CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-222

MEDICAL REVIEW

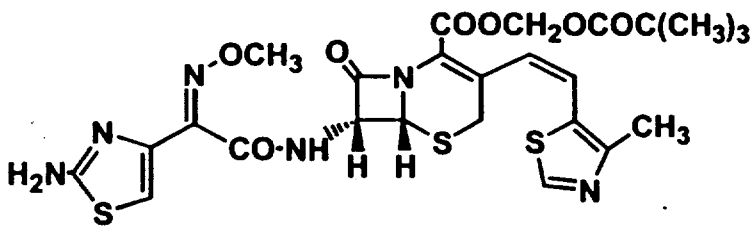
ADDENDUM TO MEDICAL OFFICER REVIEW OF ORIGINAL NDA 21-222:
Response to Approvable Letter

Date of Submission: March 02, 2001
Date Review Completed: August 17, 2001

Applicant:	TAP Holdings, Inc. 675 North Field Drive Lake Forest, IL 60045
Regulatory Contact:	Donna Helms, Associate Director of Regulatory Affairs (847) 267-4922

DRUG PRODUCT INFORMATION

Established Name:	Cefditoren Pivoxil
Trade Name:	Spectracef™
Chemical Name:	(-)-(6R,7R)-2,2-dimethylproprionyloxymethyl 7-[(Z)-2-(2-amionthiazol-4-yl)-2-methoxyimino acetamido}-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
Chem. formula:	$C_{25}H_{28}N_6O_7S_3$
Molecular weight:	620.73
Chem. structure:	



Drug Category:	Cephalosporin antibiotic
Dosage Form:	Tablet
Dosage Strength:	200 mg
Route of Administration:	Oral

Materials Reviewed:	25 volumes submitted to NDA on Jan. 15, 2001 (Received Jan. 17) Modified Integrated Summary of Microbiology – 11 volumes submitted on Feb. 28, 2001 (Received March 01) Modified Integrated Summary of Safety – 6 volumes submitted on March 01, 2001 (Received March 02)

83 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Medical Officer's Review of NDA 21-222 (Cefditoren Pivoxil) in the Treatment of Streptococcal Pharyngitis

Date of Submission: December 29, 1999

Date received: January 6, 2000

Date of Assignment: January 20, 2000

Date of Completion: September 6, 2000

Date Revisions completed: July 31, 2001

Drug:

Pharmacologic Name: Cefditoren Pivoxil
Trade Name: Spectracef ®

Sponsor: TAP Pharmaceutical Products Inc.
675 North Field drive
Lake Forest, IL 60045

INDICATION AND DOSAGE

The sponsor proposes the use of Cefditoren pivoxil 200 mg BID for 10 days for the treatment of streptococcal pharyngitis.

RESUME

Two multi-center studies (CEF-97-008 and CEF-97-010) were conducted to compare the safety and efficacy of orally administered Cefditoren pivoxil 200 mg BID and Penicillin VK 250 mg QID in the treatment of patients with streptococcal pharyngitis. 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 of the two drugs for 10 days. Patients returned for a post-therapy visit 4-7 days after the last dose and for a follow-up visit 19-25 days after the last dose. Clinical and microbiologic cures were assessed at both visits.

In study CEF-97-008, clinical cure rates were similar in the two treatment groups at the post-therapy visit and at the follow-up visit. Microbiologic eradication rates were higher in the Cefditoren group at the post-therapy visit in both intent to treat and per protocol patients. At the follow-up visit, eradication rates were higher only among the per protocol patients. In study CEF-97-010, clinical and microbiologic cure rates were similar in both treatment groups at the post therapy and follow-up visits.
Based on the two studies submitted, which demonstrated clinical and microbiologic equivalence with penicillin VK 250 mg QID for 10 days, Cefditoren pivoxil 200 mg BID for 10 days is recommended for approval for the treatment of streptococcal pharyngitis.

STUDY TITLE

Comparative safety and efficacy of Cefditoren pivoxil and Penicillin VK in the treatment of patients with streptococcal pharyngitis.

STUDY SITES

Study CEF-97-008 was conducted at 38 sites and study CEF-97-010 was conducted at 47 sites, in the United States.

STUDY PERIOD

CEF-97-008 December 11, 1997-July 10, 1998
CEF-97-010 March 24, 1998- September 11, 1998.

STUDY OBJECTIVES

To compare 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 ≥12 years of age with pharyngitis and /or tonsillitis due to *Streptococcus pyogenes.*

STUDY DESIGN

The following was abstracted from the applicant's submission. The study design applies to both studies.

These were Phase III, double-blind, randomized, active-controlled, parallel-group, multi-center studies.

Patients who presented at the Pre-Therapy Visit with a chief complaint of pharyngeal pain accompanied by at least one other sign of streptococcal pharyngitis (i.e., pharyngeal erythema/exudate, tonsillar erythema/exudate, cervical lymph node tenderness, or fever) had the nature of the study explained. After written informed consent was obtained from the patient (and parent or legal guardian of minor patients), a complete medical and social history was documented and physical examination, vital signs assessment, and laboratory evaluations were performed.

The diagnosis of pharyngitis/tonsillitis was made if the patient had sore throat plus one additional sign or symptom of streptococcal infection, as listed in Table1.

Table 1 Assessment of Clinical Signs and Symptoms		
Clinical Sign/Symptom	**Assessments**	
Sore throat	Absent	No pain (not applicable at pretreatment)
	Mild	Some discomfort upon swallowing; pain easily tolerated
	Moderate	Pain intermittently present whether swallowing or not; difficulty swallowing
	Severe	Continuous pain whether swallowing or not; swallowing very difficult
Pharyngeal erythema/exudate	Absent or present	
Tonsillar erythema/exudate	Absent or present	
Cervical lymph node tenderness	Absent or present	
Headache within the previous 24 hours	Absent or present	
Abdominal pain within the previous 24 hours	Absent or present	
Fever	Absent or present (≥ 100.4°F [oral] or ≥ 101.2°F [tympanic])	

Clinical signs and symptoms were assessed at each visit. Based on pre-treatment clinical signs and symptoms, physical findings, and laboratory test results, each patient's infection status was classified as mild, moderate or severe and each patient's overall clinical condition was assessed as good, fair or poor.

Two throat swabs were obtained pre-treatment. One swab was tested for the presence of *S. pyogenes* antigen using a rapid enzyme immunoassay. The second swab was placed in a transport medium for subsequent culture to confirm the diagnosis. If no pathogen was isolated from the pre-treatment culture, the patient was continued in the study with only clinical response assessed. All cultures positive for *S.pyogenes* were subcultured and retained at -70^0C in the laboratory. Isolates cultured at the post-therapy visit and/or the follow-up visit were paired with the isolate cultured at the pre-therapy visit for each patient. Serum for ASO and anti-DNaseB titers was collected at the pre-therapy and follow-up visits.

Patients with a positive enzyme immunoassay for *S. pyogenes* antigen and who met the selection criteria were randomly assigned to receive either Cefditoren pivoxil 200 mg BID or Penicillin VK 250 mg QID for 10 days. They received either Cefditoren pivoxil tablets 200 mg BID plus placebo capsules for Penicillin VK QID or Penicillin VK tablets 250 mg QID (placed in capsules) plus placebo tablets for Cefditoren pivoxil BID.

The investigator or study coordinator contacted the patient by telephone once during Study Days 3 to 5 to assess the patient's clinical status and determine whether an on-therapy visit was necessary. If an office visit was not clinically indicated, the investigator assessed adverse events, study drug compliance and concurrent medication use by telephone interview.

If an on-therapy visit was required, clinical signs and symptoms were assessed, blood and urine samples obtained for laboratory tests, a throat specimen obtained for culture, adverse events and concurrent medications recorded, and compliance assessed by counting the number of capsules and tablets remaining in each blister card.

