CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-222

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #	:	21-222
Drug	:	Spectracef™ (Cefditoren pivoxil tablets)
Sponsor	:	TAP Holdings, Inc.
Indications	:	Acute Exacerbation of Chronic Bronchitis, Streptococcal Pharyngitis, Uncomplicated skin and skin structure infections,
Statistical Reviewer	:	Thamban Valappil, Ph.D., HFD-725
Medical Officers	:	John Alexander, M.D., HFD-520 James Blank, Ph.D., HFD-520 Jean Mulinde, M.D., HFD-520 Sumathi Nambiar, M.D., HFD-520
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Volume Reviewed	:	Vols. 1, 269-322
User fee due date	:	October 27, 2000

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I. EXECUTIVE SUMMARY FOR ALL INDICATIONS

INTRODUCTION

The clinical program was designed to collect data on the efficacy and safety of cefditoren, a cephalosporin antibiotic discovered by Meiji Seika Kaisha Ltd. of Japan and currently being developed by TAP Holdings Inc.. TAP Holdings Inc., initiated a program to collect data on the efficacy and safety of cefditoren pivoxil for the treatment of uncomplicated skin and skin structure infections, acute exacerbation of chronic bronchitis, streptococcal pharyngitis, [redacted] The Applicant has submitted data from 8 phase III trials in support of [redacted] indications in this NDA.

This document include the statistical review for all three indications (streptococcal pharyngitis, uncomplicated skin and skin structure infections, [redacted]. For the indication of acute exacerbation of chronic bronchitis, a joint review was provided by the clinical and statistical reviewers, Jean Mulinde and Thamban Valappil. The review of this indication is not provided here.

Acute Exacerbation of Chronic Bronchitis

The sponsor has designed these studies for the statistical comparison of the cefditoren 400 mg treatment group to the comparator (CXM-AX 250 mg in study 003 and CLA 500 mg in study 005) treatment groups. Although the Applicant stated that 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. An appropriate statistical adjustment should be used for the multiple comparisons to control the overall type-I error rate and the test for equivalence should be based on 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.

In study CEF-97-003, based on the re-analysis after applying the medical officer's evaluability and outcome criteria, the 97.5% CI for the clinically evaluable population at follow-up were; CDTR-PI 200 mg (-18.8, 13.7) and CDTR-PI 400 mg (-29.9, 4.2) compared to CXM-AX 250 mg group. These results indicate that both the regimens, cefditioren 200 mg and 400 mg were not equivalent to the approved comparator, CXM-AX 250 mg, using a delta of 10%. Based on the MITT population at the follow up, the 97.5% CI for both CDTR-PI 200 mg (-20.4, 10.3) and CDTR-PI 400 mg (-11.8, 19.4), failed to demonstrate equivalence to CXM-AX 250 mg group based on a delta of 10%. For the microbiological response at follow up, 97.5% CI for the difference in rates failed to demonstrate equivalence for both the cefditoren regimens to its comparator based on a 10% delta. Therefore, the efficacy results of CEF97-003 do not support the use of CDTR-PI 200 mg BID for the treatment of AECB.

In study CEF-97-005, among the evaluable population at follow up, based on a 97.5% CI, neither regimens CDTR-PI 200 mg (-16.8, 9.1) or CDTR-PI 400mg (-24.7, 1.5) were equivalent to the approved comparator CLA 500 mg BID, using a delta of 10%. Similar conclusions were obtained using the MITT population. Based on these results, we conclude that the efficacy

results of CEF97-005 do not support the use of CDTR-PI 200 mg BID for the treatment of AECB.

The Study CEF97-003 is a weak and under-powered study due to loss of patients from questionable investigators and due to the evaluability and outcome criteria imposed by the medical reviewer.

In addition, the lack of a dose response between the CDTR-PI 200 mg group and CDTR-PI 400 mg group is unexplained and the results based on Applicant's own analysis for establishing equivalence for CDTR-PI 400 mg showed contradictory results in both the studies.

There were several sensitivity analyses performed by the reviewers and the results were consistent.

For the safety evaluations, in study CEF-97-003, the total enrollment 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. 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.

In study CEF-97-005, total enrollment was 903 patients. Of these 297 were in the CDTR-PI 200 mg arm, 302 were in the CDTR-PI 400 mg arm, and 304 were in the CLA arm. The number of adverse events and drug-related adverse events, during therapy was significantly higher in the CLA group than the CDTR-PI 200 mg group. The number of serious adverse events and withdrawals from the study due to adverse events during treatment are similar across all treatment arms. Diarrhea and vaginal moniliasis were reported significantly more often for the CDTR-PI 400 mg group in the all and treatment related analyses.

Pharyngitis/Tonsillitis

In this study, the Sponsor compared the safety and efficacy of a 10-day course of orally administered Cefditoren pivoxil 200 mg BID and a 10-day course of Penicillin VK 250 mg QID in the treatment of patients with pharyngitis and /or tonsillitis due to *Streptococcus pyogenes*, in patients who were suitable candidates for oral antibiotic therapy.

In study 008, the clinical cure rates among the evaluable patients in the CDTR-PI and PCN-VK groups at the follow-up visits were 89% and 87% and among the MITT patients (The Sponsor's ITT) were 82% and 81% respectively. The 95% confidence intervals for the differences in clinical cure rates among the evaluable and ITT population at follow-up were (-4.3, 9.1) and (-7.0, 8.3). These results demonstrated that the two treatments were equivalent based on a delta of 10%.

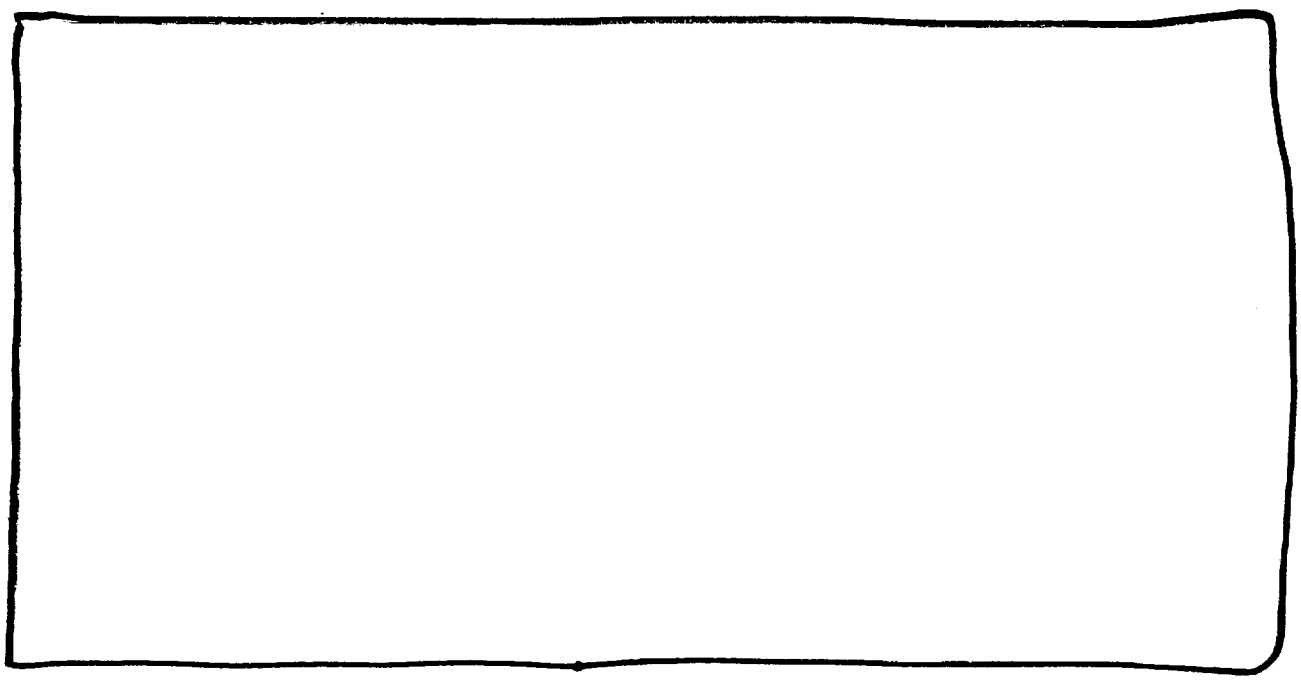
Microbiologic eradication rates among the evaluable and MITT patients in the CDTR-PI and PCN-VK groups at the follow-up visits were (85% , 75%) and (78%, 70%). The 95% confidence intervals for the differences in microbiologic eradication rates demonstrated that the two treatments were equivalent based on a delta of 10%.

