (pounds)[c]				0.826
<135	33 (16%)	38 (18%)	41 (20%)	
135 - 165	60 (30%)	57 (27%)	51 (25%)	
166 - 195	54 (27%)	50 (24%)	50 (24%)	
>195	56 (28%)	63 (30%)	65 (31%)	
Mean (SD)	178.0 (50.2)	175.3 (46.4)	175.8 (48.4)	
Range	83 - 434	90 - 340	78 - 337	
Height (inches)[c]				0.881
Mean (SD)	66.6 (4.0)	66.7 (3.9)	66.5 (4.1)	
Range	57 - 78	55 - 77	52 - 76	

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.

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Table 9. Demographic Information for Clinically Evaluable Patients According to the Applicant

Modified Table 14.1-3.2 Demographic Variables Evaluable Patients				
	Number of Patients by Treatment Group			
Demographic Characteristic	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CXM-AX 250 mg BID	P-value[a]
Total Treated	148	146	163	
Gender				
Female	77 (52%)	80 (55%)	97 (60%)	0.404
Male	71 (48%)	66 (45%)	66 (40%)	
Race[b]				
Caucasian	135 (91%)	135 (92%)	143 (88%)	0.442
Black	6 (4%)	4 (3%)	12 (7%)	
Hispanic	5 (3%)	5 (3%)	5 (3%)	
Asian	0 (0%)	2 (1%)	2 (1%)	
Other	2 (1%)	0 (0%)	1 (1%)	
Age (years)[c]				
<45	52 (35%)	57 (39%)	56 (34%)	0.824
45 - 65	69 (47%)	55 (38%)	73 (45%)	
>65	27 (18%)	34 (23%)	34 (21%)	
Mean (SD)	50.5 (16.5)	50.3 (17.5)	51.4 (16.7)	
Range	14-83	13-82	15-85	
Weight (pounds)[c]				
<135	23 (16%)	27 (18%)	29 (18%)	0.963
135 - 165	45 (30%)	40 (27%)	40 (25%)	
166 - 195	42 (28%)	32 (22%)	40 (25%)	
>195	38 (26%)	47 (32%)	54 (33%)	
Mean (SD)	178.2 (49.2)	177.5 (49.0)	179.1 (49.3)	
Range	95-434	90-340	78-337	
Height (inches)[c]				
Mean (SD)	66.6 (4.0)	66.5 (4.0)	66.5 (4.2)	0.991
Range	57-77	55-77	52-76	

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.

Statisticial Reviewer's comments: ***The Applicant's Demographic data are described for all and clinically evaluable patients in Table 8 and Table 9 and no statistically significant differences were detected for gender, age, race, weight and height between the treatment groups. The MO's reclassification of data, for the evaluable population, did not result in any statistically significant difference for the demographic variables.***

3.2.1.4.2.2 Baseline Diagnosis and Disease Characteristics

The Applicant has also examined the treatment groups by baseline diagnosis and baseline disease characteristics. In the MITT and clinically evaluable populations a statistically significant difference

was found in the number of lower respiratory tract infections (LRTIs) within the prior year, with the CDTR-PI 400 mg group having the highest percentage of patients with two to four LRTIs and the CXM-AX group having the highest percentage of patients with their first LTRI within the past year. A summary of baseline diagnosis and disease characteristics for the Applicant's MITT population is provided in Table 10. (Volume 212 of 322, page 068, Table 11.2b) and for the clinically evaluable population in Table 11. (modified from Volume 212 of 322, page 299, Table 14.1-4.2).

Table 10. Summary of Diagnoses and Baseline Characteristics for All Patients According to the Applicant

Table 11.2b. Summary of Diagnoses and Baseline Characteristics (All Patients)

Diagnoses and Baseline Characteristics	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	203	208	207	
Diagnosis				0.468
Chronic bronchitis	182 (90%)	177 (85%)	178 (86%)	
Asthmatic bronchitis	21 (10%)	29 (14%)	28 (14%)	
Missing	0 (0%)	2 (1%)	1 (<1%)	
Number of LRTIs Within Past Year				0.004**
1	37 (18%)	24 (12%)	54 (26%)	
2 - 4	138 (68%)	159 (76%)	129 (62%)	
>4	28 (14%)	25 (12%)	24 (12%)	
Infection Status				0.468
Mild	25 (12%)	31 (15%)	34 (16%)	
Moderate	174 (86%)	172 (83%)	169 (82%)	
Severe	4 (2%)	5 (2%)	3 (1%)	
Missing	0 (0%)	0 (0%)	1 (<1%)	
Clinical Condition				0.740
Good	64 (32%)	60 (29%)	67 (32%)	
Fair	135 (67%)	144 (69%)	135 (65%)	
Poor	4 (2%)	4 (2%)	4 (2%)	
Missing	0 (0%)	0 (0%)	1 (<1%)	
Smoking Status				0.640
Non-smoker	48 (24%)	51 (25%)	51 (25%)	
Smoker	92 (45%)	102 (49%)	88 (43%)	
Ex-smoker	63 (31%)	55 (26%)	68 (33%)	
Alcohol Use				0.484
Non-drinker	108 (53%)	109 (52%)	103 (50%)	
Drinker	80 (39%)	74 (36%)	85 (41%)	
Ex-drinker	15 (7%)	25 (12%)	19 (9%)	

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

** Indicates statistical significance at the 0.01 level.

[a] P-values are from Chi-square test for diagnosis, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status, clinical condition, and number of LRTIs within the past year.

Table 11. Summary of Diagnoses and Baseline Characteristics for Clinically Evaluable Patients According to the Applicant

Modified Table 14.1-4.2. Baseline Characteristics Evaluable Patients				
	Number of Patients by Treatment Group			
Diagnoses and Baseline Characteristics	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CXM-AX 250 mg BID	P-value[a]
Total Treated	148	146	163	
Diagnosis				0.501
Chronic bronchitis	133 (90%)	130 (89%)	139 (85%)	
Asthmatic bronchitis	15 (10%)	16 (11%)	23 (14%)	
Missing	0 (0%)	0 (0%)	1 (1%)	
Number of LRTIs Within Past Year				0.007**
1	24 (16%)	18 (12%)	46 (28%)	
2 - 4	105 (71%)	111 (76%)	99 (61%)	
>4	19 (13%)	17 (12%)	18 (11%)	
Infection Status				0.591
Mild	19 (13%)	25 (17%)	26 (16%)	
Moderate	125 (84%)	117 (80%)	134 (82%)	
Severe	4 (3%)	4 (3%)	3 (2%)	
Missing	0 (0%)	0 (0%)	0 (0%)	
Clinical Condition				0.961
Good	49 (33%)	45 (31%)	53 (33%)	
Fair	96 (65%)	99 (68%)	106 (65%)	
Poor	3 (2%)	2 (1%)	4 (2%)	
Missing	0 (0%)	0 (0%)	0 (0%)	
Smoking Status				0.812
Non-smoker	36 (24%)	35 (24%)	43 (26%)	
Smoker	65 (44%)	70 (48%)	67 (41%)	
Ex-smoker	47 (32%)	41 (28%)	53 (33%)	
Alcohol Use				0.831
Non-drinker	74 (50%)	77 (53%)	79 (48%)	
Drinker	62 (42%)	54 (37%)	66 (40%)	
Ex-drinker	12 (8%)	15 (10%)	18 (11%)	

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

** Indicates statistical significance at the 0.01 level.

[a] P-values are from Chi-square test for diagnosis, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status, clinical condition, and number of LRTIs within the past year.

***MO Comment:* The significantly higher frequency of more than one LRTI in the prior year seen in the CDTR-PI 400 mg group may be clinically significant because, it may predict a greater tendency toward relapse in this group.**

3.2.1.4.2.3 Pretreatment Signs and Symptoms

The Applicant also analyzed pretreatment signs and symptoms (sputum appearance, sputum volume, cough, dyspnea, fever, rales, rhonchi, wheeze, and cyanosis) in the MITT and clinically evaluable populations and found no statistically significant differences between treatment groups with the exception of rales (p=0.046) in the MITT population; 20% of the CDTR-PI 200 mg group, 12% of the CDTR-PI 400 mg group, and 13% of the CXM-AX group demonstrated rales at pretreatment.

MO Comment: ***Although the finding of rales on physical exam may be associated with the diagnosis of pneumonia, pneumonia was excluded in the pivotal studies based on the requirement for a negative CXR at baseline.***

3.2.1.4.2.4 Concurrent Medications

According to the Applicant, 92% of the patients in the CDTR-PI 200 mg group, 94% of the patients in the CDTR-PI 400 mg group, and 96% of the patients in the CXM-AX group used concurrent medications during the study. The high incidence of concurrent medications during the study resulted from use of medications generally administered for treatment of fevers, coughs, colds, and other symptoms associated with bronchitis, as well as the use of oral contraceptives and hormone replacement therapy among female patients. A summary of concurrent medication use is provided in Table 12. (Volume 212 of 322, page 072, Table 11.2d).