Patients returned to the investigator's office for a Post-Therapy Visit (4 to 7 days after the last dose) or within 48 hours of early discontinuation of study drug. Patients

also had a Follow-Up Visit (19 to 25 days after the last dose) or earlier if signs and symptoms of infection worsened or recurred.

At both post-treatment visits, specimens for throat culture were obtained, clinical assessment performed and clinical response to therapy assigned by the investigator. The total duration of each patient's participation in the study was approximately 5 weeks. The study schematic is given in Table 2.

Table 2 Study Schematic

Study Procedure	Pretreatment	During Treatment	Post-treatment***		
	Pre-Therapy Visit Study Day 1*	Telephone Contact**/ On-Therapy Visit Study Day 3 to 5	Post-Therapy Visit (4 to 7 days after last dose)	Follow-Up Visit (19 to 25 days after last dose)	Unscheduled Visit
Informed Consent	X				
Medical History	X				
Physical Examination	X		X	X	X#
Signs/Symptoms	X	X	X	X	X
Vital Signs	X	X	X	X	X#
Infection Status and Clinical Condition	X				
Pregnancy Test	X[a]				X#
Microbiology Culture	X[b]	X	X	X	X#
Laboratory Tests	X	X	X		
Serology[c]	X			X	
Dispense Study Drug	X				
Evaluate Study Drug Compliance		X**	X		
Adverse Event Assessment		X**	X	X	X
Assess Concomitant Medications	X	X**	X	X	
Assess Clinical Response to Therapy			X	X	

* Study Day 1 was the day the first dose was administered.

** Telephone contact to assess patient's status (study drug compliance, adverse event[s] and concomitant medication[s]) and schedule the On-Therapy Visit, if clinically indicated. If On-Therapy Visit was clinically indicated, all procedures were to be performed.

*** Patients who were prematurely discontinued from the study drug therapy were to complete Post-Therapy and Follow-Up Visit evaluations. Patients who were clinical failures were not required to return for the Follow-Up Visit.

[a] Pregnancy tests were to be performed on all women of childbearing potential and results must have been negative for entry into the study.

[b] Two pharyngeal swabs were obtained; the first swab was tested at Study Day 1 using a rapid enzyme immunoassay and the second swab was sent to [redacted] for culture.

[c] ASO and ADN-B.

If deemed necessary.

MEDICAL OFFICER'S COMMENTS:

Overall, the study design is strong. Subjects were selected on the basis of signs and symptoms of tonsillopharyngitis and the presence of a positive rapid enzyme immunoassay test for S. pyogenes. This will exclude at least some asymptomatic carriers of S. pyogenes, but not those carriers with an intercurrent viral infection. Serological tests performed provide evidence of recent streptococcal infection, but do not exclude a recent streptococcal infection as some patients will not demonstrate significant elevation in titers.

INCLUSION CRITERIA

Patients were required to meet all of the following criteria to be considered for inclusion in this study:

- Sore throat plus at least one other sign of streptococcal pharyngitis and/or tonsillitis (i.e., pharyngeal erythema/exudate, tonsillar erythema/exudate, cervical lymph node tenderness, or fever).
- Positive rapid enzyme immunoassay for *S. pyogenes* antigen.
- Was not seriously ill and had streptococcal pharyngitis and/or tonsillitis that was suitable for oral antibiotic therapy.
- Was 12 years of age or older and weighed at least 34 kilograms (75 pounds).
- Female patients were to be non-lactating and at no risk of pregnancy (i.e., post-menopausal for at least 1 year, hysterectomized, or had tubal ligation). A female patient with childbearing potential could be enrolled provided she had a negative pre-study urine pregnancy test and would utilize oral contraceptives, intrauterine device, Depo Provera, Norplant, or barrier contraceptive methods throughout the study. If oral contraceptives, Depo Provera, or Norplant were used, the patient must have taken the contraceptive for at least 3 months prior to study entry.
- Was otherwise in good general health.
- Voluntarily signed a consent form after the nature of the study was explained. If the patient was not of legal age, the consent form was to be signed by both the patient and the parent or legal guardian.

EXCLUSION CRITERIA

Patients were excluded from enrollment for any of the following reasons:

- History of hypersensitivity to penicillin, cephalosporins, or β-lactam antibiotics.
- Treatment with a systemic antibiotic within 7 days prior to study drug administration or treatment with a long-acting injectable antibiotic (e.g., penicillin G benzathine) within 30 days prior to study drug administration.
- Treatment with azithromycin within 2 weeks prior to study drug administration.
- Any infection which necessitated the use of a concomitant antibiotic or parenteral antibiotic therapy.
- Receipt of chronic treatment with anticoagulants.
- Treatment with an investigational drug within 4 weeks prior to study drug administration.
- Known significant renal or hepatic impairment indicated by recent chemistries:
  - Serum creatinine > 2.0 mg/dL

  - AST/ALT > 2 x the upper limit of normal
  - Alkaline phosphatase > 1.25 x the upper limit of normal
  - Total bilirubin > 2 x the upper limit of normal
  - Blood urea nitrogen (BUN) $\geq$ 30 mg/dL
- Known to have a clinically significant hematologic abnormality.
- Cardiac valvular disease, history of rheumatic fever, or rash suggestive of scarlet fever.
- Immunocompromised host status.
- Previous treatment in this study.
- Currently receiving or likely to require other concomitant oral or systemic antimicrobial therapy or any other investigational agent, during the period between the pre-therapy visit and the follow-up visit.
- Underlying condition/disease that would be likely to interfere with completion of the course of study drug therapy or follow-up.

REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were withdrawn from the study immediately if any of the following occurred:

- There was insufficient improvement in the patient's infection. If the patient had at least 3 days of therapy, the clinical response was rated as "Clinical Failure."
- The investigator believed discontinuation was in the best interest of the patient (e.g., due to an adverse event or clinically significant abnormal laboratory test during treatment).
- The patient or his/her parent or legal guardian requested withdrawal from the study.

If the study drug therapy was prematurely discontinued the primary reason for discontinuation was recorded on the appropriate case report form. Such patients were to return to the investigator's office within 48 hours of discontinuation of the drug and procedures outlined for the post-therapy visit, including clinical evaluations and throat swab, were to be completed. Clinical response to therapy was assigned. These evaluations were to be made before initiation of any new therapeutic measures, but were not in any way to delay institution of any new therapeutic modalities which, in the investigator's opinion, were necessary.

MEDICAL OFFICER'S COMMENTS:

The inclusion /exclusion criteria used by the sponsor are acceptable. Excluding patients with symptoms suggestive of streptococcal pharyngitis, but who have a negative rapid streptococcal antigen test could exclude a few patients who have a false negative rapid test. This will however not introduce a selection bias, as there is no correlation between severity of streptococcal pharyngitis and presence or absence of a positive rapid streptococcal antigen test.

STUDY DRUG ADMINISTRATION

Study medication was provided in blister cards, each containing a daily dose of the study drug. Ten blister cards were provided to each patient. The patient number was pre-printed on the labels provided with the study drug. Patients were instructed to take

one tablet and one capsule after breakfast, one capsule after lunch, one tablet and one capsule after the evening meal, and one capsule at bedtime for 10 days.

BLINDING

Cefditoren pivoxil was supplied as tablets and Penicillin VK as capsules containing the active tablets. Placebo tablets to match cefditoren pivoxil and placebo capsules to match penicillin VK were provided. All packaging was identical in appearance. If the blind was broken, the date, time, and reason the blind was broken were to be recorded on the case report form.

The investigator, all central laboratory staff, all CRO staff, and all TAP Holdings Inc. personnel involved with the conduct and/or analysis of the study were blinded to study treatment. The treatment groups remained blinded until after the study was completed, all clinical data screened, and all patients evaluated.