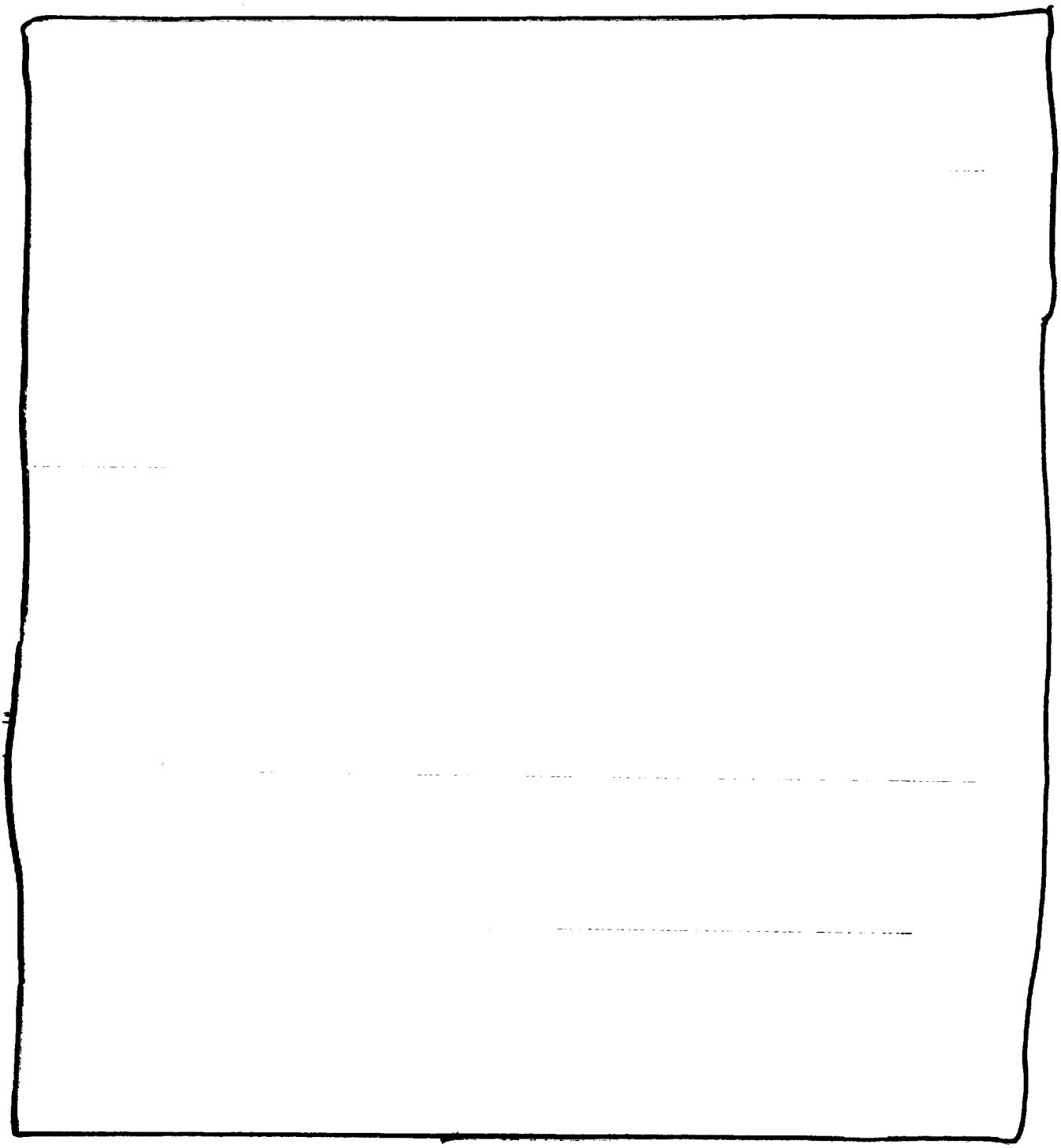
In study 010, Clinical cure rates among the evaluable in the CDTR-PI and PCN-VK groups at the follow up visits were 89% and 84% and among the MITT population were 83% and 80% respectively. The 95% confidence intervals for the differences in clinical cure rates among the evaluable and MITT population were (-2.6, 11.5) and (-4.7, 0.6). These results demonstrated that the two treatments were equivalent based on a delta of 10%.

Microbiologic eradication rates among the evaluable and MITT patients in the CDTR-PI and PCN-VK groups at the follow-up visits were (84%, 78%) and (79%, 73%). The 95% confidence intervals for the differences in microbiologic eradication rates demonstrated that the two treatments were equivalent based on a 10% delta.

For safety evaluations in study CEF-97-008, during treatment, the incidences of all adverse events and treatment-related adverse events were 36% and 20%, respectively, in the CDTR-PI group and 36% and 23%, respectively, in the PCN-VK group (Tables 1.10 and 1.11). The most frequently occurring treatment-related adverse events during treatment were diarrhea and abdominal pain in the CDTR-PI group and diarrhea and nausea in the PCN-VK group. A statistically significant treatment difference was observed in the incidence of treatment-related diarrhea, with 9% of the CDTR-PI group and 4% of the PCN-VK group reporting this adverse event (p=0.017). In study CEF-97-010, during treatment, the incidences of all adverse events and treatment-related adverse events were 38% and 26%, respectively, in the CDTR-PI group and 37% and 20%, respectively, in the PCN-VK group (Table 2.10 and Table 2.11). The most frequently occurring treatment-related adverse events during treatment in both groups were diarrhea and nausea. A statistically significant treatment difference was observed in the incidence of treatment-related diarrhea, with 11% of the CDTR-PI group and 4% of the PCN-VK group reporting this adverse event (p=0.005).

Results of these studies indicated that cefditoren pivoxil (200 mg BID for 10 days) was equivalent to penicillin VK (250 mg QID for 10 days) in eradicating *S. pyogenes* in the treatment of patients with pharyngitis and /or tonsillitis.





Uncomplicated Skin or Skin Structure Infection

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 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.