Table 12. Summary of Commonly Used Concurrent Medications in All Patients According to the Applicant

Table 11.2d. Summary of Commonly Used Concurrent Medications (All Patients)

Therapeutic Subclassification	CDTR-PI 200 mg BID (N=203)	CDTR-PI 400 mg BID (N=208)	CXM-AX 250 mg BID (N=207)
Anti-asthmatics (e.g. [redacted] theophylline, salmeterol xinafoate)	92 (45%)	114 (55%)	123 (59%)
Corticosteroids for systemic use (e.g., prednisone, beclomethasone [redacted] triamcinolone acetonide)	78 (38%)	71 (34%)	77 (37%)
Analgesics (e.g., acetylsalicylic acid, [redacted])	74 (36%)	77 (37%)	75 (36%)
Cough and cold preparations (e.g., guaifenesin, [redacted] hydrocodone)	70 (34%)	74 (36%)	74 (36%)
Anti-inflammatory and antirheumatic products (e.g., ibuprofen, naproxen)	44 (22%)	48 (23%)	47 (23%)
Sex hormones and modulators of the genital system (e.g., conjugated estrogens, medroxyprogesterone acetate)	40 (20%)	38 (18%)	45 (22%)
Antacids, drugs for treatment of peptic ulcer and flatulence (e.g., ranitidine HCl, omeprazole, cimetidine)	33 (16%)	35 (17%)	45 (22%)
Antibacterials for systemic use (e.g. [redacted] clarithromycin, levofloxacin)	41 (20%)	32 (15%)	38 (18%)
Psycholeptics (e.g. [redacted] diazepam)	39 (19%)	34 (16%)	37 (18%)
Nasal preparations (e.g., Respaire-SR-120, pseudoephedrine)	36 (18%)	35 (17%)	34 (16%)
Psychoanaleptics (e.g., [redacted])	33 (16%)	36 (17%)	34 (16%)
Antihistamines for systemic use (e.g., loratadine, fexofenadine HCl)	28 (14%)	35 (17%)	33 (16%)
Diuretics (e.g., furosemide)	24 (12%)	26 (13%)	27 (13%)
Agents acting on the renin-angiotensin system (e.g., lisinopril, enalapril maleate)	31 (15%)	21 (10%)	24 (12%)
Calcium channel blockers (e.g., [redacted] nifedipine)	17 (8%)	25 (12%)	27 (13%)

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

Twenty percent of the patients in the CDTR-PI 200 mg group, 15% of the patients in the CDTR-PI 400 mg group, and 18% of the patients in the CXM-AX group reported use of other systemic antibacterials, which according to the Applicant were generally prescribed subsequent to failing treatment or at the end of the study.

Per the Applicant, of patients that were considered clinically evaluable, 1 patient in the CDTR-PI 200 mg group received additional antimicrobials for the current infection and was considered a clinical failure at the Post-Therapy Visit; 2 patients in the CDTR-PI 200 mg group and 1 patient in the CXM-AX group, received additional antimicrobials for the current infection after the Post-Therapy Visit and were considered clinical failures at the Follow-Up Visit.

3.2.1.4.2.5 Pretreatment Susceptibility Results

Susceptibility results were generally similar for the two study drugs with one exception, of 60 *S. pneumoniae* isolates, none were resistant to cefditoren (based on MICs proposed by the Applicant) and 10 were resistant to cefuroxime. Pretreatment susceptibilities to cefditoren pivoxil and cefuroxime axetil for the target pathogens are presented in Table 13. (Volume 212 of 322, page 075, Table 11.2f.).

Table 13. Pretreatment Susceptibility Results for Target Pathogens According to the Applicant

Table 11.2f. Pretreatment Susceptibility Results for Target Pathogens

	Cefditoren Susceptibility				Cefuroxime Susceptibility				
Target Pathogen	**S**	**I**	**R**	**U**	**S**	**I**	**R**	**U**	**TOTAL**
H. parainfluenzae	336	0	0	0	335	1	0	0	336
H. influenzae	134	0	1	2	133	1	1	2	137
M. catarrhalis	73	0	0	0	72	1	0	0	73
S. pneumoniae	59	1	0	0	50	0	10	0	60
S. aureus	37	1	1	0	37	1	1	0	39
S. pyogenes	4	0	0	0	N/A	N/A	N/A	N/A	4

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

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

Susceptibility results were also assessed for selected pathogens by penicillinase production and oxacillin and/or penicillin resistance. These results are summarized in Table 14. (Volume 212 of 322, page 076, Table 11.2g.).

Table 14. Pretreatment Susceptibility Results for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Target Pathogens According to the Applicant

Table 11.2g. Pretreatment Susceptibility Results for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Target Pathogens

	Cefditoren Susceptibility			Cefuroxime Susceptibility			
	S	I	R	S	I	R	TOTAL
Penicillinase-Producing Pathogens							
H. influenzae	41	0	1	40	1	1	42
H. parainfluenzae	22	0	0	21	1	0	22
M. catarrhalis	58	0	0	57	1	0	58
S. aureus	33	1	1	33	1	1	35
Oxacillin-Resistant Pathogens							
S. aureus	2	1	1	2	1	1	4
Penicillin-Resistant Pathogens							
S. aureus	32	1	1	32	1	1	34
S. pneumoniae	5	1	0	0	0	6	6

S = susceptible; I = intermediate; R = resistant
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

3.2.1.4.2.6 Treatment Compliance

According to the Applicant, there was no statistically significant difference in treatment duration or study drug compliance between the three treatment groups in either the all patient or evaluable patient population. Duration of treatment and drug compliance, for the clinically evaluable patient population, are presented in Table 15. (Volume 212 of 322, page 077, Table 11.3a.).

Table 15. Duration of Treatment and Study Drug Compliance for Evaluable Patients According to the Applicant

Table 11.3a. Duration of Treatment and Study Drug Compliance (Evaluable Patients)

	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CXM-AX 250 mg BID		P-value[a]
Total Treated	148		146		163		
Treatment Duration (days)							0.682
<4	4	(3%)	1	(1%)	2	(1%)	
4 - 7	5	(3%)	6	(4%)	5	(3%)	
8 - 10	111	(75%)	112	(77%)	131	(80%)	
>10	28	(19%)	27	(18%)	25	(15%)	
Mean (SD)	9.8	(1.7)	9.9	(1.3)	10.0	(1.3)	
Min - Max							
Compliance[b] (percentage)							0.403
<80	10	(7%)	8	(5%)	7	(4%)	
80 - 90	8	(5%)	12	(8%)	7	(4%)	
>90	130	(88%)	126	(86%)	149	(91%)	
Mean (SD)	94.9	(16.9)	96.1	(12.7)	97.0	(12.1)	
Min - Max							

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

[a] P-value for F-test for testing equality of treatment means.

[b] For patients who did not return study drug containers, compliance was calculated using the number of days on treatment.

3.2.1.4.3 Efficacy

3.2.1.4.3.1 Clinical Efficacy

According to the Applicant, the primary outcome endpoint was clinical cure rate in the clinically evaluable population and outcome in the MITT population was considered supportive data.

Clinical cure rates in the evaluable population at the Post-Therapy Visit were 88% in the CDTR-PI 200 mg group, 89% in the CDTR-PI 400 mg group, and 89% in the CXM-AX group. The 95% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-8.5, 5.6), between patients treated with CDTR-PI 400 mg and CXM-AX was (-7.5, 6.5), and between patients treated with CDTR-PI 200 mg and 400 mg was (-8.3, 6.4).

Clinical cure rates in the evaluable population at the Follow-Up Visit were 80% in the CDTR-PI 200 mg group, 86% in the CDTR-PI 400 mg group, and 80% in the CXM-AX group. The 95% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-9.0, 8.9), between patients treated with CDTR-PI 400 mg and CXM-AX was (-2.5, 14.3), and between patients treated with CDTR-PI 200 mg and 400 mg was (-14.5, 2.7).

The Applicant's tabulations of clinical efficacy in the MITT population and the clinically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 16.

Table 16. Clinical Response at the Post-Therapy and Follow-Up Visits According to the Applicant

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Post-Therapy MITT Cures	132/159	(83%)	130/155	(84%)	146/172	(85%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		0.656		[-9.8, 6.1]		
CDTR-PI 400 mg vs CXM-AX		0.879		[-8.9, 6.9]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.880		[-9.1, 7.4]		
Post-Therapy Evaluable Cures	131/149	(88%)	128/144	(89%)	143/160	(89%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		0.722		[-8.5, 5.6]		
CDTR-PI 400 mg vs CXM-AX		>0.999		[-7.5, 6.5]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.856		[-8.3, 6.4]		
Follow-Up MITT Cures	121/159	(76%)	128/155	(83%)	135/172	(78%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		0.694		[-11.4, 6.6]		
CDTR-PI 400 mg vs CXM-AX		0.403		[-4.5, 12.7]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.166		[-15.4, 2.4]		
Follow-Up Evaluable Cures	118/148	(80%)	125/146	(86%)	130/163	(80%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		>0.999		[-9.0, 8.9]		
CDTR-PI 400 mg vs CXM-AX		0.181		[-2.5, 14.3]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.218		[-14.5,2.7]		

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] P-value for comparison between treatment groups using Fisher's exact test.
[b] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

MO Comment: ***Although the Applicant stated the primary comparison for efficacy would be between the cefditoren pivoxil 400 mg arm and the comparator arm, the Applicant has made multiple comparisons between the three treatment arms without apply an appropriate statistical adjustment for multiple comparisons (potentially inflating the Type I Error). If only the CDTR-PI 400 mg is considered, the Applicant's cure rate, in the clinically evaluable***

population at Follow-Up demonstrates equivalence to an approved comparator (using a delta of 10%). A display of the Applicant's data incorporating an appropriate adjustment for multiple comparisons for the evaluable population at Follow-Up is displayed in Table 17. Based on the adjusted analysis the CDTR-PI 400 mg group still demonstrates equivalence to an approved comparator (using a delta of 10%). However, the CDTR-PI 200 mg and CDTR-PI 400 mg groups do not demonstrate equivalence (CI, –15.7, 4.0).

Table 17. Clinical Response in Clinically Evaluable Patients at the Follow-Up Visit According to the Applicant Using 97.5% CI to Adjust for Multiple Comparisons

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Follow-Up Evaluable Cures	118/148	(80%)	125/146	(86%)	130/163	(80%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-10.3, 10.2]			
CDTR-PI 400 mg vs CXM-AX			[-3.7, 15.5]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-15.7, 4.0]			

When the Applicant's data was reanalyzed (by the FDA Biostatistics reviewer) applying the evaluability and outcome criteria defined by the MO, clinical cure rates in the evaluable population at the Post-Therapy Visit were 76% (66/87) in the CDTR-PI 200 mg group, 80% (66/83) in the CDTR-PI 400 mg group, and 76% (78/102) in the CXM-AX group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-14.6, 13.3), between patients treated with CDTR-PI 400 mg and CXM-AX was (-10.6, 16.7), and between patients treated with CDTR-PI 200 mg and 400 mg was (-18.0, 10.6).

Clinical cure rates, according to the MO, in the evaluable population at the Follow-Up Visit were 43% (37/87) in the CDTR-PI 200 mg group, 55% (46/83) in the CDTR-PI 400 mg group, and 45% (46/102) in the CXM-AX group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-18.8, 13.7), between patients treated with CDTR-PI 400 mg and CXM-AX was (--6.2, 26.8), and between patients treated with CDTR-PI 200 mg and 400 mg was (-29.9, 4.15).