TREATMENT COMPLIANCE

Patients were instructed to return the study drug including containers, even if empty, at the on-therapy visit (if scheduled) or at the post-therapy visit. Compliance was documented by counting the number of capsules and tablets remaining in each blister card and questioning the patient regarding any discrepancies between number dispensed and number returned.

LABORATORY DATA

Central laboratory services were provided by [redacted] Serotyping for *S. pyogenes* was performed by Edward L.Kaplan of the WHO collaborating Center for Reference and Research on Streptococci at the University of Minnesota. Following laboratory tests were performed:

Table 3 Laboratory Tests

Hematology		Serum Chemistry	
Hemoglobin		Blood Urea Nitrogen (BUN)	Creatinine
Hematocrit		Alkaline Phosphatase	Glucose
White Blood Cell Count (WBC) with Differential		Inorganic Phosphorus	Calcium
Platelet Count		Total Bilirubin	Albumin
		Total Protein	Sodium
Urinalysis		Lactic Dehydrogenase (LDH)	Cholesterol
Specific Gravity	Urine pH	Gamma Glutamyl Transferase (GGT)	Potassium
Glucose	Albumin (Protein)	Aspartate aminotransferase (AST)	Chloride
Hemoglobin	Microscopic examination	Alanine aminotransferase (ALT)	

If a laboratory value(s) outside the reference range occurred during the study that the investigator judged to be clinically significant, the laboratory test was repeated to ensure validity of the abnormal result. Any clinically significantly abnormal laboratory result was to be followed until it returned to normal, became stabilized, or became explainable due to another reason.

Liver and renal function test(s) were to be repeated if one or more of the following was observed:

- AST/ALT > 2 x the upper limit of normal.
- Alkaline phosphatase > 1.25 x the upper limit of normal.
- Creatinine > 2.0 mg/dL (if, creatinine was elevated due to pretreatment dehydration, serum creatinine could be repeated after rehydration)
- Blood urea nitrogen $\geq$ 30 mg/dL.
- Total bilirubin > 2 x the upper limit of normal (total bilirubin was to be repeated and a direct bilirubin was also assessed).

ADVERSE EVENTS

An adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Patients were instructed to contact the investigator if an adverse event occurred. The investigator assessed any adverse event and recorded all necessary information in the case report form. The description of each adverse event included the date of onset and remission, severity, causal relationship to study drug, results of any diagnostic procedures or laboratory tests, all treatments that were required, and the outcome of the event. All adverse events were to be followed by the investigator to a satisfactory resolution or until the event returned to baseline.

Severity of the adverse event was assessed as follows:

Mild	The adverse event was transient and was easily tolerated by the patient.
Moderate	The adverse event caused the patient discomfort and interrupted the patient's normal activities.
Severe	The adverse event caused considerable interference with the patient's normal activities and may have been incapacitating or life-threatening.

The relationship of the adverse event to the study drug was assessed as follows:

Definite	The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and satisfied any of the following: • Reappearance of similar reaction by repeated exposure (rechallenge); • Positive results in drug sensitivity tests (lymphocyte blastoid transformation test, skin test, etc.); • Toxic level of the drug in the blood or other body fluids.
Probable	The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), and the possibilities of factors other than the drug, such as underlying disease complications, concomitant drugs, or concurrent treatment, could be excluded.
Possible	The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), and the possibility of drug involvement could not be excluded, e.g., existence of similar reports attributable to the suspected drug, its analog or its pharmacological effect. However, other factors, such as underlying disease complications, concomitant drugs, or concurrent treatment, were presumable.
Not Related	The adverse event did not follow a reasonable temporal sequence from administration of the drug or it could be reasonably explained by other factors, including underlying disease complications, concomitant drugs, or concurrent treatment.

In the case of a serious adverse event, the sites were instructed to contact a TAP Holdings Inc. monitor or designee within 24 hours with subsequent notification to the IRB. A serious adverse event was defined as any drug experience, at any dose, that resulted in any of the following outcomes:

- Death
- Life-threatening (patient was at risk of death at the time the event occurred)
- Inpatient hospitalization (>23 hours) or prolongation of existing hospitalization
- Congenital anomaly or birth defect
- Persistent or significant disability or incapacity.

MEDICAL OFFICER'S COMMENTS:

The medical officer concurs with the safety criteria outlined by the sponsor.

EFFICACY VARIABLES

Primary Variables

The primary efficacy endpoints used to summarize clinical and microbiologic outcomes at the Post-Therapy and Follow-Up Visits were clinical cure rate and microbiologic cure rate. They were defined as the percentage of patients who had a

clinical response of cure and the percentage of patients in whom *S.pyogenes* was eradicated respectively.

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 definitions in the following tables. 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.

In order to analyze the data according to the July 1998 FDA draft guidelines for anti-infective studies, all clinical responses of "Clinical Improvement" were reassessed at TAP Holdings Inc. as either "Clinical Cure" or "Clinical Failure" based on the following definitions. These reassessed clinical responses were used in the efficacy analyses, as follows:

Clinical Cure	The pretreatment signs and symptoms of the infection resolved or improved without the need for additional antimicrobial therapy.
Clinical Failure	(Applicable for the Post-Therapy Visit only) The pretreatment signs and symptoms of the infection improved with the need for additional antimicrobial therapy, did not improve, or worsened.
Clinical Relapse	(Applicable for the Follow-Up Visit only) The signs and symptoms of the infection improved without the need for additional antimicrobial therapy at the Post-Therapy Visit and worsened or reappeared during the follow-up period.
Indeterminate	Clinical response to therapy could not be determined.

Microbiologic Response Definitions

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

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 strain of *S. pyogenes*.
Indeterminate	Microbiologic response to therapy could not be assigned.

A microbiologic response of recurrence, reinfection, or persistence was determined based upon the serotype of the pretreatment *S. pyogenes* as compared to the serotype of the *S. pyogenes* isolated at the Post-Therapy or Follow-Up Visit. If serotype was unknown, it was assumed that the *S. pyogenes* was the same as the one isolated at the Pre-Therapy Visit.

Secondary Variables

The secondary efficacy endpoint was the change in clinical signs and symptoms from the Pre-Therapy Visit to the Post-Therapy and Follow-Up Visits.

MEDICAL OFFICER'S COMMENTS:
The medical officer agrees with the sponsor's definitions for clinical and microbiologic cures.

DATA ANALYSIS

SAMPLE SIZE

A sample size of 140 per protocol patients per treatment group was chosen to give at least 80% power to meet the criteria that the absolute value of the lower bound of a two-sided 95% confidence interval for the difference in clinical cure rates between the two groups not exceed 10%. This calculation assumed that the true clinical cure rates of both treatment groups were 90%. Assuming an evaluability rate of at least 60%, it was calculated that approximately 500 patients would be needed for enrollment to obtain 280 evaluable patients.

- **DATA SETS**

A per protocol data set and an intent-to-treat data set were analyzed for efficacy. An all patients data set was analyzed for safety only. Patients were classified into different data sets as follows:

All Patients: All patients who were enrolled in the study and who took at least one dose of study drug were included in the all patients data set.

Intent-to-Treat Patients: All patients who were enrolled in the study and had *S. pyogenes* isolated pre-treatment were included in the intent-to-treat data set.

Per protocol Patients: The following criteria had to be satisfied for patients to be considered evaluable per protocol for clinical and microbiologic efficacy analyses respectively.