In study CEF-97-009, based on Sponsor's analysis, clinical cure rates among the evaluable patients at the Follow-Up Visit were; CDTR-PI 200 mg (84%), CDTR-PI 400 mg (84%), and CXM-AX (88%). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg group (-10.0, 1.7) and CDTR-PI 400 mg (-10.2, 1.7) compared to cefuroxime axetil group using a delta of 12%. The clinical cure rates among the MITT patients at the Follow-Up Visit were; CDTR-PI 200 mg (78%), CDTR-PI 400 mg (78%), and CXM-AX (83%). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg (-11.8, 1.1) and CDTR-PI 400 mg group (-11.8, 1.2) compared to the cefuroxime axetil group, using a delta of 12%.

Based on the Sponsor's re-analysis using the medical officer's criteria, 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%). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg (-10.7, 2.4) and failed to demonstrate equivalence of CDTR-PI 400 mg group (-12.6, 0.8) compared to cefuroxime axetil group using a delta of 12%. The clinical cure rates among the MITT patients at the Follow-Up Visit were; CDTR-PI 200 mg (74%), CDTR-PI 400 mg (73%), and CXM-AX (80%). The 95% CI for clinical cure rates failed to demonstrate equivalence of CDTR-PI 200 mg (-12.5, 1.3) and CDTR-PI 400 mg group (-13.7, 0.3) compared to the cefuroxime axetil group using a delta of 12%.

In study, CEF-97-011, based on Sponsor's analysis, the clinical cure rates among the evaluable patients at the Follow-Up Visit were; CDTR-PI 200 mg (85%), CDTR-PI 400 mg (81%), and CFDX-MN (85%). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg group (-6.0, 6.4) and CDTR-PI 400 (-10.1, 2.9) compared to cefadroxil monohydrate group using a delta of 12%. The clinical cure rates among the MITT patients at the Follow-Up Visit were; CDTR-PI 200 mg (83%), CDTR-PI 400 mg (79%), and CFDX-MN (82%). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg (-5.0, 7.8) and CDTR-PI 400 mg (-9.6, 3.7) compared to the cefadroxil monohydrate group using a delta of 12%.

Based on Sponsor's re-analysis, the clinical cure rates of the evaluable patients at the Follow-Up Visit were; CDTR-PI 200 mg (79%), CDTR-PI 400 mg (75%), and CFDX-MN (79%). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg (-6.3, 7.9) and CDTR-PI 400 (-11.5, 3.2) compared to cefadroxil monohydrate group using a delta of 12%. The clinical cure rates among the MITT patients at the Follow-Up Visit were; CDTR-PI 200 mg (77%), CDTR-PI 400 mg (72%), and CFDX-MN (76%). The 95% CI for clinical cure rates demonstrated equivalence of CDTR-PI 200 mg (-5.6, 8.6) and CDTR-PI 400 mg (-11.3, 3.4) compared to the cefadroxil monohydrate group using a delta of 12%.

The re-analysis using the medical officer's assessment of clinical cures and improvements resulted in low cure rates for both the studies compared to the Applicant's earlier analyses.

For Safety evaluations, in study CEF-97-009, 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.

In study CEF-97-011, 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).

Because the sponsor had performed these studies prior to the 1998 advisory committee meeting where a fixed delta issue was discussed, a 12% delta was used in this study as a compromise to establish equivalence.

III. PHARYNGITIS/TONSILLITIS

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

CEF-97-008: "Comparative Safety and Efficacy of Cefditoren Pivoxil and Penicillin VK in the Treatment of Patients with Streptococcal Pharyngitis"

CEF-97-010: Comparative Safety and Efficacy of Cefditoren Pivoxil and Penicillin VK in the Treatment of Patients with Streptococcal Pharyngitis

STUDY : CEF-97-008

INTRODUCTION

Study Objectives

In this study, the Sponsor compared the safety and efficacy of a 10-day course of orally administered Cefditoren pivoxil 200 mg BID and a 10-day course of Penicillin VK 250 mg QID in the treatment of patients with pharyngitis and /or tonsillitis due to *Streptococcus pyogenes*, in patients who were suitable candidates for oral antibiotic therapy.

Study Design

This was a Phase III, randomized, double-blind, active-controlled, parallel-group, multicenter study in outpatients with streptococcal pharyngitis and/or tonsillitis. Approximately 30 investigators were to enroll 500 eligible patients (approximately 16 patients per investigator). Patients with a positive enzyme immunoassay for *S. pyogenes* antigen who met the selection criteria were randomly assigned in a 1:1 ratio to receive either cefditoren pivoxil tablets, 200 mg BID for 10 days, or penicillin VK tablets, 250 mg QID 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 an on-therapy visit was conducted, the investigator assessed clinical signs and symptoms; obtained vital signs, a specimen for throat culture, and blood and urine samples for laboratory tests; documented compliance by pill count and by questioning the patient; and recorded adverse events and concomitant medications. Patients returned to the clinic 4 to 7 days after the last dose (Post-Therapy Visit) and 19 to 25 days after the last dose (Follow-Up Visit). At both post-treatment visits, physical examinations and vital signs measurements were performed, signs and symptoms were assessed and a clinical response to therapy was assigned, a specimen for throat culture was obtained, and adverse events and concomitant medications were recorded. In addition, laboratory tests were performed and compliance was determined at the Post-Therapy Visit, and a convalescent-phase serum specimen was obtained for serology tests at the Follow-Up Visit.

Efficacy Evaluation

All efficacy analyses excluded patients who did not have *S. pyogenes* isolated pretreatment.

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 *S. pyogenes* was eradicated).

The secondary efficacy endpoints included changes in clinical signs and symptoms from the Pre-Therapy Visit to the Post-Therapy and Follow-Up Visits.

Safety endpoints included adverse events, clinical laboratory variables, and vital signs.

Statistical Reviewer's Comments:

The Medical Officer concurs with the overall evaluability criteria defined and the outcome assessment classified by the sponsor. Subjects were selected on the basis of signs and symptoms of tonsillopharyngitis and the presence of a positive rapid test for S. pyogenes.

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

Efficacy Variables

Primary Variables

The primary efficacy endpoints used to summarize clinical and microbiologic outcomes at the Post-Therapy and Follow Up Visits included the clinical cure rate and the patient microbiologic cure rate. These endpoints are defined as follows:

The Clinical Cure Rate	The percentage of patients who had a clinical response of "Cure."
The Patient Microbiologic Cure Rate	The percentage of patients for whom *S. pyogenes* was eradicated.

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 Sponsor at the Post-Therapy and Follow-Up Visits based on the culture results.

Eradication	Absence of *S. pyogenes.*
Persistence	(Applicable for the Post-Therapy Visit only) Presence of the same *S. pyogenes.*
Recurrence	(Applicable for the Follow-Up Visit only) Absence of *S. pyogenes* at the Post-Therapy Visit with reappearance of the same *S. pyogenes* during the Follow-Up period.
Reinfection	Presence of a new *S. pyogenes.*
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 between 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 between the treatment groups using Fisher's exact test.

The baseline characteristics of diagnosis, smoking status, alcohol use, and the number of streptococcal pharyngitis and/or tonsillitis infections treated with antimicrobials within the past 12 months were analyzed for differences between the treatment groups by Fisher's exact test. The baseline characteristics of infection status and clinical condition were compared between the treatment groups using Cochran-Mantel-Haenszel methodology for ordered response variables.