The confidence interval around the difference in efficacy rates, in the MO's evaluable population at Follow-Up, between the CDTR-PI 400 mg group and the CXM-AX group suggests equivalence. However, the total population available for the MO's analyses was dramatically reduced primarily due to the MO's requirement that the gram stain at the central lab be read as "good," resulting in a study that is grossly underpowered.

The MO's tabulations of clinical efficacy in the MITT population and the clinically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 18.

Table 18. Clinical Response at the Post-Therapy and Follow-Up Visits According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Post-Therapy MITT Cures	71/96	(74%)	71/95	(75%)	85/112	(75%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-14.6, 12.6]			
CDTR-PI 400 mg vs CXM-AX			[-13.8, 13.3]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-14.9, 13.4]			
Post-Therapy Evaluable Cures	66/87	(76%)	66/83	(80%)	78/102	(77%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-14.6, 13.3]			
CDTR-PI 400 mg vs CXM-AX			[-10.6, 16.7]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-18.0, 10.6]			
Follow-Up MITT Cures	38/96	(40%)	46/95	(48%)	50/112	(45%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-20.4, 10.3]			
CDTR-PI 400 mg vs CXM-AX			[-11.8, 19.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-24.9, 7.2]			
Follow-Up Evaluable Cures	37/87	(43%)	46/83	(55%)	46/102	(45%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-18.8, 13.7]			
CDTR-PI 400 mg vs CXM-AX			[-6.2, 26.8]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-29.9, 4.2]			

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons

<u>Statistical Reviewer's Comment:</u> The Applicant's ITT(MITT) population was reclassified by excluding patients who had negative pretreatment sputum sample with at least one protocol defined respiratory pathogen and the gram stain at the central lab to be "good" and that the patient had at least two pre-treatment signs or symptoms.

There is substantial reduction in the evaluability rate compared to the applicant's analyses after the reclassification. The percentage of the clinically evaluable subjects at the test-of-cure visit is 43% in CDTR-PI 200 mg group, 40% in CDTR-PI 400 mg group and 49% in CXM-AX 250 mg group as given in Table 7. The applicant has used three treatment arm comparisons and an appropriate statistical adjustment should be used for the multiple comparisons to control the overall type-I error rate.

At the follow-up visit, the evaluable cure rates were substantially low given in Table 18 and the 97.5% CI for the patients treated with CDTR-PI 200 mg and CXM-AX 250 mg was (-18.8, 13.7); CDTR-PI 400 mg and CXM-AX 250 mg was (-6.2, 26.8) and CDTR-PI 200 mg and 400 mg was (-29.9, 4.2). Though using a delta of 10%, we could conclude that CDTR-PI 400 mg and the comparator CXM-AX 250 mg demonstrates similarity, it is of great concern to the reviewer over the drop in cure rates.

3.2.1.4.3.2 Microbiologic Efficacy

According to the Applicant, microbiologic cure rates in the evaluable population at the Post-Therapy Visit were 80% in the CDTR-PI 200 mg group, 76% in the CDTR-PI 400 mg group, and 78% in the CXM-AX group. The 95% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-6.9, 11.4), between patients treated with CDTR-PI 400 mg and CXM-AX was (-10.6, 8.4), and between patients treated with CDTR-PI 200 mg and 400 mg was (-6.1, 12.8).

Microbiologic cure rates in the evaluable population at the Follow-Up Visit were 66% in the CDTR-PI 200 mg group, 72% in the CDTR-PI 400 mg group, and 70% in the CXM-AX group. The 95% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-14.0, 6.6), between patients treated with CDTR-PI 400 mg and CXM-AX was (-8.3, 11.9), and between patients treated with CDTR-PI 200 mg and 400 mg was (-16.0, 5.0).

The Applicant's tabulations of microbiologic efficacy in the MITT population and the microbiologically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 19. (modified from Volume 212 of 322, page 084-Table 11.4c., page 087-Table 11.4d and Volume 213 of 322, page 086-Table 14.2-6.2 and page 115-Table 14.2-7.2).

Table 19. Microbiologic Response at the Post-Therapy and Follow-Up Visits According to the Applicant

Microbiologic Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Post-Therapy MITT Cures	119/159	(75%)	113/155	(73%)	127/172	(74%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		0.900		[-8.4, 10.4]		
CDTR-PI 400 mg vs CXM-AX		0.900		[-10.5, 8.7]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.702		[-7.8, 11.7]		
Post-Therapy Evaluable Cures	118/148	(80%)	110/144	(76%)	124/160	(78%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		0.678		[-6.9, 11.4]		
CDTR-PI 400 mg vs CXM-AX		0.892		[-10.6, 8.4]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.572		[-6.1, 12.8]		
Follow-Up MITT Cures	103/159	(65%)	109/155	(70%)	120/172	(70%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		0.350		[-15.1, 5.1]		
CDTR-PI 400 mg vs CXM-AX		>0.999		[-9.4,10.5]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.335		[-15.9, 4.8]		
Follow-Up Evaluable Cures	99/149	(66%)	105/146	(72%)	115/164	(70%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CXM-AX		0.543		[-14.0, 6.6]		
CDTR-PI 400 mg vs CXM-AX		0.802		[-8.3, 11.9]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.317		[-16.0, 5.0]		

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[a] P-value for comparison between treatment groups using Fisher's exact test.
[b] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

MO Comment: ***Although the Applicant stated the primary comparison for efficacy would be between the cefditoren pivoxil 400 mg arm and the comparator arm, the Applicant has made multiple comparisons between the three treatment arms without apply an appropriate statistical adjustment for multiple comparisons (potentially inflating the Type I Error). If only the CDTR-PI 400 mg is considered, the Applicant's cure rate, in the microbiologically evaluable population at Follow-Up demonstrates equivalence to an approved comparator (using a delta of 10%). A display of the Applicant's data incorporating an appropriate adjustment for multiple comparisons for the***

evaluable population at Follow-Up is displayed in Table 20. Based on the adjusted analysis the CDTR-PI 400 mg group still demonstrates equivalence to an approved comparator (using a delta of 10%). However, the CDTR-PI 200 mg does not demonstrate equivalence to either the CXM-AX group (CI, -15.5, 8.1) or the CDTR-PI 400 mg group (CI, -17.5 ,6.6).

Table 20. Microbiologic Response in Microbiologically Evaluable Patients at the Follow-Up Visit According to the Applicant Using 97.5% CI to Adjust for Multiple Comparisons

Microbiologic Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Follow-Up Evaluable Cures	99/149	(66%)	105/146	(72%)	115/164	(70%)
Comparison of Cure Rates	**97.5% CI for Difference in Cure Rate[b]**					
CDTR-PI 200 mg vs CXM-AX	[-15.5, 8.1]					
CDTR-PI 400 mg vs CXM-AX	[-9.8, 13.4]					
CDTR-PI 200 mg vs CDTR-PI 400 mg	[-17.5, 6.6]					

When the Applicant's data was reanalyzed (by the FDA Biostatistics reviewer) applying the evaluability and outcome criteria defined by the MO, microbiologic cure rates in the evaluable population at the Post-Therapy Visit were 75% (65/87) in the CDTR-PI 200 mg group, 72% (59/82) in the CDTR-PI 400 mg group, and 73% (74/101) in the CXM-AX group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-12.9, 15.8), between patients treated with CDTR-PI 400 mg and CXM-AX was (-16.2, 13.6), and between patients treated with CDTR-PI 200 mg and 400 mg was (-12.5, 18.0).

Microbiologic cure rates, according to the MO's criteria, in the evaluable population at the Follow-Up Visit were 40% (34/86) in the CDTR-PI 200 mg group, 48% (40/83) in the CDTR-PI 400 mg group, and 45% (46/102) in the CXM-AX group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CXM-AX was (-21.7, 10.6), between patients treated with CDTR-PI 400 mg and CXM-AX was (-13.4, 19.6), and between patients treated with CDTR-PI 200 mg and 400 mg was (-25.7, 8.4).

The confidence intervals around the difference in efficacy rates, in the MO's evaluable population at Follow-Up, between the CDTR-PI 200 mg group or the CDTR-PI 400 mg group and the CXM-AX group does not suggest equivalence (if a delta of 10% is required). However, as previously noted, the total population available for the MO's analyses was dramatically reduced primarily due to the MO's requirement that the gram stain at the central lab be read as "good," resulting in a study that is grossly underpowered.

The MO's tabulations of microbiologic efficacy in the MITT population and the microbiologically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 21.

Table 21. Microbiologic Response at the Post-Therapy and Follow-Up Visits According to the MO

Microbiologic Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
Post-Therapy MITT Cures	66/96	(69%)	60/90	(63%)	77/112	(69%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-14.5, 14.5]			
CDTR-PI 400 mg vs CXM-AX			[-20.4, 9.2]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-9.8, 20.9]			
Post-Therapy Evaluable Cures	65/87	(75%)	59/82	(72%)	74/101	(73%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-12.9, 15.8]			
CDTR-PI 400 mg vs CXM-AX			[-16.2, 13.6]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-12.5, 18.0]			
Follow-Up MITT Cures	34/96	(35%)	40/95	(42%)	50/112	(45%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-24.4, 6.0]			
CDTR-PI 400 mg vs CXM-AX			[-18.0, 12.9]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-22.5, 9.1]			
Follow-Up Evaluable Cures	34/86	(40%)	40/83	(48%)	46/102	(45%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CXM-AX			[-21.7, 10.6]			
CDTR-PI 400 mg vs CXM-AX			[-13.4, 19.6]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-25.7, 8.4]			

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[b] The 97.5% CI for the difference in microbiologic cure rates was used to adjust for multiple comparisons

<u>Statistical Reviwer's comments:</u> The applicant's analysis results of the Microbiologic responses at the post-therapy and follow-up are given in table 19. Appropriate multiplicity adjustments were applied as before for the three treatment arm comparisons, Based on the results we can conclude that CDTR-PI 400 mg group demonstrates equivalence to the comparator CXM-AX 250 mg group. The CDTR-PI 200 mg group failed to show any similarity to both the comparators CDTR-PI 400 mg and CXM-AX 250 mg, using a delta of 10%.