Clinical efficacy analyses

- The patient's pre-treatment (within 4 days prior to the start of study drug) signs and symptoms included sore throat and at least one of the following: pharyngeal erythema/exudate, tonsillar erythema/exudate, cervical lymph node tenderness, or fever.
- The pretreatment throat swab specimen for routine bacterial culture was obtained within 4 days prior to the start of study drug and *S. pyogenes* was isolated.
- The patient took at least 80% of the scheduled medication. If the patient was considered to be a clinical failure, the patient was still evaluable if he/she had received at least 3 days of study drug.
- No more than one oral dose of another systemic antimicrobial agent that was known to have activity against *S. pyogenes* was taken during the period from the start of study drug to the follow-up visit, unless the patient was considered a study treatment failure.
- The study treatment blind was not broken prior to a clinical evaluation.
- In order to be considered clinically evaluable at the Post-Therapy Visit (3 to 16 days after the end of treatment), a clinical evaluation was made at the Post-Therapy Visit, unless the patient was a "clinical failure" prior to this visit, in which case the patient was also considered to be a "clinical failure" at the Post-Therapy Visit.
- In order to be considered clinically evaluable at the Follow-Up Visit (at least 17 days after the end of treatment), a clinical evaluation was made at the Follow-up Visit, unless the patient was a "clinical failure" at the Post-Therapy Visit, in which case the patient was also considered a "clinical failure" at the Follow-Up Visit.

A patient who received additional antimicrobials for the current infection prior to a given visit was considered clinically evaluable for that and subsequent visits if the patient received at least 3 days of study drug and the patient was considered a "clinical failure" at that and subsequent visits. If a patient prematurely discontinued from study drug therapy a clinical response of "clinical failure" was assigned and the patient was considered clinically evaluable at that and subsequent visits.

Microbiologic efficacy analyses:

- The patient was clinically evaluable.
- In order to be considered microbiologically evaluable at the Post-Therapy Visit (3 to 16 days after the end of treatment), a throat swab specimen for routine bacterial culture was obtained at the Post-Therapy Visit, unless the microbiologic response prior to this visit was "persistence," in which case the microbiologic response at the Post-Therapy Visit was also "persistence."
- In order to be considered microbiologically evaluable at the Follow-Up Visit (at least 17 days after the end of treatment), a throat swab specimen for routine bacterial culture was obtained at the Follow-Up Visit, unless the microbiologic response at the Post-Therapy Visit was "persistence," in which case the microbiologic response at the Follow-Up Visit was also "persistence."

A patient who received additional antimicrobials for the current infection prior to a given visit was considered microbiologically evaluable for that and subsequent visits if the patient received at least 3 days of study drug; a microbiologic response of "persistence" was assigned at that and subsequent visits. If a patient prematurely discontinued from study drug therapy a microbiologic response of "persistence" was assigned and the patient was considered microbiologically evaluable at that and subsequent visits.

Medical Officer's Comments:

The window for evaluability for post-therapy visit has been extended to 3-16 days post- treatment as against 4-7 days post-treatment in the original study plan. As Cefditoren has a short half-life, the likelihood of post-antibiotic effect persisting at day 3 is unlikely. The follow-up visit in the original study plan was from 19-25 days post treatment. The sponsor has not mentioned a specific end date for consideration for evaluablility at the follow-up visit. In the medical officer's opinion, a window from 17-25 days post- treatment should be considered for evaluablity at the follow-up visit. Patients with mistiming of visits were evaluated as evaluable with variation by the sponsor.

- **Demographic and Baseline Variables**

The quantitative variables, age, height, and weight were analyzed for differences between the treatment groups using a one-way ANOVA with treatment group as the factor. The categorical variables gender and race were analyzed for differences between the treatment groups using Fisher's exact test.

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.

- **Efficacy Analyses**

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 Post-Therapy Visit and 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 in the clinical cure rate and patient microbiologic cure rate. Criteria developed by the FDA which require that 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 for establishing efficacy equivalence were used.

Clinical and 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.

- **SAFETY ANALYSES**

- **Adverse Events**

Adverse event incidence rates were calculated by COSTART term and body system and summarized by treatment group during treatment (from the first day of study drug to 3 days after the last dose of study drug) and post-treatment (at least 4 days after the last dose of study drug). The incidence rates were summarized separately for all adverse events and for those considered possibly, probably, or definitely study drug-related. Fisher's exact test was used to assess treatment group differences in adverse event incidence rates.

A patient with two or more adverse events with the same COSTART term was counted only once for that term. In addition, a patient who reported two or more different COSTART terms within the same body system was counted only once in the body system total, and a patient with two or more adverse events in different body systems was counted only once in the overall total. In the tabulations of adverse events by severity, patients who had more than one designation of severity for the same event were counted only once based on the most severe occurrence of that event. Patients with multiple events of varying severity were counted only once in the overall total based on their most severe event. Subgroup analyses of adverse event rates during treatment, adjusted for age, gender, and race, were performed using Cochran-Mantel-Haenszel methodology.

- **Laboratory Data**

Mean baseline values and the mean change from baseline to the Post-Therapy Visit were analyzed for differences between the treatment groups by using a one-way ANOVA, with treatment group as the factor, for each laboratory test variable. The

percentage of patients who had a change in the direction of concern was summarized and compared between treatment groups using Fisher's exact test.

- **Vital Signs**

Mean baseline values for sitting blood pressure, pulse rate, temperature, respiratory rate, and body weight and the mean change from baseline to the Post-Therapy Visit were analyzed for differences between the treatment groups using a one-way ANOVA.

PROTOCOL CHANGES

CEF-97-008

The original protocol was amended once and had one administrative change during the study. These changes did not affect medical care, evaluations, or the planned statistical analyses.

Amendment No. 1, 6/Feb/98

- The investigational drug shipping order (IDSO) form was removed from use and Subsection 5.2 (Packaging, Labeling and Storage) was amended to reflect this change.
- Routine laboratory tests were deleted from the Follow-Up Visit; the study schematic and Subsection 7.5 (Follow-Up Visit) were amended to reflect this change.
- A paragraph referencing the *Plus-Strep-A with OBC* was deleted to allow the use of other rapid immunoassay kits.
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were deleted from the hematology and coagulation profiles.
- The use of pregnancy kits other than the Abbott kit provided with the clinical laboratory supplies was allowed.
- Serology procedures were changed to indicate that the serum specimens for serology were to be sent ambient to [redacted] on the day of collection and were to be stored frozen until receipt of the convalescent-phase serum specimens at which time the samples were to be assayed.
- Details for procedures to be conducted in the event of an unscheduled visit were added to the study schematic and to Subsection 7.6 (Unscheduled Visits).
- Subsection 8.2 (Adverse Events) was updated and amended for clarity; overdose was deleted from events constituting a serious adverse event.
- Subpart 8.5.2 (Procedures for Discontinuation) was amended to clarify that procedures outlined in the section applied to patients who prematurely discontinued study drug rather than patients who prematurely withdrew from the study.
- Subsection 10.1 (Sample Size Calculation) was updated to reflect changes in the methods and assumptions used in the sample size calculations.
- The informed consent form was amended to correct the description of the daily dosing regimen (the word "tablet" was replaced with the word "capsule"); the wording of the Potential Risks section was clarified; the second signature line in the Confidentiality section was corrected to read "Parent (or Legal Guardian)" rather than "Patient (or Legal Guardian)."

Administrative Change No. 1, 5/May/98

- Section 8.0 (Management of Intercurrent Events) was updated and amended for clarity; the new FDA serious adverse event definitions and new TAP Holdings Inc. categories for causality and corresponding causality definitions were incorporated.

CEF-97-010

The original protocol had one administrative change during the study. The changes did not affect medical care, evaluations, or the planned statistical analyses.

Administrative Change No. 1, 17 October 1997

- Deleted the manufacturers' names from the cefditoren pivoxil tablets and penicillin VK tablets in Subsection 5.1 (Test Preparations).
- Presented the procedures to be conducted during unscheduled visits in Subsection 7.6 and added these procedures to the study schematic.
- Deleted reference to a particular rapid immunoassay test and allowed investigators to use tests other than the Abbott kit provided with clinical laboratory supplies.
- Allowed the use of pregnancy tests other than the Abbott kit provided with clinical laboratory supplies.
- Clarified that the serum specimen for serology was to be sent ambient to [redacted] on the day of collection.
- Revised Section 8.0 (Management of Intercurrent Events) for clarity. Updated contact names and added new FDA serious adverse event definitions and new TAP Holdings Inc. categories for causality and causality assessment. The term "prematurely withdrawn" was changed to "prematurely discontinued study drug."
- Updated sample size calculation (Subsection 10.1) to reflect changes in the methods and assumptions used in the sample size calculation.
- Clarified statements regarding potential risks in the sample informed consent form (Appendix E).