The severity of clinical signs and symptoms at baseline were compared between 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 Post-Therapy Visit.

Efficacy Analyses

The primary data set consisted of patients who were clinically evaluable and microbiologically evaluable. A supportive data set of all randomized patients who received at least one dose of study drug and whose pretreatment throat cultures obtained prior to initiating therapy were positive for *S. pyogenes* was also analyzed (intent-to-treat patients). Clinical and microbiologic outcomes were summarized at the Post-Therapy Visit and the Follow-Up Visit.

The primary efficacy endpoints of clinical cure rate and patient microbiologic cure rate were summarized by treatment group and analyzed with Fisher's exact test at the Follow-Up Visit.

If the patient was considered a "clinical failure" or a "persistence" at the Post-Therapy Visit, the patient was also considered a "clinical failure" or a "persistence" at the Follow-Up Visit. Binomial 95% confidence intervals, based on normal approximation for the binomial distribution, were also calculated for the difference between the treatment groups for the clinical cure rate and patient microbiologic cure rate.

The clinical cure rate and patient microbiologic cure rate were also summarized by investigator, age, race, gender, infection status, clinical condition, diagnosis, smoking status, alcohol use, compliance, treatment duration, weight, and the number of streptococcal pharyngitis and/or tonsillitis infections treated with antimicrobials within the past year. Investigator by treatment interaction was tested using logistic regression. Investigative sites enrolling fewer than 4 patients were combined in this analysis. The Cochran-Mantel-Haenszel test was used as a supportive analysis to assess treatment group differences with the other factors as strata. The Breslow-Day test was used to assess the homogeneity of treatment group differences across the strata. Clinical response versus microbiologic response was also summarized by treatment group at the Post-Therapy and Follow-Up Visits.

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

Statistical Reviewer's Comments:

The Sponsor's efficacy and other analyses were validated by the reviewer and the results were consistent. The test for equivalence would assessed by the reviewer using a delta of 10%.

The disposition of the patients is given in Table 1.1. A total of 503 patients were randomized in the study and received study drug; 256 patients received cefditoren pivoxil 200 mg BID (CDTR-PI) and 247 patients received penicillin VK 250 mg QID (PCN-VK).

At the Follow-Up Visit, 354 (178 in the CDTR-PI group and 176 in the PCN-VK group) patients were clinically evaluable and 149 (78 in the CDTR-PI group and 71 in the PCN-VK group) were excluded from the clinically evaluable efficacy analyses. At the Follow-Up Visit, 352 (177 in the CDTR-PI group and 175 in the PCN-VK group) patients were microbiologically evaluable and 151 (79 in the CDTR-PI group and 72 in the PCN-VK group) were excluded from the microbiologically evaluable efficacy analyses

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Table 1.1. Disposition of Patients by Data Set

	CDTR-PI	PCN-VK
All Patients: Total Randomized and Received Study Drug	256	247
S. pyogenes not isolated pretreatment	54	52
Intent-to-Treat Analyses	202	195
Included in the Clinically Evaluable Efficacy Analyses:		
Post-Therapy	186	182
Follow-Up	178	176
Excluded at Post-Therapy:	70	65
No target pathogen isolated pretreatment	54	52
Lost to follow-up	5	4
Received less than 3 days of study drug	3	5
No clinical response assessment within visit window	4	3
Received less than 80% of study drug	3	1
Received additional antimicrobials	1	0
Excluded at Follow-Up:	78	71
No target pathogen isolated pretreatment	54	52
Received additional antimicrobials	7	5
No clinical response assessment within visit window	6	4
Lost to follow-up	5	4
Received less than 3 days of study drug	3	5
Received less than 80% of study drug	3	1
Included in the Microbiologically Evaluable Efficacy Analyses:		
Post-Therapy	183	181
Follow-Up	177	175
Excluded at Post-Therapy:	73	66
No target pathogen isolated pretreatment	54	52
No culture obtained within visit window	7	4
Lost to follow-up	5	4
Received less than 3 days of study drug	3	5
Received less than 80% of study drug	3	1
Received additional antimicrobials	1	0
Excluded at Follow-Up:	79	72
No target pathogen isolated pretreatment	54	52
No culture obtained within visit window	7	6
Received additional antimicrobials	7	4
Lost to follow-up	5	4
Received less than 3 days of study drug	3	5
Received less than 80% of study drug	3	1

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK
Sponsor's Table

Table 1.2. Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group CDTR-PI		PCN-VK		P-value[a]
Total Treated	256		247		
Gender					0.714
Female	161	(63%)	151	(61%)	
Male	95	(37%)	96	(39%)	
Race[b]					0.426
Caucasian	215	(84%)	221	(89%)	
Black	24	(9%)	14	(6%)	
Hispanic	14	(5%)	10	(4%)	
Asian	1	(<1%)	1	(<1%)	
Other	2	(1%)	1	(<1%)	
Age (years)[c]					0.549
<18	51	(20%)	49	(20%)	
18 – 30	95	(37%)	84	(34%)	
31 – 45	96	(38%)	101	(41%)	
>45	14	(5%)	13	(5%)	
Mean (SD)	28.5 (10.9)		29.1 (11.3)		
Range	12 - 67		12 - 80		
Weight (pounds)[c]					0.415
<135	69	(27%)	55	(22%)	
135 – 165	66	(26%)	73	(30%)	
166 – 195	56	(22%)	57	(23%)	
>195	64	(25%)	61	(25%)	
Missing	1	(<1%)	1	(<1%)	
Mean (SD)	166.3 (44.8)		169.5 (43.7)		
Range	76 - 316		82 - 300		
Height (inches)[c]					0.661
Mean (SD)	66.2 (4.1)		66.4 (4.1)		
Range	55 - 77		57 - 77		

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; SD = standard deviation

[a] P-values are from Fisher's exact 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 Fisher's exact test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Table 1.3. Demographic Information (Clinically Evaluable Patients)

Demographic Characteristic	Number of Patients by Treatment Group CDTR-PI		PCN-VK		P-value[a]
Total Treated	186		182		
Gender					0.745
Female	121	(65%)	115	(61%)	
Male	65	(35%)	67	(39%)	
Race[b]					0.961
Caucasian	163	(88%)	161	(88%)	
Black	12	(6%)	11	(6%)	
Hispanic	10	(5%)	8	(4%)	
Asian	0	(0%)	1	(1%)	
Other	1	(1%)	1	(1%)	
Age (years)[c]					0.873
<18	35	(19%)	42	(23%)	
18 - 30	71	(38%)	63	(35%)	
31 - 45	70	(38%)	69	(38%)	
>45	10	(5%)	8	(4%)	
Mean (SD)	28.4 (10.4)		28.2 (10.9)		
Range	12 – 60		12 – 67		
Weight (pounds)[c]					0.781
N	185		181		
<135	50	(27%)	40	(22%)	
135 - 165	46	(25%)	59	(32%)	
166 - 195	41	(22%)	40	(22%)	
>195	48	(26%)	42	(23%)	
Missing	1	(<1%)	1	(<1%)	
Mean (SD)	166.8 (45.1)		168.1 (43.8)		
Range	76 – 316		82 – 300		
Height (inches)[c]					0.994
N	185		182		
Mean (SD)	66.2 (4.0)		66.2 (4.2)		
Range	55 - 77		57 – 77		

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; SD = standard deviation

[a] P-values are from Fisher's exact 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 Fisher's exact test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Statistical Reviewer's Comments:

The demographic information for all patients and evaluable patients are given in Table 1.2 and Table 1.3. *There were no statistically significant differences between the treatment groups in gender, age, race, weight, or height in either all patients or evaluable patients. Among the evaluable patients, Sixty-two percent (63%) of the patients were females and 88% were*

Caucasian. Mean age of the study population was 28.8 years and age ranged from 12 to 80 years.