The data was re-analyzed for the post therapy and follow up visits after applying the evaluability and outcome criteria in consultation with the medical officer and the analyses results are given in table 21. As we would notice from the table that the cure rates and the number of patients were considerably reduced after the reclassification criteria was applied. Multiplicity adjustments were applied to controll the overall type-I error rate.

Based on the microbiologic cure rates and the 97.5% confidence intervals for the difference in rates in the evaluable and MITT population at follow-up, neither CDTR-PI 200 mg nor the CDTR-PI 400 mg demonstrated equivalence to the approved comparator CXM-AX 250 mg, if we consider using a delta of 10%.

3.2.1.4.3.3 Pathogen Eradication Rates

According to the Applicant, no statistically significant pairwise differences were observed in overall pathogen eradication rates at the Post-Therapy or Follow-Up visits. Of all causative respiratory pathogens isolated at pretreatment, 83% were eradicated in the CDTR-PI 200 mg group, 80% were eradicated in the CDTR-PI 400 mg group, and 81% were eradicated in the CXM-AX group at the Post-Therapy visit. Of all causative respiratory pathogens isolated at pretreatment, 71% were eradicated in the CDTR-PI 200 mg group, 76% were eradicated in the CDTR-PI 400 mg group, and 75% were eradicated in the CXM-AX group at the Follow-Up visit. Pathogen eradication rates for the microbiologically evaluable population are displayed in Table 22. (modified from Volume 212 of 322, page 089-Table 11.4e and page 092-Table 11.4g).

Table 22. Eradication Rates for Target Pathogens at the Post-Therapy and Follow-Up Visits in the Microbiologically Evaluable Population According to the Applicant.

Post-Therapy Visit						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CXM-AX 250 mg BID n/N (%)**	
OVERALL	170/204	(83%)	163/203	(80%)	175/215	(81%)
**H. influenzae*	35/39	(90%)	36/47	(77%)	39/43	(91%)
**H. parainfluenzae*	83/106	(78%)	81/101	(80%)	78/108	(72%)
**M. catarrhalis*	17/20	(85%)	18/21	(86%)	27/28	(96%)
**S. aureus*	13/15	(87%)	9/9	(100%)	9/11	(82%)
**S. pneumoniae*	16/17	(94%)	15/18	(83%)	17/19	(89%)
S. pyogenes	1/1	(100%)	3/3	(100%)	0/0	
Other Pathogens[a]	5/6	(83%)	1/4	(25%)	5/6	(83%)
Comparison of Overall Eradication Rates						
CDTR-PI 200 mg vs CXM-AX			0.443			
CDTR-PI 400 mg vs CXM-AX			0.611			
CDTR-PI 200 mg vs CDTR-PI 400 mg			0.804			

Follow-Up Visit						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CXM-AX 250 mg BID n/N (%)**	
OVERALL	147/206	(71%)	158/207	(76%)	164/220	(75%)
**H. influenzae*	31/42	(74%)	32/46	(70%)	33/41	(80%)
**H. parainfluenzae*	73/105	(70%)	81/104	(78%)	76/112	(68%)
**M. catarrhalis*	16/20	(80%)	19/23	(83%)	23/29	(79%)
**S. aureus*	9/15	(60%)	8/9	(89%)	9/11	(82%)
**S. pneumoniae*	13/18	(72%)	14/18	(78%)	18/21	(86%)
S. pyogenes	1/1	(100%)	3/3	(100%)	0/0	
Other Pathogens[a]	4/5	(80%)	1/4	(25%)	5/6	(83%)
Comparison of Overall Eradication Rates			**P-value[b]**			
CDTR-PI 200 mg vs CXM-AX			0.264			
CDTR-PI 400 mg vs CXM-AX			0.513			
CDTR-PI 200 mg vs CDTR-PI 400 mg			0.736			

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment
[a] Include *Haemophilus parahaemolyticus, Klebsiella pneumoniae, Neisseria meningitidis,* and *Streptococcus agalactiae.*
[b] P-value for comparison between treatment groups using Fisher's exact test.
* Pathogens sought in the label.

The Applicant also assessed eradication rates for selected pathogens classified by pretreatment penicillinase production, oxacillin resistance and/or penicillin resistance at the Post-Therapy and Follow-Up visits. Eradication rates were similar among the three treatment groups; however, for penicillinase-producing *H. parainfluenzae*, the eradication rates in the CDTR-PI 400 mg group (90-91%) were higher than in the other two groups (50%) at

the Post-Therapy and Follow-Up visits. Pathogen eradication rates for selected resistant pathogens in the microbiologically evaluable population are displayed in Table 23. (modified from Volume 212 of 322, page 090-Table 11.4f and page 093-Table 11.4h).

Statistical Reviwer's comments:
The sponsor has reported p-value in Table 22 and that is incorrect in equivalence trials. Also, each patient may have multiple pathogens and the observations cannot be treated as independent.

Table 23. Eradication Rates for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Pathogens at the Post-Therapy and Follow-Up Visits in Microbiologically Evaluable Patients According to the Applicant

Post-Therapy Visit						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CXM-AX 250 mg BID n/N (%)**	
Penicillinase-Producing Pathogens						
H. influenzae	13/14	(93%)	13/17	(76%)	9/10	(90%)
H. parainfluenzae	3/6	(50%)	9/10	(90%)	2/4	(50%)
M. catarrhalis	12/14	(86%)	14/16	(88%)	25/25	(100%)
S. aureus	12/14	(86%)	7/7	(100%)	8/10	(80%)
Oxacillin-Resistant Pathogens						
S. aureus	1/1	(100%)	3/3	(100%)	0/0	
Penicillin-Resistant Pathogens						
S. aureus	11/13	(85%)	7/7	(100%)	8/10	(80%)
S. pneumoniae	1/1	(100%)	2/2	(100%)	3/3	(100%)
Follow-Up Visit						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CXM-AX 250 mg BID n/N (%)**	
Penicillinase-Producing Pathogens						
H. influenzae	11/14	(79%)	11/16	(69%)	8/10	(80%)
H. parainfluenzae	3/6	(50%)	10/11	(91%)	2/4	(50%)
M. catarrhalis	11/14	(79%)	15/18	(83%)	21/26	(81%)
S. aureus	9/15	(60%)	7/8	(88%)	8/10	(80%)
Oxacillin-Resistant Pathogens						
S. aureus	1/1	(100%)	3/3	(100%)	0/0	
Penicillin-Resistant Pathogens						
S. aureus	8/14	(57%)	7/8	(88%)	8/10	(80%)
S. pneumoniae	0/1	(0%)	1/1	(100%)	3/3	(100%)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment

MO Comment: ***When the Applicant's data was reanalyzed (by the FDA Biostatistics reviewer) applying the evaluability and outcome criteria defined by the MO, overall pathogen eradication rates in the microbiologically evaluable population were 77% (132/172) in the CDTR-PI 200 mg group, 77% (127/165) in the CDTR-PI 400 mg group, and 76% (156/206) in the CXM-AX group at the Post-Therapy Visit and 65% (108/166) in the CDTR-PI 200 mg group, 73% (125/165) in the CDTR-PI 400 mg group, and 70% (142/203) in the CXM-AX***

group at the Follow-Up visit. Although the numbers are small, eradication rates for S. aureus appear better in both the CDTR-PI groups than in the CXM-AX group and for penicillin-resistant S. pneumoniae better in the CXM-AX group than either CDTR-PI group. Pathogen eradication rates, according to the MO, for the microbiologically evaluable population are displayed in Table 24. Eradication rates for selected resistant pathogens, according to the MO, in the microbiologically evaluable population are displayed in Table 25.

Table 24. Eradication Rates for Target Pathogens at the Post-Therapy and Follow-Up Visits in the Microbiologically Evaluable Population According to the MO.

Post-Therapy Visit

Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
OVERALL	132/172	(77%)	127/165	(77%)	156/206	(76%)
**H. influenzae*	29/34	(85%)	28/37	(76%)	40/43	(93%)
**H. parainfluenzae*	62/91	(68%)	66/86	(77%)	74/112	(66%)
**M. catarrhalis*	15/17	(88%)	17/21	(81%)	23/26	(89%)
**S. aureus*	10/11	(91%)	5/6	(83%)	5/8	(63%)
**S. pneumoniae*	15/18	(83%)	8/12	(67%)	14/17	(82%)
S. pyogenes	1/1	(100%)	3/3	(100%)	0/0	-
Other Pathogens[a]	-		-		-	

Follow-Up Visit

Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
OVERALL	108/166	(65%)	121/165	(73%)	142/203	(70%)
**H. influenzae*	24/36	(67%)	25/37	(66%)	34/40	(85%)
**H. parainfluenzae*	54/84	(65%)	65/86	(76%)	71/111	(64%)
**M. catarrhalis*	13/17	(76%)	17/22	(77%)	19/26	(73%)
**S. aureus*	5/11	(45%)	5/5	(100%)	5/7	(71%)
**S. pneumoniae*	11/17	(65%)	6/12	(50%)	13/19	(68%)
S. pyogenes	1/1	(100%)	3/3	(100%)	0/0	-
Other Pathogens[a]	-	-	-	-	-	-

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment
[a] Not included in MO analysis
[b] P-value for comparison between treatment groups using Fisher's exact test.
* Pathogens sought in the label.