PROTOCOL DEVIATIONS

Patients with protocol deviations determined to have an effect on the efficacy analysis were considered not evaluable and were excluded from the per protocol analysis. Patients who had minor deviations from the protocol that were determined not to affect the efficacy analysis, such as mistiming of a visit, were considered to be "evaluable with variation" and were included in the per protocol analysis. Additional minor deviations included receipt of excluded medications other than antibiotics, mistimed doses, and mistimed or missing laboratory evaluations or physical examinations. None of the deviations noted affected the safety analyses.

STUDY NUMBER CEF-97-008

Evaluation of a random sample of 61 case report forms showed no significant discrepancies, hence sponsor's data are used for this review without re-adjudication of results by the medical officer. Comments by the medical officer are provided in the sections titled Medical Officer's Comments.

A list of study investigators and number of enrolled patients is presented in Table 4.

Table 4 Distribution of All Enrolled Patients by Investigator

Investigator	Site	Treatment Group	
		CDTR-PI 200 mg BID	PCN-VK 250 mg QID
Adelglass	Dallas, TX	2	0
Arcuri	Philadelphia, PA	3	2
Bernstein	Cincinnati, OH	4	3
Block	Chicago, IL	2	1
Brooks	Ypsilanti, MI	0	1
Brownstone	Boulder, CO	2	3
Burnett	Atlanta, GA	10	11
Champlin	Carmichael, CA	9	10
Coalson	Beaver Creek, OH	15	14
England	Eugene, OR	11	12
Ervin	Kansas City, MO	8	8
Fisher	Providence, RI	3	2
Garner	Boise, ID	2	3
Glovinsky	Rogue River, OR	1	0
Harper	Raleigh, NC	6	6
Hippert	Fleetwood, PA	2	2
Mayer	Avenel, NJ	6	6
Mello	Swansea, MA	2	1
Nayak	Normal, IL	4	4
Nielsen	Salt Lake City, UT	7	7
Osei	West Nyack, NY	8	7
Pappas	Lexington, KY	7	6
Poling	Wichita, KS	34	33
Pollard	Louisville, KY	7	6
Reina	Tampa, FL	2	2
Ruoff	Kalamazoo, MI	4	4
Schmidt	Philadelphia, PA	2	2
Scholar	Walla Walla, WA	2	2
Schwartz	Miami, FL	4	3
Shearer	Nashville, TN	12	10
Shepard	Washington, DC	7	8
Sperling	Fountain Valley, CA	8	7
D. Thompson	Portland, OR	6	6
V. Thompson	Buffalo, NY	1	2
Tucker	Wenatchee, WA	19	19
Wade	Salt Lake City, UT	27	28
Walden	Ypsilanti, MI	2	2
Wong	Lafayette, LA	5	4
	TOTAL	**256**	**247**

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

Of the 503 randomized patients, 368 (186 in the CDTR-PI group and 182 in the PCN-VK group) were clinically evaluable and 135 (70 in the CDTR-PI group and 65 in the PCN-VK group) were excluded from the per protocol efficacy analyses at the Post-Therapy Visit. Of the 135 patients who were not evaluable, 106 (54 and 52 in the CDTR-PI and PCN-VK groups, respectively) did not have a pre-treatment culture positive for *S. pyogenes*, 9 patients were lost to follow-up, 8 patients received less than 3 days of study drug, 7 patients did not have a clinical response assessed within the specified visit window, 4 patients received less than 80% of the prescribed study drug, and 1 patient received additional antimicrobials.

At the Follow-Up Visit, 354 patients (178 in the CDTR-PI group and 176 in the PCN-VK group) 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.

Of the 503 randomized patients, 364 (183 in the CDTR-PI group and 181 in the PCN-VK group) were microbiologically evaluable and 139 (73 in the CDTR-PI group and 66 in the PCN-VK group) were excluded from the evaluable microbiologic efficacy analyses at the Post-Therapy Visit. Reasons patients were not evaluable microbiologically were the same as for clinically; 4 additional patients did not have a culture obtained within the visit window.

At the Follow-Up Visit, 352 patients (177 in the CDTR-PI group and 175 in the PCN-VK group) 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.

Disposition of patients by data set is presented in Table 5.

Table 5 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 Per protocol 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

DEMOGRAPHICS

The two treatment groups were comparable regarding age, sex, race, height and weight in all and per protocol patients. Sixty-two percent of the patients were females and 87% were Caucasian. The mean age of the study population was 28.8 years with a range from 12 to 80 years. The following tables summarize demographic data on all and per protocol patients respectively.

Table 6 Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
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.

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Table 7 Demographic Information (Per protocol patients)

Demographic Characteristic	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
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.

MEDICAL OFFICER'S COMENTS:

The two treatment groups were comparable with respect to age, sex, race, height and weight in both all and per protocol patients.

DIAGNOSIS AND BASELINE CHARACTERISTICS

Baseline characteristics of the two treatment groups were similar for all and per protocol patients. 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. The following two tables summarize diagnoses and baseline characteristics in all and per protocol respectively:

Table 8 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.

Table 9 Summary of Diagnoses and Baseline Characteristics (Per protocol patients)

Diagnoses and Baseline Characteristics	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	186		182		
Diagnosis					0.700
Pharyngitis and tonsillitis	132	(71%)	137	(75%)	
Pharyngitis	49	(26%)	41	(23%)	
Tonsillitis	5	(3%)	4	(2%)	
Number of Infections Within Past Year[b]					0.114
1	142	(76%)	149	(82%)	
2 – 4	43	(23%)	29	(16%)	
>4	1	(1%)	4	(2%)	
Infection Status					0.769
Mild	28	(15%)	24	(13%)	
Moderate	132	(71%)	133	(73%)	
Severe	26	(14%)	25	(14%)	
Clinical Condition					0.714
Good	100	(54%)	92	(51%)	
Fair	83	(45%)	86	(47%)	
Poor	3	(2%)	4	(2%)	
Smoking Status					0.325
Non-smoker	140	(75%)	138	(76%)	
Smoker	22	(12%)	28	(15%)	
Ex-smoker	24	(13%)	16	(9%)	
Alcohol Use					0.525
Non-drinker	97	(52%)	103	(57%)	
Drinker	84	(45%)	72	(40%)	
Ex-drinker	5	(3%)	7	(4%)	

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.

MEDICAL OFFICER'S COMMENTS:

The two treatment groups were comparable with regard to diagnosis of pharyngitis and /or tonsillitis, number of infections within the past year, infection status, clinical condition, smoking status and alcohol use in both all and per protocol patients.

PRE-TREATMENT SIGNS AND SYMPTOMS

Pretreatment signs and symptoms in both all and per protocol patients were similar between the two treatment groups, with the exception of a statistically significant treatment difference in the incidence of 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). Overall, the most frequently reported signs or symptoms other than sore throat were pharyngeal erythema and tonsillar erythema. A summary of pre-treatment signs and symptoms for all and per protocol patients is presented in the following two tables.

Table 10 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.