Table 1.4 Summary of Diagnoses and Baseline Characteristics (All Patients)

Diagnoses and Baseline Characteristics	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	256		247		
Diagnosis					0.768
Pharyngitis and tonsillitis	180	(70%)	180	(73%)	
Pharyngitis	67	(26%)	59	(24%)	
Tonsillitis	9	(4%)	7	(3%)	
Missing	0	(0%)	1	(<1%)	
Number of Infections Within Past Year[b]					0.102
1	196	(77%)	202	(82%)	
2 - 4	59	(23%)	41	(17%)	
>4	1	(<1%)	4	(2%)	
Infection Status					0.851
Mild	39	(15%)	42	(17%)	
Moderate	184	(72%)	170	(69%)	
Severe	33	(13%)	34	(14%)	
Missing	0	(0%)	1	(<1%)	
Clinical Condition					0.840
Good	129	(50%)	126	(51%)	
Fair	123	(48%)	116	(47%)	
Poor	4	(2%)	4	(2%)	
Missing	0	(0%)	1	(<1%)	
Smoking Status					0.574
Non-smoker	187	(73%)	181	(73%)	
Smoker	40	(16%)	44	(18%)	
Ex-smoker	29	(11%)	22	(9%)	
Alcohol Use					0.744
Non-drinker	138	(54%)	141	(57%)	
Drinker	111	(43%)	99	(40%)	
Ex-drinker	7	(3%)	7	(3%)	

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK

[a] P-values are from Fisher's exact test for diagnosis, number of infections within the past year, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status and clinical condition.

[b] Number of streptococcal pharyngitis/tonsillitis infections in past 12 months, including current infection.

Statistical Reviewer's Comments:
Baseline characteristics of the two treatment groups were similar for both all patients and evaluable patients, with no statistically significant differences (Table 1.4). The majority (72%) of patients had a diagnosis of pharyngitis and tonsillitis; the infection was considered moderate

(70%) in most patients. Clinical condition was considered to be good (51%) or fair (48%) in most patients; 79% of the patients reported that this was their first streptococcal pharyngitis and/or tonsillitis infection within the past year while 20% reported two to four infections (including the current infection) within the past year.

Table 1.5. Summary of Pretreatment Signs and Symptoms (All Patients)

Sign/Symptom	Number of Patients by Treatment Group		P-value[a]
	CDTR-PI	PCN-VK	
Total Treated	256	247	
Sore Throat	(N=256)	(N=247)	0.739
Mild	37 (14%)	35 (14%)	
Moderate	124 (48%)	126 (51%)	
Severe	95 (37%)	86 (35%)	
Fever	(N=256)	(N=247)	0.387
Absent	207 (81%)	207 (84%)	
Present	49 (19%)	40 (16%)	
Pharyngeal Erythema	(N=256)	(N=246)	0.442
Absent	8 (3%)	5 (2%)	
Present	248 (97%)	241 (98%)	
Pharyngeal Exudate	(N=256)	(N=246)	0.376
Absent	135 (53%)	120 (49%)	
Present	121 (47%)	126 (51%)	
Tonsillar Erythema	(N=229)	(N=220)	0.220
Absent	23 (10%)	15 (7%)	
Present	206 (90%)	205 (93%)	
Tonsillar Exudate	(N=229)	(N=220)	0.016*
Absent	110 (48%)	81 (37%)	
Present	119 (52%)	139 (63%)	
Cervical Lymph Node Tenderness	(N=256)	(N=246)	0.934
Absent	43 (17%)	42 (17%)	
Present	213 (83%)	204 (83%)	
Headache	(N=256)	(N=247)	0.590
Absent	94 (37%)	85 (34%)	
Present	162 (63%)	162 (66%)	
Abdominal Pain	(N=256)	(N=247)	0.376
Absent	214 (84%)	199 (81%)	
Present	42 (16%)	48 (19%)	

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK,
* Indicates statistical significance at the 0.05 level.
[a] P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.
Sponsor's Table

Statistical Reviewer's Comments:

Pretreatment signs and symptoms in all patients and in evaluable patients were similar between the two treatment groups, with the exception of a statistically significant treatment difference in tonsillar exudate. Fifty-two percent (52%) of patients in the CDTR-PI group reported tonsillar exudate compared to 63% of patients in the PCN-VK group (p=0.016). All patients reported sore throat, as required for entry by the protocol. Overall, the most frequently reported signs or symptoms other than sore throat were pharyngeal erythema and tonsillar erythema (Table 1.5).

Table 1.6 Clinical Response at the Follow-Up Visit (Evaluable Patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		[95% CI for Difference][a]
Cure	159/178	(89%)	153/176	(87%)	
Failure	19/178	(11%)	23/176	(13%)	[-4.3, 9.1]

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; CI = confidence interval
[a] The 95% CI for the difference in cure rates was calculated using normal approximation for the binomial distribution.

Table 1.7 Clinical Response at the Follow-Up Visit (Intent to treat Patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		[95% CI for Difference][b]
Cure	165/202	(82%)	158/195	(81%)	
Failure	37/202	(18%)	37/195	(19%)	[-7.0, 8.3]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval
[a] The 95% CI for the difference in cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

The clinical cure rates in the CDTR-PI and PCN-VK groups among the evaluable were 89% and 87% at the follow up visit as given in Table 1.6. The 95% CI for the difference in clinical cure rates demonstrated that the CDTR-PI group was equivalent to the PCN-VK group. The clinical cure rates were 82% and 81% among the ITT population and the 95% CI for the difference in the clinical cure rates demonstrated that the CDTR-PI group was equivalent to the PCN-VK group using a delta of 10% as given in Table 1.7.

Table 1.8. Microbiologic Response at the Follow-Up Visit (Evaluable Patients)

Microbiologic Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		[95% CI for Difference][a]
Eradication	150/177	(85%)	131/175	(75%)	
Persistence	27/177	(15%)	44/175	(25%)	[1.6, 18.2]

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; CI = confidence interval
[*] Indicates statistical significance at the 0.05 level.
[a] The 95% CI for the difference in eradication rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Among the evaluable patients at follow up a higher microbiologic eradication rate was observed in the CDTR-PI group (85%) than in the PCN-VK group (75%). Microbiologic eradication and persistence rates at the follow up visit and the 95% confidence limits (CI) are given in Table 1.8. The 95% CI for the difference in eradication rates demonstrated that the CDTR-PI group was equivalent to the PCN-VK group, using a delta of 10%.