Table 25. Eradication Rates for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Pathogens at the Post-Therapy and Follow-Up Visits in Microbiologically Evaluable Patients According to the MO

Post-Therapy Visit						
	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CXM-AX 250 mg BID	
Pre-Therapy Pathogen	n/N (%)		n/N (%)		n/N (%)	
Penicillinase-Producing Pathogens						
H. influenzae	14/16	(88%)	8/11	(73%)	9/12	(75%)
H. parainfluenzae	0/4	(0%)	9/9	(100%)	4/9	(44%)
M. catarrhalis	12/13	(92%)	13/16	(81%)	22/24	(92%)
S. aureus	10/11	(91%)	3/3	(100%)	5/8	(63%)
Oxacillin-Resistant Pathogens						
S. aureus	1/1	(100%)	2/2	(100%)	0/1	(0%)
Penicillin-Resistant Pathogens						
S. aureus	10/11	(91%)	3/3	(100%)	4/7	(57%)
S. pneumoniae	2/3	(67%)	0/1	(0%)	3/3	(100%)
Follow-Up Visit						
	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CXM-AX 250 mg BID	
Pre-Therapy Pathogen	n/N (%)		n/N (%)		n/N (%)	
Penicillinase-Producing Pathogens						
H. influenzae	11/14	(80%)	7/11	(64%)	9/11	(82%)
H. parainfluenzae	0/3	(0%)	10/10	(100%)	4/6	(67%)
M. catarrhalis	10/13	(77%)	13/17	(77%)	18/24	(75%)
S. aureus	5/11	(46%)	3/3	(100%)	5/7	(71%)
Oxacillin-Resistant Pathogens						
S. aureus	1/1	(100%)	2/2	(100%)	0/0	-
Penicillin-Resistant Pathogens						
S. aureus	5/11	(46%)	3/3	(100%)	4/6	(67%)
S. pneumoniae	0/2	(0%)	0/0	-	3/3	(100%)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment

3.2.1.4.3.4 Secondary Efficacy Variables

According to the Applicant, there were no statistically significant pairwise differences in the percentage of evaluable patients showing resolution and improvement in sputum volume, cough, dyspnea, or resolution in fever, rales, rhonchi, wheezes, or cyanosis at the Follow-Up Visit. A statistically significant treatment difference was observed between the CDTR-PI 400 mg and CXM-AX groups in sputum appearance, with 81% of the CDTR-PI 400 mg patients and 71% of the CXM-AX patients showing resolution of this symptom (p=0.047).

MO Comment: ***The time to resolution of these signs and symptoms, for the indication of AECB, has not been shown by the literature to affect overall outcome.***

3.2.1.4.4 Safety

3.2.1.4.4.1 Adverse Events (AE)

Total enrollment for this study was 618 patients. Of these 203 were in the CDTR-PI 200 mg arm, 208 were in the CDTR-PI 400 mg arm, and 207 were in the CXM-AX arm. No patients were excluded from the safety database. The number of adverse events, drug-related events, serious adverse events, and withdrawals from the study due to adverse events during treatment (between study day 1 and 3 days post-therapy) and during post-treatment (at least 4 days post-therapy) by treatment arm is summarized in Table 26. (Volume 212 of 322, pages 105-109).

Table 26. Summary of Adverse Events in the "All" Population According to the Applicant

	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CXM-AX 250 mg BID n/N (%)	
During Treatment (Study Day 1 to 3 Days Post-Therapy)						
Any AE	85/203	(42%)	83/208	(40%)	68/207	(33%)
Any Drug Related AE	41/203	(20%)	53/208	(25%)	46/207	(22%)
Any Serious AE	7/203	(4%)	8/208	(4%)	5/207	(2%)
Prematurely Discont. Due to AE	10/203	(5%)	9/208	(4%)	7/207	(3%)
Post-Therapy (At Least 4 Days After the Last Dose of Study Drug)						
Any AE	21/203	(10%)	21/208	(10%)	21/207	(10%)
Any Drug Related AE	3/203	(1%)	4/208	(2%)	0/207	(0%)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N=number of patients with event/total number of patients

3.2.1.4.4.1.1 All Adverse Events

According to the Applicant, during treatment, 85 patients (42%) in the CDTR-PI 200 mg group, 83 patients (40%) in the CDTR-PI 400 mg group, and 68 patients (33%) in the CXM-AX group reported at least one adverse event. The most commonly reported adverse events during treatment in all three treatment groups (CDTR-PI 200 mg, CDTR-PI 400 mg, and CXM-AX) were diarrhea (11%, 15%, and 9%, respectively), headache (4%, 4%, and 6%, respectively), nausea (3%, 4%, and 6%, respectively), and vaginal moniliasis (3%, 9%, and 4% of female patients, respectively). A statistically significant difference (p=0.049) was observed between the CDTR-PI 400 mg treatment group and the CXM-AX treatment group for the incidence of diarrhea (15% vs 9%, respectively). Nine severe events were reported in the CDTR-PI 200 mg group (headache by 2 patients and abdominal pain, chest pain, eructation, normocytic anemia, asthma, dyspnea, and herpes simplex by 1 patient each). Fourteen severe events were reported in the CDTR-PI 400 mg group (diarrhea by 4 patients, headache by 2 patients, migraine, mouth ulceration, vomiting, pathological fracture, nervousness, respiratory disorder, rhinitis and kidney

pain by 1 patient each). Sixteen severe events were reported in the CXM-AX group (headache and diarrhea by 2 patients each, and chills, gamma glutamyl transpeptidase (GGT) increase, pseudomembranous colitis, vomiting, insomnia, bronchitis, hypoxia, lung disorder, pharyngitis, rhinitis, sweating, and vaginal moniliasis by 1 patient each). A summary of all adverse events during treatment reported by ≥2% of patients in any of the three treatment groups is presented by treatment group in Table 27. (Volume 212 of 322, page 107).

Table 27. Summary of Common[a] Adverse Events Grouped by COSTART Term During Treatment According to the Applicant

	CDTR-PI 200 mg BID (N=203)					CDTR-PI 400 mg BID (N=208)					CXM-AX 250 mg BID (N=207)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				85	42%				83	40%				68	33%
BODY AS A WHOLE				22	11%				24	12%				24	12%
Abdominal pain	4	0	1	5	2%	0	3	0	3	1%	1	2	0	3	1%
Accidental injury	2	3	0	5	2%	1	1	0	2	1%	1	1	0	2	1%
Chest Pain	2	1	1	4	2%	1	0	0	1	<1%	0	1	0	1	<1%
Headache	1	5	2	8	4%	4	3	2	9	4%	7	3	2	12	6%
DIGESTIVE SYSTEM				35	17%				44	21%				35	17%
Diarrhea	13	10	0	23	11%	18	10	4	32	15%	11	5	2	18	9%
Nausea	4	2	0	6	3%	5	4	0	9	4%	10	2	0	12	6%
Vomiting	1	2	0	3	1%	2	3	1	6	3%	0	2	1	3	1%
NERVOUS SYSTEM				7	3%				8	4%				9	4%
Dizziness	3	1	0	4	2%	0	1	0	1	<1%	2	0	0	2	1%
Somnolence	0	0	0	0	0%	2	2	0	4	2%	0	0	0	0	0%
RESPIRATORY SYSTEM				17	8%				13	6%				14	7%
Asthma	0	3	1	4	2%	0	3	0	3	1%	0	1	0	1	<1%
Rhinitis	0	4	0	4	2%	2	1	1	4	2%	1	1	1	3	1%
Sinusitis	3	1	0	4	2%	0	1	0	1	<1%	1	0	0	1	<1%
UROGENITAL SYSTEM[d]				5	4%				10	9%				7	6%
Vaginal Moniliasis[d]	2	2	0	4	3%	5	5	0	10	9%	3	1	1	5	4%

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.

According to the Applicant, 21 (10%) patients in the CDTR-PI 200 mg group, 21 (10%) patients in the CDTR-PI 400 mg group, and 21 (10%) patients in the CXM-AX group reported at least one adverse event during posttreatment. Headache was reported by 4 (2%) patients in the CDTR-PI 400 mg group and sinusitis was reported by 4 (2%) patients in the CXM-AX

group; no other specific adverse event reported by patients in the three treatment groups had an incidence greater than 1% during posttreatment. Five severe events (headache, congestive heart failure, diarrhea, speech disorder, and lung disorder) were reported in the CDTR-PI 200 mg group, four severe events (cellulitis, chest pain, headache, and pulmonary embolus) were reported in the CDTR-PI 400 mg group, and one severe event (lung disorder) was reported in the CXM-AX group during posttreatment.

3.2.1.4.4.1.2 Treatment Related Adverse Events

During treatment, 41 (20%) patients in the CDTR-PI 200 mg group, 53 (25%) patients in the CDTR-PI 400 mg group, and 46 (22%) 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. The most frequently occurring treatment-related adverse events were diarrhea (10%) in the CDTR-PI 200 mg group; diarrhea (14%), nausea (4%), and vaginal moniliasis (9% of female patients) in the CDTR-PI 400 mg group; and diarrhea (8%), nausea (6%), and vaginal moniliasis (4% of female patients) in the CXM-AX group. No statistically significant differences were observed between the treatment groups for the incidence of any specific treatment-related adverse event. Two severe treatment-related adverse events were reported in the CDTR-PI 200 mg group (headache and eructation by 1 patient each). Seven severe treatment-related adverse events were reported in the CDTR-PI 400 mg group (diarrhea by 4 patients; migraine, vomiting, and nervousness by 1 patient each). Seven severe treatment-related adverse events were reported in the CXM-AX group (diarrhea by 2 patients, and headache, pseudomembranous colitis, vomiting, insomnia, and vaginal moniliasis by 1 patient each) (Table 14.3.1--5.1). A summary of treatment-related adverse events, reported by ≥2% of patients in any treatment group, is presented by treatment group in Table 28. (Volume 212 of 322, page 109).

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Table 28. Summary of Common Treatment Related Adverse Events Grouped by COSTART Term, During Treatment, According to the Applicant

	CDTR-PI 200 mg BID (N=203)					CDTR-PI 400 mg BID (N=208)					CXM-AX 250 mg BID (N=207)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				41	20%				53	25%				46	22%
BODY AS A WHOLE				6	3%				10	5%				11	5%
Abdominal Pain	4	0	0	4	2%	0	3	0	3	1%	1	2	0	3	1%
Headache	1	0	1	2	1%	1	0	0	1	<1%	3	1	1	5	2%
DIGESTIVE SYSTEM				29	14%				38	18%				30	14%
Diarrhea	14	7	0	21	10%	16	9	4	29	14%	11	4	2	17	8%
Nausea	2	2	0	4	2%	5	4	0	9	4%	10	2	0	12	6%
UROGENITAL SYSTEM[d]				5	4%				10	9%				5	4%
Vaginal Moniliasis[d]	2	2	0	4	3%	5	5	0	10	9%	3	1	1	5	4%

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.