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Table 11 Summary of Pretreatment Signs and Symptoms (Per protocol patients)

Sign/Symptom	Number of Patients by Treatment Group				P-value[a]
	CDTR-PI		PCN-VK		
Total Treated	186		182		
Sore Throat	(N=186)		(N=182)		0.354
Mild	25	(13%)	22	(12%)	
Moderate	81	(44%)	96	(53%)	
Severe	80	(43%)	64	(35%)	
Fever					0.264
Absent	148	(80%)	153	(84%)	
Present	38	(20%)	29	(16%)	
Pharyngeal Erythema					0.761
Absent	5	(3%)	4	(2%)	
Present	181	(97%)	178	(98%)	
Pharyngeal Exudate					0.145
Absent	100	(54%)	84	(46%)	
Present	86	(46%)	98	(54%)	
Tonsillar Erythema	(N=165)		(N=167)		0.194
Absent	15	(9%)	9	(5%)	
Present	150	(91%)	158	(95%)	
Tonsillar Exudate	(N=165)		(N=167)		0.008*
Absent	85	(52%)	62	(37%)	
Present	80	(48%)	105	(63%)	
Cervical Lymph Node Tenderness					0.508
Absent	27	(15%)	31	(17%)	
Present	159	(85%)	151	(83%)	
Headache					0.945
Absent	64	(34%)	62	(34%)	
Present	122	(66%)	120	(66%)	
Abdominal Pain					0.228
Absent	159	(85%)	147	(81%)	
Present	27	(15%)	35	(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.

MEDICAL OFFICER'S COMMENTS:

Pre-treatment signs and symptoms in all and per protocol patients were similar in the two treatment groups with the exception of tonsillar exudate. A higher number of patients in the PCN-VK group had tonsillar exudate. This difference in the two groups should have no impact on the outcome of this study.

MEASUREMENT OF TREATMENT COMPLIANCE

Treatment duration and study drug compliance were similar for the two treatment groups. Eight patients (3 in the CDTR-PI group and 5 in the PCN-VK group) were clinically and microbiologically not evaluable as they had received less than 3 days of study drug. In addition, 3 patients in the CDTR-PI group and 1 patient in the PCN-VK group were not evaluable because they took less than 80% of the prescribed study drug.

Duration of treatment and study drug compliance for per protocol patients are presented in Table 12.

Table 12 Duration of Treatment and Study Drug Compliance (Per protocol Patients)

	CDTR-PI		PCN-VK		
Total Treated	186		182		P-value[a]
Treatment Duration (Days)					0.270
<4	4	(2%)	3	(2%)	
4-7	2	(1%)	0	(0%)	
8-10	70	(38%)	57	(31%)	
>10	110	(59%)	122	(67%)	
Mean (SD)	10.4	(1.5)	10.6	(1.3)	
Min - Max					
Compliance (percentage)[b]					0.579
< 80	6	(3%)	3	(2%)	
80 - 90	8	(4%)	8	(4%)	
>90	172	(92%)	171	(94%)	
Mean (SD)	96.5%	(13.4%)	97.2%	(10.9%)	
Min - Max					

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

[a] P-value for comparison between treatment groups using an F-test.

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

MEDICAL OFFICER'S COMMENTS:

Treatment duration and study drug compliance of per protocol patients were similar in the two treatment groups.

PRIMARY EFFICACY RESULTS

(Excerpted from the sponsor's data)

Clinical Response at Post Therapy Visit

PER PROTOCOL PATIENTS

Clinical cure rates at the Post-Therapy Visit were similar in the CDTR-PI (95%) and PCN-VK (92%) treatment groups.

Clinical cure and failure rates at the Post-Therapy Visit for per protocol patients and the confidence interval around the difference in cure rates are presented in the following table:

Clinical Response at the Post-Therapy Visit (Per protocol Patients)					
Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	176/186	(95%)	168/182	(92%)	0.404
Failure	10/186	(5%)	14/182	(8%)	[-2.7, 7.4]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

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

Clinical cure rates at the Post-Therapy Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections within the past year. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression, was not statistically significant.

INTENT-TO-TREAT

Results in ITT patients were similar to those in per protocol patients. Clinical cure rates at the Post-Therapy Visit were 90% in the CDTR-PI group and 88% in the PCN-VK group.

Clinical cure and failure rates at the Post-Therapy Visit for ITT patients and the confidence interval around the difference in cure rates are presented in the following table:

Clinical Response at the Post-Therapy Visit (ITT Patients)					
Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	182/202	(90%)	171/195	(88%)	0.523
Failure	20/202	(10%)	24/195	(12%)	[-3.8, 8.6]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

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

After adjusting for concomitant factors (age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal infections within the past year), no statistically significant differences were observed between treatment groups.

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

At the post-therapy visit, a total of 42 patients, 18 patients in the CDTR-PI group and 24 patients in the PCN-VK group, were classified by the investigator as clinical improvement. When the sponsor reassessed the clinical responses for these patients, 17 patients in the CDTR-PI group were classified as clinical cures and 1 as clinical failure. In the PCN-VK group, 22 patients were classified as clinical cures and 2 as clinical failures.

MEDICAL OFFICER'S COMMENTS:

Clinical cure rates were similar in the CDTR-PI and PCN-VK groups among per protocol (95% and 92% respectively) and ITT patients (90% and 88% respectively) at the post therapy visit. The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero.

Out of the sixty-one case report forms reviewed, discrepancy in classification at the post-therapy visit was noted in one patient. A patient initially classified as clinical improvement by the investigator was re-classified as cure by the sponsor. The medical officer classified this patient as failure as the patient had received additional antibiotics. One patient classified as EF-501 (Prematurely discontinued due to adverse event related to study drug) by the sponsor was classified as not evaluable by the medical officer as the patient had received less than three days of study drug.

Clinical Response at Follow-Up Visit

PER PROTOCOL PATIENTS

Clinical cure rates were similar at the Follow-Up Visit in the CDTR-PI (89%) and PCN-VK (87%) treatment groups.

The clinical response at the Follow-Up Visit for per protocol patients and the confidence interval around the difference in cure rates are presented in the following table.

Clinical Response at the Post-Therapy Visit (Per protocol Patients)					
Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	159/178	(89%)	153/176	(87%)	0.515
Failure	19/178	(11%)	23/176	(13%)	[-4.3, 9.1]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

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

Clinical cure rates at the Follow-Up Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections within the past year.

After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

INTENT-TO-TREAT

Results were similar between the two treatment groups in the ITT patients. Clinical cure rates at the Follow-Up Visit were 82% in the CDTR-PI group and 81% in the PCN-VK group.

Clinical response at the Follow-Up Visit for the ITT patients and the confidence interval around the difference in cure rates are presented in the following table:

Clinical Response at the Follow-Up Visit (ITT Patients)					
Clinical Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Cure	165/202	(82%)	158/195	(81%)	0.898
Failure	37/202	(18%)	37/195	(19%)	[-7.0, 8.3]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

[a] P-value for comparison between treatment groups using Fisher's exact test.

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

After adjusting for concomitant factors (age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal infections within the past year), no statistically significant differences were observed between treatment groups.

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

MEDICAL OFFICER'S COMMENTS:

Clinical cure rates were similar in the CDTR-PI and PCN-VK groups among per protocol (89% and 87% respectively) and ITT patients (82% and 81% respectively) at the follow-up visit.

The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10% and the confidence intervals cross zero.

Microbiologic Response at Post-Therapy Visit

PER PROTOCOL PATIENTS

A statistically significant difference in microbiologic eradication rate was observed, with a higher eradication rate for the CDTR-PI group (92%) compared with the PCN-VK group (81%) (p=0.001).

Microbiologic eradication and persistence rates at the Post-Therapy Visit and the confidence interval around the difference in eradication rates for per protocol patients are presented in the following table.

Microbiologic Response at the Post-Therapy Visit (Per protocol Patients)

Microbiologic Response	CDTR-PI n/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	169/183	(92%)	146/181	(81%)	0.001***
Persistence	14/183	(8%)	35/181	(19%)	[4.8, 18.6]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

*** Indicates statistical significance at the 0.001 level.

[a] P-value for comparison between treatment groups using Fisher's exact test.