Table 1.9 Microbiologic Response at the Follow-Up Visit (Intent to treat Patients)

Microbiologic Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		[95% CI for Difference][a]
Eradication	157/202	(78%)	136/195	(70%)	
Persistence	45/202	(22%)	59/195	(30%)	[-0.7, 16.6]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval
* Indicates statistical significance at the 0.05 level.
[a] The 95% CI for the difference in eradication rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

Microbiologic eradication and persistence rates at follow-up in intent-to-treat patients differed from those in evaluable patients (Table 1.9). Eradication rates were 78% in the CDTR-PI group and 70% in the PCN-VK group. The 95% CI for the difference in eradication rates demonstrated that the CDTR-PI group was equivalent to the PCN-VK group, using a delta of 10%.

SAFETY

All patients who received at least one dose of study drug (N=503) were included in the safety analyses.

Table 1.10 Summary of Common[a] Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI (N=256)					PCN-VK (N=247)				
	Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				91	36%				89	36%
BODY AS A WHOLE				32	13%				34	14%
Headache	3	6	2	11	4%	8	3	1	12	5%
Abdominal pain	4	2	2	8	3%	2	0	0	2	1%
Infection	1	2	0	3	1%	9	0	0	9	4%
DIGESTIVE SYSTEM				42	16%				30	12%
Diarrhea*	14	9	1	24	9%	5	3	1	9	4%
Nausea	4	2	0	6	2%	7	1	0	8	3%
RESPIRATORY SYSTEM				15	6%				23	9%
Rhinitis	2	2	0	4	2%	5	1	1	7	3%

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; Mod = moderate; Sev = severe
* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.
[a] Adverse events occurring in ≥3% of patients in either 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.
Sponsor's Table

Table 1.11 Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI (N=256)					PCN-VK (N=247)				
	Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				51	20%				56	23%
BODY AS A WHOLE				13	5%				14	6%
Abdominal pain	4	1	2	7	3%	2	0	0	2	1%
DIGESTIVE SYSTEM				37	14%				26	11%
Diarrhea*	14	8	1	23	9%	5	3	1	9	4%
Nausea	3	2	0	5	2%	6	1	0	7	3%

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; Mod = moderate; Sev = severe
* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.
[a] Treatment-related adverse events occurring in ≥3% of patients in either 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.
Sponsor's Table

Statistical Reviewer's Comments:

During treatment, the incidences of all adverse events and treatment-related adverse events were 36% and 20%, respectively, in the CDTR-PI group and 36% and 23%, respectively, in the PCN-VK group (Tables 1.10 and 1.11). The most frequently occurring treatment-related adverse events during treatment were diarrhea and abdominal pain in the CDTR-PI group and diarrhea and nausea in the PCN-VK group. A statistically significant treatment difference was observed in the incidence of treatment-related diarrhea, with 9% of the CDTR-PI group and 4% of the PCN-VK group reporting this adverse event (p=0.017).

APPEARS THIS WAY
ON ORIGINAL

STUDY NUMBER: CEF-97-0010

INTRODUCTION

Study Objectives

In this study, the sponsor compared the safety and efficacy of orally administered cefditoren pivoxil 200 mg BID and penicillin VK 250 mg QID in the treatment of patients with pharyngitis and/or tonsillitis of proven *Streptococcal pyogenes* etiology who were suitable candidates for oral antibiotic therapy.

Study Design

This was a Phase III, randomized, double-blind, active-controlled, parallel-group, multicenter study in outpatients with streptococcal pharyngitis and/or tonsillitis. Approximately 30 investigators were to enroll 500 eligible patients. Patients with a positive enzyme immunoassay for *S. pyogenes* antigen who met the selection criteria were randomly assigned in a 1:1 ratio to receive either cefditoren pivoxil (CDTR-PI) tablets, 200 mg BID for 10 days, or penicillin VK (PCN-VK) tablets, 250 mg QID 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

The efficacy evaluation, efficacy variables for clinical and microbiologic responses, the demographic and baseline variables and the methodology for analyses are similar as in Study CEF-97-008.

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 10%, to establish equivalence for this indication

RESULTS

EFFICACY

The patient disposition is given in Table 2.1. A total of 508 patients were randomized in the study and received study drug; 254 patients received cefditoren pivoxil 200 mg BID (CDTR-PI) and 254 patients received penicillin VK 250 mg QID (PCN-VK).

At the Follow-Up Visit, 360 (180 in the CDTR-PI group and 180 in the PCN-VK group) patients were clinically evaluable and 148 (74 in the CDTR-PI group and 74 in the PCN-VK group) were excluded from the clinically evaluable efficacy analyses. At the Follow-Up Visit, 355 (179 in the CDTR-PI group and 176 in the PCN-VK group) patients were microbiologically evaluable and 153 (75 in the CDTR-PI group and 78 in the PCN-VK group) were excluded from the microbiologically evaluable efficacy analyses.

APPEARS THIS WAY
ON ORIGINAL

Table 2.1. Disposition of Patients by Data Set

	CDTR-PI	PCN-VK
All Patients: Total Randomized and Received Study Drug	254	254
S. pyogenes not isolated pretreatment	53	53
Intent-to-Treat Analyses	201	201
Included in the Clinically Evaluable Efficacy Analyses:		
Post-Therapy	183	185
Follow-Up	180	180
Excluded at Post-Therapy:	71	69
No target pathogen isolated pretreatment	53	53
No clinical response assessment within visit window	4	7
Received less than 3 consecutive days of study drug	6	3
Received less than 80% of study drug	3	5
Lost to follow-up	3	0
Received additional antimicrobials	1	1
Treatment blind broken prior to visit	1	0
Excluded at Follow-Up:	74	74
No target pathogen isolated pretreatment	53	53
No clinical response assessment within visit window	5	8
Received less than 3 consecutive days of study drug	6	3
Received less than 80% of study drug	3	5
Received additional antimicrobials	3	5
Lost to follow-up	3	0
Treatment blind broken prior to visit	1	0
Included in the Microbiologically Evaluable Efficacy Analyses:		
Post-Therapy	181	183
Follow-Up	179	176
Excluded at Post-Therapy:	73	71
No target pathogen isolated pretreatment	53	53
No culture obtained within visit window	6	9
Received less than 3 consecutive days of study drug	6	3
Received less than 80% of study drug	3	5
Lost to follow-up	3	0
Received additional antimicrobials	1	1
Treatment blind broken prior to visit	1	0
Excluded at Follow-Up:	75	78
No target pathogen isolated pretreatment	53	53
No culture obtained within visit window	6	12
Received less than 3 consecutive days of study drug	6	3
Received additional antimicrobials	3	5
Received less than 80% of study drug	3	5
Lost to follow-up	3	0
Treatment blind broken prior to visit	1	0

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK : Sponsor's Table

Table 2.2 Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group		P-value[a]
	CDTR-PI	PCN-VK	
Total Treated	254	254	
Gender			0.228
Female	157 (62%)	171 (67%)	
Male	97 (38%)	83 (33%)	
Race			0.742[b]
Caucasian	219 (86%)	225 (89%)	
Hispanic	20 (8%)	17 (7%)	
Black	10 (4%)	10 (4%)	
Asian	1 (<1%)	1 (<1%)	
Other	4 (2%)	1 (<1%)	
Age (years)[c]			0.475
<18	72 (28%)	56 (22%)	
18 – 30	93 (37%)	99 (39%)	
31 – 45	77 (30%)	81 (32%)	
>45	12 (5%)	18 (7%)	
Mean (SD)	26.4 (10.9)	27.1 (11.0)	
Range	11 - 74	12 - 72	
Weight (pounds)[c]			0.053
<135	82 (32%)	74 (29%)	
135 – 165	85 (33%)	66 (26%)	
166 – 195	43 (17%)	58 (23%)	
>195	44 (17%)	56 (22%)	
Mean (SD)	156.9 (41.6)	164.3 (43.9)	
Range	75 - 311	83 - 342	
Height (inches)[c]			0.650
Mean (SD)	66.0 (4.0)	66.2 (3.9)	
Range	55 - 78	54 - 76	