During posttreatment, 3 (1%) patients in the CDTR-PI 200 mg group and 4 (2%) patients in the CDTR-PI 400 mg group reported at least one treatment-related adverse event (Table 14.3.1--2.2). No posttreatment treatment-related adverse events were reported in the CXM-AX group. Oral moniliasis, stomatitis, and vaginal moniliasis were reported by 1 patient each in the CDTR-PI 200 mg group; gastrointestinal disorder, pseudomembranous colitis, eye disorder, and vaginal moniliasis were reported by 1 patient each in the CDTR-PI 400 mg group. No severe treatment-related adverse events were reported during the posttreatment period.

3.2.1.4.4.1.3 Discontinuations Due to Adverse Events

Twenty-six patients were prematurely discontinued from study drug due to the occurrence of at least one adverse event: 10 in the CDTR-PI 200 mg group, 9 in the CDTR-PI 400 mg group, and 7 in the CXM-AX group. The majority of the adverse events leading to discontinuation in all three treatment groups were associated with the digestive system. A summary of patients who prematurely discontinued treatment due to adverse events is presented by treatment group in Table 29. (Volume 312 of 322, page 117).

Table 29. Patients Who Prematurely Discontinued treatment Due to Adverse Events According to the Applicant

Investigator Patient Number	Age/Sex	Day of Onset[a]	Day of Resolution[a]	Body System	COSTART Term
Patients Discontinued from the Cefditoren Pivoxil 200 mg BID Treatment Group					
Durden 3347	60/M	2 (0)	11 (9)	Digestive	Nausea and vomiting[b]
Fisher 3721	25/F	3 (0)	4 (1)	Digestive	Nausea and vomiting[b]
Fogarty 3311	68/F	4	10 (5)	Digestive	Diarrhea[b]
		7 (2)	32 (27)	Metabolic/nutritional	Edema peripheral[b]
Handshoe 3910	73/M	9 (0)	22 (13)	Respiratory	Pneumonia
Maggiacomo 3274	59/F	6 (0)	9 (3)	Respiratory	Asthma
Marinelli 3076	90/F	3 (1)	5 (3)	Respiratory	Apnea
McAdoo 3552	62/F	2	3 (0)	Digestive	Nausea[b]
Rhudy 3415	16/M	6	8 (1)	Body as a whole	Abdominal pain
Rosemore 3987	79/F	4	7 (1)	Digestive	Diarrhea[b]
Zekert 3300	50/F	3	8 (3)	Skin and appendages	Rash[b]
Patients Discontinued from the Cefditoren Pivoxil 400 mg BID Treatment Group					
Bensch 3866	53/F	4	43 (38)	Body as a whole	Pain[b]
S. Christensen 3822	68/F	1	8 (3)	Digestive	Nausea[b]
		1	8 (3)	Digestive	Vomiting[b]
Dalgin 3485	87/F	3	8 (2)	Digestive	Diarrhea[b]
Fogarty 3315	74/F	9 (0)	14 (5)	Digestive	Diarrhea[b]
		9 (0)	14 (5)	Digestive	Nausea[b]
		9 (0)	Cont: 33 (24)	Body as a whole	Asthenia[b]
Henry 3477	17/F	1	6 (2)	Nervous	Dizziness[b]
Miskin 3021	38/M	3 (0)	5 (2)	Digestive	Mouth ulceration[b]
Page 3129	54/F	4	12 (3)	Digestive	Diarrhea[b]
		4	9 (6)	Urogenital	Vaginal moniliasis[b]
		5	7 (1)	Digestive	Nausea and vomiting[b]
Simon 3165	75/F	7 (0)	9 (2)	Nervous	Nervousness[b]
Upchurch 3377	46/F	4 (0)	4 [5 min]	Skin and appendages	Sweating[b]
Patients Discontinued from the Cefuroxime Axetil 250 mg BID Treatment Group					
Bettis 3529	70/M	1	32 (23)	Digestive	Flatulence[b]
Dalgin 3766	59/F	4 (1)	11 (8)	Digestive	Diarrhea[b]
Handshoe 3835	62/M	5	40 (33)	Digestive	Pseudomembranous colitis[b]
Mazzone 3235	71/F	1	3	Body as a whole	Headache[b]
		1	3	Nervous	Insomnia[b]
		1	3	Digestive	Nausea[b]
		1	3	Respiratory	Dyspnea[b]
Menendez 3748	21/M	1 (0)	1 [<1 hr]	Body as a whole	Abdominal pain[b]
Rhudy 3285	32/F	1	8 (2)	Digestive	Vomiting[b]
		4	8 (2)	Digestive	Diarrhea[b]
Rhudy 3414	30/M	7 (0)	7 [< 5 hrs]	Body as a whole	Chills
		8 (1)	8 [<1 hr]	Skin and appendages	Sweating

Note: Study drug was prematurely discontinued for an additional patient, Rhudy 3286 in the CDTR-PI 200 mg group (listed in Appendix 16.2.7.4), who was classified as discontinuing primarily due to therapeutic failure rather than adverse event.

[a] Days posttreatment are presented in parentheses; (0) = study drug discontinued as of specified day; Cont. = event continued as of specified day; if less than 1 day, duration in hours is presented in brackets.

[b] Drug-relationship classified as possible, probable, or definite.

3.2.1.4.4.1.4 Serious Adverse Events

Twenty patients had a serious adverse event during the study: 7 in the CDTR-PI 200 mg group, 8 in the CDTR-PI 400 mg group (including 1 death), and 5 in the CXM-AX group (including 1 death). Of the 20 patients who reported serious

adverse events, 3 (2 CDTR-PI 400 mg patients and 1 CFX-AX patient) had serious adverse events, including diarrhea, vomiting, nausea, asthenia, and pseudomembranous colitis, that were considered by the investigator to be possibly or probably related to study drug administration. A summary of patients who experienced serious adverse events is presented by treatment group in Table 30. (Volume 312 of 322, page 115).

3.2.1.4.4.1.5 Deaths

Two deaths were reported during the study. Neither death was felt to be treatment related by the investigators. Deaths are summarized below:

Patient #3082 (Inv. Interiano) - A 63-year-old male assigned to the CXM-AX group, was hospitalized 5 days after the last dose of study drug for treatment of chronic obstructive pulmonary disease. The patient's symptoms resolved in 13 days (Study Day 29) following treatment with an antifungal. Two days later, however, the patient returned to the hospital (Study Day 31) for treatment of chronic obstructive pulmonary disease, but did not respond to therapy and death resulted.

Patient #3160 (Inv. Wallace) – A 77-year-old male assigned to the CDTR-PI 400 mg group, who experienced a pulmonary embolism resulting in death 49 days after the last dose of study drug.

MO Comment: ***The MO reviewed these cases and found no relation to study drug.***

Table 30. Patients Who Experienced Serious Adverse Events According to the Applicant

Investigator Patient Number	Age/Sex	Day of Onset[a]	Day of Resolution[a]	Body System	COSTART Term	SAE Criteria
Patients with Serious Adverse Events in the Cefditoren Pivoxil 200 mg BID Treatment Group						
Handshoe 3222	72/M	25 (15)	27 (17)	Cardiovascular	Congestive heart failure	Hospitalization
Handshoe 3460	64/M	29 (19)	40 (30)	Respiratory	Lung disorder	Hospitalization
Maggiacomo 3274#	59/F	6 (0)	9 (3)	Respiratory	Asthma	Hospitalization
Marinelli 3076#	90/F	3 (1)	5 (3)	Respiratory	Apnea	Hospitalization; Life-threatening
Rhudy 3415#	16/M	5	47 (40)	Body as a whole	Accidental injury	Hospitalization
Thompson 3812	62/F	1	Cont: 25 (14)	Hemic and Lymphatic	Normocytic anemia	Hospitalization; Prolonged Hospitalization
Upchurch 3374	61/F	1	41 (31)	Respiratory	Lung disorder	Hospitalization
Patients with Serious Adverse Events in the Cefditoren Pivoxil 400 mg BID Treatment Group						
Bettis 3323	64/F	30 (20)	50 (40)	Respiratory	Pneumonia	Hospitalization
Dalgin 3621	52/F	10 (0)	19 (9)	Digestive	Diarrhea[b]	Required Intervention
		10 (0)	12 (2)	Digestive	Vomiting[b]	Required Intervention
Fogarty 3315#	74/F	9 (0)	14 (5)	Digestive	Diarrhea[b]	Hospitalization
			14 (5)	Digestive	Nausea[b]	Hospitalization
			Cont: 33 (24)	Body as a whole	Asthenia[b]	Hospitalization
		27 (18)	33 (24)	Digestive	Pseudomembranous colitis[b]	Hospitalization
Fogarty 3657	38/M	35 (25)	38 (28)	Metabolic/ nutritional	Dehydration	Hospitalization
		35 (25)	38 (28)	Digestive	Nausea	Hospitalization
		35 (25)	38 (28)	Digestive	Vomiting	Hospitalization
Handshoe 3837	51/F	3	7	Nervous	Somnolence	Hospitalization
		3	7	Respiratory	Dyspnea	Hospitalization
Lewin 3226	33/M	13 (3)	17 (7)	Respiratory	Respiratory disorder	Hospitalization
		14 (4)	17 (7)	Body as a whole	Headache	Hospitalization
Simon 3993	61/F	18 (7)	34 (23)	Body as a whole	Cellulitis	Hospitalization
		18 (7)	34 (23)	Body as a whole	Pain	Hospitalization
Wallace 3160	77/M	60 (49)	60 (49)	Respiratory	Pulmonary embolus	Death
Patients with Serious Adverse Events in the Cefuroxime Axetil 250 mg BID Treatment Group						
Handshoe 3835#	62/M	5	40 (33)	Digestive	Pseudomembranous colitis[b]	Hospitalization
Interiano 3082	63/M	16 (5)	28 (17)	Respiratory	Lung disorder	Hospitalization
		31 (20)	52 (41)	Respiratory	Lung disorder	Hospitalization/ Death
Page 3126	80/F	12 (2)	16 (6)	Respiratory	Hypoxia	Hospitalization
Simon 3057	44/F	11 (1)	15 (5)	Respiratory	Bronchitis	Hospitalization
Simon 3164	51/M	2	9	Respiratory	Lung disorder	Hospitalization

Patient prematurely discontinued from the study.
[a] Days posttreatment are presented in parentheses; Cont. = event continued as of specified day.
[b] Drug-relationship classified as possible, probable, or definite.