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

When eradication rates at the Post-Therapy Visit were compared using Cochran-Mantel-Haenszel methodology adjusting for concomitant factors, including age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections in the past year, statistically significant differences were also observed between the two treatment groups ($p \leq 0.001$), with higher eradication rates in the CDTR-PI group than in the PCN-VK group.

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

INTENT-TO-TREAT

A statistically significant difference in microbiologic eradication rate was observed, with a higher eradication rate for the CDTR-PI group (88%) compared with the PCN-VK group (76%) (p = 0.002).

Microbiologic eradication and persistence rates at the Post-Therapy Visit and the confidence interval around the difference in eradication rates for ITT patients are presented in the following table.

Microbiologic Response at the Post-Therapy Visit (ITT Patients)					
Microbiologic Response	CDTR-PI N/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	178/202	(88%)	149/195	(76%)	0.002*
Persistence	24/202	(12%)	46/195	(24%)	[4.3, 19.2]

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK; CI = confidence interval

* Indicates statistical significance at the 0.05 level.

[a] P-value for comparison between treatment groups using Fisher's exact test.

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

Statistically significant treatment differences were also observed after adjusting for age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections in the past year ($p \leq 0.003$).

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

Based on serotyping results, 3 CDTR-PI patients (8302, 8082, and 8095) and no PCN-VK patients were re-infected with a new strain of *S. pyogenes* at the Post-Therapy Visit.

MEDICAL OFFICER"S COMMENTS:

Microbiologic eradication rates in the CDTR-PI group were higher than those in the PCN-VK group among per protocol (92% and 81% respectively) and ITT patients (88% and 76% respectively) at the post- therapy visit. After adjusting for concomitant factors statistically significant differences were observed between the two treatment groups.

The p values for difference in eradication among per protocol and ITT patients were 0.001 and 0.002 respectively and the 95% confidence intervals did not cross zero.

Microbiologic Response-Follow-Up Visit

PER PROTOCOL PATIENTS

A statistically significantly higher microbiologic eradication rate was observed in the CDTR-PI group (85%) than in the PCN-VK group (75%) (p = 0.024).

Microbiologic eradication and persistence rates at the Follow-Up Visit and the confidence interval around the difference in eradication rates for per protocol patients are presented in the following table.

Microbiologic Response at the Follow-Up Visit (Per protocol Patients)

Microbiologic Response	CDTR-PI N/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	150/177	(85%)	131/175	(75%)	0.024*
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] P-value for comparison between treatment groups using Fisher's exact test.

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

Eradication rates at the Follow-Up Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for concomitant factors, including age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, compliance, treatment duration, weight, and number of streptococcal pharyngitis and/or tonsillitis infections in the past year. Statistically significant differences were observed between the two treatment groups ($p \leq 0.029$) after adjusting for concomitant factors, with higher eradication rates in the CDTR-PI group than in the PCN-VK group.

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

INTENT-TO-TREAT

In the ITT patients, no statistically significant differences were observed between the two groups. Eradication rates at the Follow-Up Visit were 78% in the CDTR-PI group and 70% in the PCN-VK group.

Microbiologic eradication and persistence rates at the Follow-Up Visit and the confidence interval around the difference in eradication rates for ITT patients are presented in the following table.

Microbiologic Response at the Follow-Up Visit (ITT Patients)					
Microbiologic Response	CDTR-PI N/N (%)		PCN-VK n/N (%)		P-value[a] [95% CI for Difference][b]
Eradication	157/202	(78%)	136/195	(70%)	0.087
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] P-value for comparison between treatment groups using Fisher's exact test.

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

No significant treatment differences were observed after adjusting for concomitant factors, including age, gender, race, diagnosis, smoking status, alcohol use, infection status, clinical condition, and weight.

No statistically significant differences were observed when the homogeneity of treatment differences across levels of each concomitant factor was tested using the Breslow-Day test.

The investigator by treatment interaction, assessed using logistic regression was not statistically significant.

Based on serotyping results, 4 CDTR-PI patients and 2 PCN-VK patients were re-infected with a new strain of *S. pyogenes* at the Follow-Up Visit.

MEDICAL OFFICER'S COMMENTS:

Microbiologic eradication rates in the CDTR-PI group were higher than those in the PCN-VK group among per protocol patients (85% and75% respectively) at the follow-up visit. The p value for difference in eradication among per protocol patients was 0.024 and the 95% confidence intervals did not cross zero.

Microbiologic eradication rates in the CDTR-PI group were similar to those in the PCN-VK group among ITT patients (78% and 70% respectively) at the follow-up visit. The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. The lower bound of the confidence interval is less than the pre-determined value of 10 % and the confidence intervals cross zero.

Clinical Response Versus Microbiologic Response at the Post-Therapy Visit

Microbiologic responses were compared with clinical responses in both treatment groups at the Post-Therapy Visit. Differences occurred in 8 patients in the CDTR-PI group and 21 patients in the PCN-VK treatment group. Six CDTR-PI and 21 PCN-VK patients demonstrated persistence of *S. pyogenes* while the clinical response was cure. Two patients in the CDTR-PI group demonstrated eradication of *S. pyogenes* while clinical response was assessed as failure.

Results in intent-to-treat patients were generally similar. Nine CDTR-PI and 23 PCN-VK patients demonstrated persistence of *S. pyogenes* while the clinical response was cure. Five CDTR-PI patients and 1 PCN-VK patient demonstrated eradication of *S. pyogenes* while clinical response was assessed as failure.

Clinical Response Versus Microbiologic Response at the Follow-Up Visit

Microbiologic responses were also compared with the clinical responses in both treatment groups at the Follow-Up Visit. Differences occurred in 12 patients in the CDTR-PI treatment group and 22 patients in the PCN-VK treatment group. Ten patients in the CDTR-PI group and 21 patients in the PCN-VK group demonstrated persistence of *S. pyogenes* while the clinical response was cure. Two patients in the CDTR-PI group and one patient in the PCN-VK group demonstrated eradication of *S. pyogenes* while the clinical response was failure.

Results in intent-to-treat patients were generally similar. Twelve patients in the CDTR-PI group and 24 patients in the PCN-VK group demonstrated persistence of *S. pyogenes* while the clinical response was cure. Four patients in the CDTR-PI group and two patients in the PCN-VK group demonstrated eradication of *S. pyogenes* while the clinical response was failure.

SECONDARY EFFICACY VARIABLES

Change from Pre-treatment to Post-Therapy in Signs and Symptoms

There were no statistically significant differences between treatment groups in the percentage of per protocol patients showing resolution or improvement in sore throat or resolution in fever, pharyngeal erythema, pharyngeal exudate, tonsillar erythema, tonsillar exudate, cervical node tenderness, headache, or abdominal pain at the Post-Therapy Visit. Table 13 summarizes the resolution and resolution/improvement rates for signs and symptoms in per protocol patients at the Post-Therapy Visit.

Table 13 Resolution and Resolution/Improvement of Pretreatment Signs and Symptoms Compared to the Post-Therapy Visit (Per protocol Patients)					
Sign/Symptom	CDTR-PI		PCN-VK		P-value[a]
Sore Throat					
Resolution	166/186	(89%)	149/181	(82%)	0.072
Resolution/Improvement	177/186	(95%)	168/181	(93%)	0.385
Fever					
Resolution	37/38	(97%)	29/29	(100%)	1.000
Pharyngeal Erythema					
Resolution	162/181	(90%)	146/177	(82%)	0.067
Pharyngeal Exudate					
Resolution	84/86	(98%)	94/98	(96%)	0.686
Tonsillar Erythema					
Resolution	133/150	(89%)	133/157	(85%)	0.320
Tonsillar Exudate					
Resolution	79/80	(99%)	99/105	(94%)	0.142
Cervical Lymph Node Tenderness					
Resolution	145/159	(91%)	133/150	(89%)	0.570
Headache					
Resolution	105/122	(86%)	102/120	(85%)	0.856
Abdominal Pain					
Resolution	24/27	(89%)	31/35	(89%)	1.000

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK

[a] P-values for comparison between treatment groups using Fisher's exact test.