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; SD = standard deviation

[a] P-values are from Fisher's exact 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 Fisher's exact test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Table 2.3 Demographic Information (Evaluable Patients)

Demographic Characteristic	Number of Patients by Treatment Group CDTR-PI		PCN-VK		P-value[a]
Total Treated	183		185		
Gender					0.912
Female	121	(66%)	124	(67%)	
Male	62	(34%)	61	(33%)	
Race[b]					0.697
Caucasian	163	(89%)	171	(92%)	
Black	4	(2%)	3	(2%)	
Hispanic	12	(7%)	10	(5%)	
Asian	1	(1%)	0	(0%)	
Other	3	(2%)	1	(1%)	
Age (years)[c]					0.345
<18	55	(30%)	41	(22%)	
18 - 30	68	(37%)	73	(39%)	
31 - 45	55	(30%)	63	(34%)	
>45	5	(3%)	8	(4%)	
Mean (SD)	25.6 (10.2)		26.6 (10.2)		
Range	12 - 64		12 – 58		
Weight (pounds)[c]					0.018
<135	65	(36%)	58	(31%)	
135 - 165	63	(34%)	48	(26%)	
166 - 195	29	(16%)	38	(21%)	
>195	26	(14%)	41	(22%)	
Mean (SD)	152.2 (37.8)		162.2 (42.9)		
Range	75 - 311		83 – 323		
Height (inches)[c]					0.179
Mean (SD)	65.8 (3.9)		66.4 (3.7)		
Range	55 - 75		54 – 76		

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; SD = standard deviation

[a] P-values are from Fisher's exact 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 Fisher's exact test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Statistical Reviewer's Comments:

The demographic information for all patients and evaluable patients are given in Table 2.2 and Table 2.3. *There were no statistically significant differences between the treatment groups in gender, age, race, weight, or height in all patients. Sixty-five percent (65%) of all the patients were females and 87% were Caucasian. Mean age of the study population was 26.8 years and age ranged from 11 to 74 years.*

Demographic variables in the evaluable population, *the two treatment groups were comparable regarding the variables of age, sex, race, height and weight. Among evaluable patients, there is statistically significant difference (p=0.018) in weight between the two treatment groups.*

Table 2.4 Summary of Diagnoses and Baseline Characteristics (All Patients)

Diagnoses and Baseline Characteristics	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	254		254		
Diagnosis					0.756
Pharyngitis and tonsillitis	183	(72%)	189	(74%)	
Pharyngitis	59	(23%)	52	(20%)	
Tonsillitis	12	(5%)	13	(5%)	
Number of Infections Within Past Year[b]					0.441
1	185	(73%)	197	(78%)	
2 - 4	67	(26%)	56	(22%)	
>4	2	(1%)	1	(<1%)	
Infection Status					0.099
Mild	44	(17%)	29	(11%)	
Moderate	182	(72%)	193	(76%)	
Severe	28	(11%)	32	(13%)	
Clinical Condition					0.168
Good	153	(60%)	137	(54%)	
Fair	98	(39%)	114	(45%)	
Poor	3	(1%)	3	(1%)	
Smoking Status					0.580
Non-smoker	187	(74%)	193	(76%)	
Smoker	40	(16%)	41	(16%)	
Ex-smoker	27	(11%)	20	(8%)	
Alcohol Use					0.166
Non-drinker	168	(66%)	173	(68%)	
Drinker	76	(30%)	78	(31%)	
Ex-drinker	10	(4%)	3	(1%)	

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK

[a] P-values are from Fisher's exact test for diagnosis, number of infections within the past year, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status and clinical condition.

[b] Number of streptococcal pharyngitis/tonsillitis infections in past 12 months, including current infection.

Statistical Reviewer's Comments:

Baseline characteristics of the two treatment groups were similar for all patients, with no statistically significant differences (Table 2.4). The majority (73%) of patients had a diagnosis of pharyngitis and tonsillitis; the infection was considered moderate (74%) in most patients.

Clinical condition was considered to be good (57%) or fair (42%) in most patients; 75% of the patients reported that this was their first streptococcal pharyngitis and/or tonsillitis infection within the past year while 24% reported two to four infections (including the current infection) within the past year.

Table 2.5 Summary of Pretreatment Signs and Symptoms (All Patients)

Sign/Symptom	Number of Patients by Treatment Group		P-value[a]
	CDTR-PI	PCN-VK	
Total Treated	254	254	
Sore Throat	(N=254)	(N=254)	0.204
Mild	36 (14%)	27 (11%)	
Moderate	126 (50%)	125 (49%)	
Severe	92 (36%)	102 (40%)	
Fever	(N=254)	(N=254)	0.633
Absent	234 (92%)	231 (91%)	
Present	20 (8%)	23 (9%)	
Pharyngeal Erythema	(N=254)	(N=254)	0.437
Absent	16 (6%)	12 (5%)	
Present	238 (94%)	242 (95%)	
Pharyngeal Exudate	(N=254)	(N=254)	0.101
Absent	165 (65%)	147 (58%)	
Present	89 (35%)	107 (42%)	
Tonsillar Erythema	(N=220)	(N=225)	0.920
Absent	18 (8%)	19 (8%)	
Present	202 (92%)	206 (92%)	
Tonsillar Exudate	(N=220)	(N=225)	0.619
Absent	100 (45%)	97 (43%)	
Present	120 (55%)	128 (57%)	
Cervical Lymph Node Tenderness	(N=254)	(N=254)	0.254
Absent	52 (20%)	42 (17%)	
Present	202 (80%)	212 (83%)	
Headache	(N=254)	(N=254)	0.926
Absent	90 (35%)	89 (35%)	
Present	164 (65%)	165 (65%)	
Abdominal Pain	(N=254)	(N=254)	0.576
Absent	207 (81%)	202 (80%)	
Present	47 (19%)	52 (20%)	

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK

[a] P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.

Statistical Reviewer's Comments:

Pretreatment signs and symptoms in all patients were similar between the two treatment groups, with no statistically significant differences (Table 2.5). All patients reported sore throat, as required for entry by the protocol. Overall, the most frequently reported signs or symptoms other than sore throat were pharyngeal erythema and tonsillar erythema. Pretreatment signs and symptoms of evaluable patients were similar to those of all patients.

Primary Efficacy Variables

Clinical Response

Efficacy Results:

Table 2.6 Clinical Response at the Follow-Up Visit (Evaluable Patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		[95% CI for Difference][a]
Cure	160/180	(89%)	152/180	(84%)	
Failure	20/180	(11%)	28/180	(16%)	[-2.6, 11.5]

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; CI = confidence interval
[a] The 95% CI for the difference in cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's comments:

Clinical cure rates among the evaluable patients were similar at the Follow-Up Visit in the CDTR-PI (89%) and PCN-VK (84%) treatment groups(Table 2.6). The 95% CI for the difference (-2.6, 11.5) in clinical cure rates demonstrated that the CDTR-PI group was equivalent to the PCN-VK group using a delta of 10%.