3.2.1.4.4.2 Clinical Laboratory

Statistically significant treatment differences were observed among the treatment groups in mean change from baseline to post-therapy in sodium, alkaline phosphatase, total protein, albumin, calcium, and creatinine. The Applicant stated "the differences among the treatment groups were not considered to

be clinically meaningful." A summary of the laboratory parameters for which statistically significant differences among treatment groups were observed in mean change from baseline to post-therapy is presented in Table 31. (Volume 312 of 322, page 120).

MO Comment: ***The MO agrees that these changes are not clinically significant.***

According to the Applicant, the proportions of patients with potentially clinically significant laboratory values were similar among the treatment groups. No patients were prematurely discontinued from the study due the abnormal laboratory value and no serious adverse events associated with laboratory abnormalities were reported. The proportions of patients with potentially clinically significant laboratory values are presented in Table 32. (Volume 312 of 322, page 121).

Table 31. Statistically Significant Differences Among Treatment Groups in Mean Change From Baseline to Post-Therapy for Laboratory Test Parameters According to the Applicant

	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CXM-AX 250 mg BID	
Chemistry Parameter (unit)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Sodium (mEq/dL)						
Baseline	201	140.16 (3.23)	202	140.45 (2.34)	202	140.00 (3.20)
Post-Therapy	186	140.69 (2.83)	189	140.25 (2.67)	189	139.72 (2.99)
Mean Change to Post-Therapy (p=0.031)	184	0.46 (2.92)@$	185	-0.18 (2.89)	185	-0.27 (2.91)
Alkaline Phosphatase (U/L)						
Baseline	200	81.44 (31.22)	203	78.87 (26.06)	202	75.21 (25.45)
Post-Therapy	186	77.07 (25.45)	188	74.41 (23.68)	190	74.21 (29.75)
Mean Change to Post-Therapy (p=0.006)	183	-3.13 (11.09)	185	-4.78 (12.28)#	186	-0.74 (13.08)
Total Protein (g/dL)						
Baseline	202	7.21 (0.54)	204	7.19 (0.51)	205	7.21 (0.54)
Post-Therapy	186	7.10 (0.47)	189	7.12 (0.44)	191	7.03 (0.50)
Mean Change to Post-Therapy (p=0.008)	185	-0.11 (0.44)	187	-0.05 (0.42)#	189	-0.19 (0.38)
Albumin (g/dL)						
Baseline	201	4.00 (0.38)	203	4.05 (0.38)	203	4.05 (0.38)
Post-Therapy	185	3.94 (0.37)	186	4.04 (0.37)	191	3.96 (0.36)
Mean Change to Post-Therapy (p=0.008)	183	-0.05 (0.29)@	183	0.01 (0.32)#	188	-0.08 (0.27)
Calcium (mg/dL)						
Baseline	202	9.31 (0.48)	204	9.27 (0.46)	205	9.30 (0.42)
Post-Therapy	186	9.30 (0.45)	189	9.36 (0.39)	191	9.24 (0.39)
Mean Change to Post-Therapy (p=0.010)	185	-0.02 (0.40)@	187	0.08 (0.46)#	189	-0.05 (0.43)
Creatinine (mg/dL)						
Baseline	202	0.83 (0.21)	203	0.82 (0.22)	204	0.84 (0.22)
Post-Therapy	186	0.83 (0.20)	189	0.82 (0.20)	191	0.79 (0.19)
Mean Change to Post-Therapy (p=0.008)	185	0.00 (0.15)$	186	0.00 (0.14)#	188	-0.04 (0.13)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil; SD = standard deviation
@ = Statistically significant difference between CDTR-PI 200 mg and CDTR-PI 400 mg.
$ = Statistically significant difference between CDTR-PI 200 mg and CXM-AX.
# = Statistically significant difference between CDTR-PI 400 mg and CXM-AX.

Table 32. Proportions of Patients with Potentially Clinically Significant Laboratory Values According to the Applicant

		CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CXM-AX 250 mg BID	
Laboratory Parameter (unit)	**Potentially Clinically Significant Criteria**	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Hematology		**6/192**	**(3%)**	**8/198**	**(4%)**	**5/202**	**(2%)**
Hemoglobin (g/Dl)	↓ from BL of ≥2, or < NL limit if BL value missing	3/192	(2%)	6/198	(3%)	3/202	(1%)
Hematocrit (%)	<37 male; <32 female	3/191	(2%)	2/196	(1%)	3/198	(2%)
Platelet Count ($x10^3$ mcL)	<100	0/192	(0)	0/197	(0)	0/202	(0)
Hepatic Chemistry		**0/194**	**(0)**	**4/200**	**(2%)**	**0/202**	**(0)**
Total Bilirubin (mg/dL)	NL, Low, Missing BL: >2.0 High BL: >2.5	0/194	(0)	1/200	(1%)	0/202	(0)
AST (U/L)		0/194	(0)	1/200	(1%)	0/202	(0)
	NL, Low, Missing BL: ≥2xULN	0/194	(0)	1/200	(1%)	0/202	(0)
	≥3xULN	0/194	(0)	0/200	(0)	0/202	(0)
	≥5xULN	0/194	(0)	0/200	(0)	0/202	(0)
	High BL: ≥3xBL	0/194	(0)	0/200	(0)	0/202	(0)
ALT (U/L)		0/194	(0)	3/200	(2%)	0/202	(0)
	NL, Low, Missing BL: ≥2xULN	0/194	(0)	3/200	(2%)	0/202	(0)
	≥3xULN	0/194	(0)	1/200	(<1%)	0/202	(0)
	≥5xULN	0/194	(0)	0/200	(0)	0/202	(0)
	High BL: ≥3xBL	0/194	(0)	0/200	(0)	0/202	(0)
Metabolic/Nutritional Chemistry		**0/194**	**(0)**	**0/200**	**(0)**	**1/202**	**(<1%)**
Glucose (mg/dL)	<45	0/194	(0)	0/200	(0)	1/202	(<1%)
Renal Chemistry		**2/195**	**(1%)**	**3/202**	**(1%)**	**1/202**	**(<1%)**
BUN (mg/dL)	>30	2/195	(1%)	3/202	(1%)	1/202	(<1%)
Creatinine (mg/dL)	NL, Low, Missing BL: >2.0 High BL: >2.5	0/195	(0)	0/202	(0)	0/202	(0)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil;
BL = baseline; NL = normal; ULN = upper limit of normal range

3.2.1.4.4.3 Vital Signs

No statistically significant differences were observed among the treatment groups in mean change from baseline to post-therapy or follow-up in systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, temperature, or body weight.

3.2.1.5 Reviewer's Comments and Conclusions

3.2.3.1.1 Efficacy

The efficacy results of CEF97-003 do not support the use of cefditoren-pivoxil 200 mg PO BID for the treatment of AECB. Although the Applicant's data analyses (when adjusted for multiple comparisons) suggest that CDTR-PI 200 mg [97.5% CI –10.3, 10.2] and CDTR-PI 400 mg [97.5% CI –3.7, 15.5] are equivalent to CXM 250 mg in the clinically evaluable population at Follow-Up, the MO disagrees with the evaluability and outcome criteria defined by the Applicant and used by the Applicant in their analyses. Based on the MO's reanalysis CDTR-PI 400 mg appears to be equivalent to CXM 250 mg [97.5% CI –6.2, 26.8] in the evaluable population at Follow-Up; however, CDTR-PI 200 mg

does not appear to be equivalent to either CXM 250 mg [97.5% CI –18.8, 13.7] or CDTR-PI 400 mg [97.5% CI –29.9, 4.2]. While CDTR-PI 400 mg appears efficacious in the MO's analyses, the number of patients included in the MO's MITT and evaluable populations was so small that the reliability of the data is questionable.

Although the Applicant's data analyses (when adjusted for multiple comparisons) suggest that CDTR-PI 400 mg is equivalent to CXM 250 mg [97.5% CI –9.8, 13.4] in the microbiologically evaluable population at Follow-Up, the MO disagrees with the evaluability and outcome criteria defined by the Applicant and used by the Applicant in their analyses. Based on the MO's reanalysis CDTR-PI 400 mg does not appear to be equivalent to CXM 250 mg [97.5% CI –13.4, 19.6] in the evaluable population at Follow-Up if a delta of 10% is used, but would be considered equivalent if a delta of 15% is used. However, CDTR-PI 200 mg does not appear to be equivalent to either CXM 250 mg [97.5% CI –21.7, 10.6] or CDTR-PI 400 mg [97.5% CI –25.7, 8.4].

Of interest the cure rates at Follow-Up determined using the stricter criteria defined by the MO approach those that might be expected for placebo. This yet again, raises the issue of the utility of the use of antimicrobials for the treatment of AECB.

CEF97-003 does not contain adequate data on which to base an approval for the indication of AECB; however, the data is adequate to serve as supportive evidence in conjunction with a second well designed, statistically adequate study of CDTR-PI 400 mg versus and approved comparator.

3.2.3.1.2 Safety

The number of adverse events, drug-related adverse events, serious adverse events, and withdrawals from the study due to adverse events during treatment (between study day 1 and 3 days post-therapy) and during post-treatment (at least 4 days post-therapy) are similar across all treatment arms. No statistically significant differences were observed between the treatment groups for the incidence of any specific treatment-related adverse event. The most frequently occurring treatment-related adverse events were diarrhea (10%) in the CDTR-PI 200 mg group; diarrhea (14%), nausea (4%), and vaginal moniliasis (9% of female patients) in the CDTR-PI 400 mg group; and diarrhea (8%), nausea (6%), and vaginal moniliasis (4% of female patients) in the CXM-AX group. Changes in laboratory findings and vital signs were consistent between treatment arms.

Statistical Reviewer's Comments and Conclusions:

Efficacy Results:

Based on the reanalysis of the Applicant's data by applying the medical officer's evaluability and outcome criteria, CDTR-PI 200 mg does not appear to be equivalent to the approved comparator CXM-AX 250 mg (97.5% CI: -18.8, 13.7) or the CDTR-PI 400 mg (97.5% CI: -29.9, 4.2) in the clinically evaluable population at follow up, using a delta of 10%. Therefore, the efficacy results of CEF97-003 do not support the use of CDTR-PI 200 mg PO BID for the treatment of AECB.