Table 2.7 Clinical Response at the Follow-Up Visit (Intent to treat Patients)

Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		[95% CI for Difference][a]
Cure	166/201	(83%)	160/201	(80%)	
Failure	35/201	(17%)	41/201	(20%)	[-4.7, 10.6]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval
[a] The 95% CI for the difference in cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's comments:

Clinical cure rates among the ITT patients were at the Follow-Up Visit in the CDTR-PI (83%) and PCN-VK (80%) treatment groups (Table 2.7). The 95% CI for the difference (-4.7, 10.6) in clinical cure rates demonstrated that the CDTR-PI group was equivalent to the PCN-VK group using a delta of 10%.

Microbiologic Response

Table 2.8 Microbiologic Response at the Follow-Up Visit (Evaluable Patients)					
Microbiologic Response	**CDTR-PI n/N (%)**		**PCN-VK n/N (%)**		**[95% CI for Difference]•**
Eradication	151/179	(84%)	138/176	(78%)	
Persistence	28/179	(16%)	38/176	(22%)	[-2.1,-14.0]
CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; CI = confidence interval • The 95% CI for the difference in eradication rates was calculated using normal approximation for the binomial distribution.					

Statistical Reviewer's comments:

Among the evaluable patients at the Follow-Up Visit, microbiologic eradication rates were 84% in the CDTR-PI group and 78% in the PCN-VK group (Table 2.8). The 95% CI for the difference in eradication rates (-2.1, 14.0) demonstrated that the CDTR-PI group was equivalent to the PCN-VK group, using a delta of 10%.

Table 2.9 Microbiologic Response at the Follow-Up Visit (Intent to treat patients)					
Microbiologic Response	**CDTR-PI n/N (%)**		**PCN-VK n/N (%)**		**[95% CI for Difference]•**
Eradication	158/201	(79%)	147/201	(73%)	
Persistence	43/201	(21%)	54/201	(27%)	[-2.9, 13.8]
CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval • The 95% CI for the difference in eradication rates was calculated using normal approximation for the binomial distribution.					

Statistical Reviewer's comments:

Among the ITT patients at the Follow-Up Visit, microbiologic eradication rates were 79% in the CDTR-PI group and 73% in the PCN-VK group (Table 2.9). The 95% CI for the difference in eradication rates (-2.9, 13.8) demonstrated that the CDTR-PI group was equivalent to the PCN-VK group, using a delta of 10%.

SAFETY

All patients who received at least one dose of study drug (N=508) were included in the safety analyses.

Table 2.10 Summary of Common[a] Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI (N=254)					PCN-VK (N=254)				
	Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				96	38%				93	37%
BODY AS A WHOLE				32	13%				37	15%
Headache	8	6	1	15	6%	7	11	0	18	7%
Abdominal pain*	6	4	0	10	4%	0	2	0	2	1%
DIGESTIVE SYSTEM				51	20%				31	12%
Diarrhea*	16	13	1	30	12%	7	3	1	11	4%
Nausea	7	7	1	15	6%	11	4	0	15	6%
Vomiting	3	4	0	7	3%	1	4	0	5	2%
NERVOUS SYSTEM				8	3%				16	6%
Dizziness	2	0	0	2	1%	4	3	0	7	3%
RESPIRATORY SYSTEM				10	4%				17	7%
Rhinitis	2	0	0	2	1%	4	4	0	8	3%
Cough increased	2	0	1	3	1%	1	6	0	7	3%
SKIN & APPENDAGES				14	6%				11	4%
Rash	6	1	0	7	3%	2	0	0	2	1%
UROGENITAL SYSTEM				N=157					N=171	
(FEMALE)[d]				5	3%				7	4%
Vaginal moniliasis	2	0	0	2	1%	5	1	0	6	4%

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; Mod = moderate; Sev = severe

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[a] Adverse events occurring in ≥3% of patients in either 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] Female-specific adverse events.

Sponsor's Table

Table 2.11 Summary of Common[a] Treatment-Related Adverse Events Grouped by COSTART Term (During Treatment)

	CDTR-PI (N=254)					PCN-VK (N=254)				
	Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[c]				65	26%				50	20%
BODY AS A WHOLE				16	6%				12	5%
Abdominal pain	5	4	0	9	4%	0	2	0	2	1%
Headache	3	3	0	6	2%	3	4	0	7	3%
DIGESTIVE SYSTEM				45	18%				26	10%
Diarrhea*	16	12	1	29	11%	7	3	1	11	4%
Nausea	7	6	0	13	5%	8	4	0	12	5%
UROGENITAL				N=157					N=171	
SYSTEM (FEMALE)[d]				4	3%				6	4%
Vaginal moniliasis	2	0	0	2	1%	5	1	0	6	4%

CDTR-PI = cefditoren pivoxil; PCN-VK = penicillin VK; Mod = moderate; Sev = severe

* Indicates statistical significance at the 0.05 level, using Fisher's exact test to compare treatment groups.

[a] Treatment-related adverse events occurring in ≥3% of patients in either 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] Female-specific adverse events.

Statistical Reviewer's Comments:

During treatment, the incidences of all adverse events and treatment-related adverse events were 38% and 26%, respectively, in the CDTR-PI group and 37% and 20%, respectively, in the PCN-VK group (Table 2.10 and Table 2.11). The most frequently occurring treatment-related adverse events during treatment in both groups were diarrhea and nausea. A statistically significant treatment difference was observed in the incidence of treatment-related diarrhea, with 11% of the CDTR-PI group and 4% of the PCN-VK group reporting this adverse event (p=0.005).

OVERALL SUMMARY AND CONCLUSIONS

In study 008, the clinical cure rates among the evaluable and intent-to-treat patients in the CDTR-PI and PCN-VK groups at the Follow-Up visits were (89% , 87%) and (82%, 81%) respectively. The 95% confidence intervals for the differences in clinical cure rates demonstrated that the two treatments were equivalent using a delta of 10%.

Microbiologic eradication rates among the evaluable and intent-to-treat patients in the CDTR-PI and PCN-VK groups at the Follow-Up visits were (85% , 75%) and (78%, 70%). The 95% confidence intervals for the differences in microbiologic eradication rates demonstrated that the two treatments were equivalent using a delta of 10%.

In study 010, Clinical cure rates among the evaluable and intent-to-treat patients in the CDTR-PI and PCN-VK groups at the follow up visits were (89%, 84%) and (83% and 80%) respectively. The 95% confidence intervals for the differences in clinical cure rates demonstrated that the two treatments were equivalent using a delta of 10%.

Microbiologic eradication rates among the evaluable and intent-to-treat patients in the CDTR-PI and PCN-VK groups at the Follow-Up visits were (84%, 78%) and (79%, 73%). The 95% confidence intervals for the differences in microbiologic eradication rates demonstrated that the two treatments were equivalent using a delta of 10%.

Results of these studies indicated that cefditoren pivoxil (200 mg BID for 10 days) was equivalent to penicillin VK (250 mg QID for 10 days) in eradicating *S. pyogenes* in the treatment of patients with pharyngitis and /or tonsillitis.

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