Although CDTR-PI 400 mg appears to equivalent to the approved comparator CXM-AX 250 mg (97.5 CI: -6.2, 26.8) at follow-up in the evluable population, the significant drop in cure rates and the total number of patients in the evaluable population and MITT raise serious concern over the reliability of the conclusion. Had there been a placebo arm, these rates would probably fall below or equal to the placebo response rate in this population.

APPEARS THIS WAY
ON ORIGINAL

3.2.2 **Study CEF-97-005** "Comparative Safety and Efficacy of Cefditoren Pivoxil and Clarithromycin in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis"

Enrollment Period
Start: April 6, 1998
Completion: May 24, 1999

3.2.2.1 Objective

"To compare the safety and efficacy of orally administered cefditoren pivoxil 200 mg BID and 400 mg BID and clarithromycin 500 mg BID in the treatment of patients with an acute bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis who were suitable candidates for oral antibiotic therapy." (Volume 217 of 322, page 003)

3.2.2.2 Design

Study CEF-97-005 was a randomized, double-blind, comparative, multiple dose, multicenter trial that was conducted in the United States. The randomization ratio was 1:1:1 (cefditoren pivoxil 200 mg BID:cefditoren pivoxil 400 mg BID: clarithromycin 500 mg BID). Although two dosage regimens for cefditoren pivoxil were included in this study, the study was not designed specifically as a dose-ranging study.

MO Comments: ***The Applicant has stated that "the doses of cefditoren pivoxil tablets, 200 mg BID and 400 mg BID, for 10 days were chosen for the treatment of bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis based on the in vitro susceptibility data of respiratory pathogens (i.e., S. pneumoniae, H. influenzae, and M. catarrhalis) to cefditoren pivoxil and the time that serum levels of cefditoren exceeded the MIC of these pathogens" and that "the primary comparison for efficacy endpoints will be made between the cefditoren 400 mg BID treatment group and the clarithromycin treatment group." (Volume 217 of 322, page 031 and Volume 219 of 322, page 052) Based on these statements the MO presumes the expectation of the Applicant was that the 400 mg treatment group would do better (provided the adverse event profile was not higher in this group) than the 200 mg treatment group.***

Patients who were at least 12 years old and presented with the clinical signs and symptoms of an acute bacterial exacerbation of chronic bronchitis or chronic asthmatic bronchitis, who had a chest x-ray demonstrating the absence of pneumonia, who had a sputum qualified by Gram stain at the investigator site, and who met the selection criteria were eligible for entry into the study. Patients who met the selection criteria were randomly assigned to receive one of three treatment regimens for 10 days:

cefditoren 200 mg BID as cefditoren pivoxil
or
cefditoren 400 mg BID as cefditoren pivoxil
or
clarithromycin 500 mg BID

Patients returned to the investigator's office for an On-Therapy Visit, if it was felt necessary based on telephone contact during Study Days 3 to 5. All patients returned to the investigator's office for a Post-Therapy Visit within 48 hours after the last dose of study medication and a Follow-Up Visit 7 to 14 days after the last dose of study medication. Microbiologic evaluation (if sputum was available) and assessment of the clinical signs and symptoms of infection were performed at each study visit. Safety was evaluated by laboratory tests, physical examination, and monitoring of adverse events at each study visit.

3.2.2.3 Protocol Review

The protocol design for study CEF97-005 is identical to that of study CEF97-003 with the exception that the comparator used was clarithromycin rather than cefuroxime axetil. The reader is referred to Section 3.2.1.3 of this review for details regarding the protocol design and MO's comments.

3.2.2.4 Study Results

3.2.2.4.1 Evaluability

A total of 73 principal investigators, at 73 US sites participated in this study. Data from two investigative sites (DeAbate, #4637 and Mathew, #13004) were exclude from all analyses, by the Applicant, because "important study procedures were not being followed, rendering the information gathered unreliable" (efficacy and safety data for these two investigators were presented separately by the Applicant). Exclusion of patients from these two sites resulted in a loss of data for 88 patients, leaving a total of 903 patients in the ITT population for analysis. Table 33. provides a summary of investigators, investigator sites, and distribution of enrolled and evaluable patients by site and treatment arm (modified from Table 6a., Volume 212 of 322, page 019).

Table 33. Distribution of Enrolled Patients by Investigator According to the Applicant

Investigator (Invest. #) Location	Treatment Group					
	@CDTR-PI 200 mg		@CDTR-PI 400 mg		+ CLA 500 mg	
	!Enrolled	^Eval(%)	!Enrolled	^Eval(%)	!Enrolled	^Eval(%)
Berley (#14123) Lindenhurst, NY	2	2 (100%)	2	2 (100%)	2	2 (100%)
Bernstein (#13105) Cincinnati, OH	3	3 (100%)	3	2 (67%)	3	0 (0%)
Bettis (#12571) Edmonds, WA	12	10 (83%)	11	8 (73%)	12	9 (75%)
Block (#12889) Chicago, IL	2	2 (100%)	2	1 (50%)	1	1 (100%)
Casale (#7163) Papillion, NE	1	1 (100%)	0	-	0	-
S. Christensen (#13235) Salt Lake City, UT	13	9 (69%)	13	11 (85%)	14	9 (64%)
Clifford (#13441) Wheat Ridge, CO	0	-	1	1 (100%)	0	-
Coalson (#9374) Beavercreek, OH	1	0 (0%)	2	2 (100%)	1	1 (100%)
Cobb (#13322) Richmond Hill, GA	6	3 (50%)	6	4 (67%)	6	2 (33%)
Cohen (# 13536) San Diego, CA	5	3 (60%)	5	5 (80%)	5	5 (100%)
Durden (#12998) Tallahassee, AL	3	2 (67%)	3	3 (100%)	2	0 (0%)
England (#13108) Eugene, OR	3	2 (67%)	3	3 (100%)	4	4 (100%)
Epstein (#14397) Lakewood, CA	5	3 (60%)	6	5 (83%)	5	5 (100%)
Fiel (#14131) Tempe, AZ	16	14 (88%)	15	12 (80%)	16	10 (63%)
Fogarty (# 12973) Spartanburg, SC	8	6 (75%)	9	7 (78%)	8	6 (75%)
Galant (#4817) Orange, CA	1	1 (100%)	1	0 (0%)	1	0 (0%)
Gaona (#13444) San Antonio, TX	5	3 (100%)	5	4 (80%)	6	4 (67%)
Goldstein (#13430) Philadelphia, PA	3	3 (100%)	3	3 (100%)	3	1 (33%)
Hall (#14133) Mount Sterling, KY	7	6 (86%)	8	5 (63%)	8	5 (63%)
Handshoe (#12974) Charleston, SC	7	4 (57%)	6	3 (50%)	7	4 (57%)
Harris, III (#4745) South Bend, IN	1	1 (100%)	1	1 (100%)	1	1 (100%)
Harrison (#13432) Haleyville, AL	12	6 (50%)	13	8 (62%)	13	10 (77%)
Henry (#5516) Salt Lake City, UT	6	5 (83%)	7	6 (86%)	7	4 (57%)

Huerta (#13379)						
Omaha, NE	5	5 (100%)	4	3 (75%)	5	3 (60%)
Hunt (#12798)						
Blue Ridge, GA	4	4 (100%)	4	3 (75%)	3	2 (67%)
Hyers (#14317)						
St. Louis, MO	1	1 (100%)	1	1 (100%)	1	1 (100%)
Ilowite (#6566)						
Mineola, NY	2	2 (100%)	2	2 (100%)	3	3 (100%)
Jones (#13113)						
Denver, CO	4	3 (75%)	3	1 (33%)	4	4 (100%)
Karetzky (#3397)						
Newark, NJ	2	1 (50%)	3	2 (67%)	2	2 (100%)
Kelsey (#13001)						
San Diego, CA	6	4 (67%)	6	4 (67%)	6	5 (83%)
Larson (#13094)						
Salt Lake City, UT	1	0 (0%)	1	1 (100%)	0	-
Lazarus (#14302)						
Bremerton, WA	3	3 (100%)	4	4 (100%)	4	4 (100%)
Lewin (#1939)						
Los Angeles, CA	5	2 (40%)	4	3 (75%)	5	3 (60%)
Maggiacomo (#12528)						
Cranston, RI	3	2 (67%)	3	3 (100%)	2	2 (100%)
Mayer (#13292)						
South Plainfield, NJ	0	-	1	1 (100%)	0	-
McAdoo (#12957)						
Milan, TN	1	1 (100%)	1	0 (0%)	1	1 (100%)
Merrin (#13021)						
SantaBarbara, CA	4	4 (75%)	4	4 (100%)	4	2 (50%)
Mishkin (#13491)						
Baltimore, MD	3	3 (100%)	4	3 (75%)	4	4 (100%)
Mitra (# 13429)						
Ocala, FL	0	-	0	-	1	0 (0%)
Nayak (#7721)						
Normal, IL	0	-	1	1 (100%)	0	-
Netzel (#11279)						
Monroe, WI	1	1 (100%)	1	1 (100%)	1	1 (100%)
Newcomb (#13661)						
Tuscaloosa, AL	13	9 (69%)	14	8 (57%)	14	11 (79%)
Osei (#13114)						
West Nyack, NY	1	1 (100%)	1	0 (0%)	0	-
Ovetsky (#12217)						
Atlanta, GA	4	3 (75%)	5	3 (60%)	4	3 (75%)
Poling (#13115)						
Wichita, KS	4	3 (75%)	4	2 (50%)	4	2 (50%)
Pollard (#12262)						
Louisville, KY	3	3 (100%)	2	0 (0%)	2	1 (50%)
Reina (#13918)						
Tampa, FL	2	1 (50%)	1	1 (100%)	2	2 (100%)
Rhudy (#12960)						
Salt Lake City, UT	17	12 (71%)	18	9 (50%)	18	13 (72%)
Rodrigues (#14310)						
Somerset, KY	2	1 (50%)	3	2 (67%)	2	1 (50%)
Rosemore (#13007)						
Hueytown, AL	9	6 (67%)	8	6 (75%)	9	9 (100%)
Rudolph (#9475)						
Albuquerque, NM	1	1 (100%)	2	2 (100%)	1	1 (100%)