Change from Pre-treatment to the Follow-Up Visit in Signs and Symptoms

There were no statistically significant differences between treatment groups in the percentage of evaluable patients showing resolution or improvement in sore throat, or resolution in fever, pharyngeal erythema, pharyngeal exudate, tonsillar erythema, cervical node tenderness, headache, or abdominal pain at the Follow-Up Visit. A statistically significant difference was observed in resolution of tonsillar exudate, with 97% of the CDTR-PI patients and 87% of the PCN-VK patients who presented with tonsillar exudate demonstrating resolution of this sign (p=0.015). Table 14 summarizes the resolution and resolution/improvement rates for signs and symptoms in per protocol patients at the Follow-Up Visit.

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Table 14 Resolution and Resolution/Improvement of Pre-treatment Signs and Symptoms Compared to the Follow-Up Visit (Per protocol Patients)					
Sign/Symptom	CDTR-PI		PCN-VK		P-value[a]
Sore Throat					
Resolution	157/178	(88%)	148/176	(84%)	0.284
Resolution/Improvement	163/178	(92%)	155/176	(88%)	0.296
Fever					
Resolution	30/33	(91%)	25/28	(89%)	1.000
Pharyngeal Erythema					
Resolution	152/173	(88%)	148/172	(86%)	0.635
Pharyngeal Exudate					
Resolution	77/80	(96%)	85/96	(89%)	0.091
Tonsillar Erythema					
Resolution	130/146	(89%)	126/152	(83%)	0.137
Tonsillar Exudate					
Resolution	76/78	(97%)	90/104	(87%)	0.015*
Cervical Lymph Node Tenderness					
Resolution	138/152	(91%)	126/147	(86%)	0.209
Headache					
Resolution	99/115	(86%)	98/116	(84%)	0.853
Abdominal Pain					
Resolution	23/26	(88%)	30/34	(88%)	1.000

CDTR-PI = Cefditoren pivoxil; PCN-VK = Penicillin VK
* Indicates statistical significance at the 0.05 level.
[a] P-values for comparison between treatment groups using Fisher's exact test.

MEDICAL OFFICER'S COMMENTS:

The difference in resolution of tonsillar exudate between the two groups at the follow-up visit is not clinically significant. More patients in the PCN-VK group had tonsillar exudate pretreatment.

EFFICACY CONCLUSIONS *(As provided by the sponsor)*

Clinical cure rates among per protocol patients in the CDTR-PI and PCN-VK groups were similar at the Post-Therapy Visit (95% and 92%, respectively) and the Follow-Up Visit (89% and 87%, respectively). No statistically significant difference between the treatment groups was seen at the Post-Therapy Visit. At the Follow-Up Visit, a statistically significant treatment difference was observed in tonsillar exudate, with a higher proportion of patients in the CDTR-PI group than in the PCN-VK group (97% versus 87%) demonstrating resolution of this sign.

At the Post-Therapy Visit, per protocol patients who received Cefditoren pivoxil demonstrated statistically significantly higher microbiologic eradication rates (92%) compared to per protocol patients who received Penicillin VK (81%). Significant treatment differences remained after adjusting for potentially influential factors.
At the Follow-Up Visit, the eradication rate for the CDTR-PI group (85%) was also statistically significantly higher than for the PCN-VK group (75%). Significant treatment differences were also observed after adjusting for potentially influential factors.
Results of this study indicate that Cefditoren pivoxil (200 mg BID for 10 days) was more effective in eradicating *S. pyogenes* than Penicillin VK (250 mg QID for 10 days).

MEDICAL OFFICER'S COMMENTS:

Clinical cure rates in the per protocol patients in the CDTR-PI and PCN-VK groups were similar at the post-therapy visit (95% and 92% respectively) and at the follow-up visit (89% and 87% respectively). The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent. Clinical cure rates in the ITT patients in the CDTR-PI and PCN-VK groups were similar at the post-therapy visit (90% and 88% respectively) and at the follow-up visit (82% and 81% respectively). The 95% confidence intervals around the difference in cure rates demonstrated that the two treatment regimens were equivalent.

The difference in resolution of tonsillar exudate between the two groups is not significant as fewer patients in the CDTR-PI group had tonsillar exudate at the time of enrollment in the study. Presence or absence of exudate in itself does not signify clinical failure or improvement.

The microbiologic eradication rate in the per protocol patient population in the CDTR-PI group was higher than for the PCN-VK group at the post-therapy visit (92% and 81% respectively) and at the follow-up visit (85% and 75% respectively). The 95% confidence intervals around the difference in eradication rates demonstrated that the eradication rates were higher in the CDTR-PI group.

The microbiologic eradication rate in the ITT patient population was higher in the CDTR-PI group than in the PCN-VK group (88% and 76% respectively) at the post-therapy visit. The 95% confidence intervals around the difference in eradication rate demonstrated that the eradication rate was superior in the CDTR-PI group. At the follow-up visit no significant differences (78% and 70% respectively) were noted between the two groups. The 95% confidence intervals around the difference in eradication rates demonstrated that the two treatment regimens were equivalent.

SAFETY EVALUATION

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

- **Extent of Exposure**

Of the 503 patients enrolled in the study, 237/256 (93%) patients assigned to CDTR-PI and 228/247 (92%) patients assigned to PCN-VK completed the 10-day treatment regimen. A summary of the extent of exposure is presented Table 15.

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Table 15 Extent of Exposure (All Patients)				
	CDTR-PI		PCN-VK	
Total Treated	256		247	
Treatment Duration (Days)				
<4	11	(4%)	9	(4%)
4-7	4	(2%)	6	(2%)
8-10	89	(35%)	72	(29%)
>10	152	(59%)	160	(65%)
Mean (SD)	10.2	(2.0)	10.3	(1.9)
Min – Max				

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

BRIEF SUMMARY OF ADVERSE EVENTS

(As provided by the sponsor)

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. 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).

No deaths were reported during this study. One patient in each treatment group had a serious adverse event during the study. A 27-year-old female assigned to the CDTR-PI group, was hospitalized on Day 28 (18 days after the last dose of study drug) for treatment of dehydration and bilateral tonsillitis infection. This patient was considered an evaluable failure. A 13-year-old male assigned to the PCN-VK group, was hospitalized on Day 25 (14 days after the last dose of study drug) for treatment of anger, recurrent major depression, and attention deficit hyperactivity disorder that were considered to be unrelated to study drug.

Eight patients in each treatment group were prematurely discontinued from treatment due to the occurrence of at least one adverse event. Adverse events leading to discontinuation were most commonly associated with the body as a whole and digestive body systems in the CDTR-PI group and with the skin and appendages and digestive body systems in the PCN-VK group.

All Adverse Events During Treatment (from the first day of study drug to 3 days after the last dose of study drug)

Of the 503 randomized patients who received study drug, 91 patients (36%) in the CDTR-PI group and 89 (36%) in the PCN-VK group reported at least one adverse event during treatment. The most commonly reported adverse events during treatment in the CDTR-PI and PCN-VK groups included diarrhea (9% and 4%, respectively) and headache (4% and 5%, respectively). The difference between treatment groups in the incidence of diarrhea was statistically significant (p=0.011).

Most adverse events in both treatment groups were mild or moderate in intensity. Eight severe events were reported in the CDTR-PI group (abdominal pain, headache, and gastrointestinal disorder by 2 patients each, and diarrhea and dyspepsia by 1 patient each). Ten severe events were reported in the PCN-VK group (back pain, flu syndrome, headache, diarrhea, vomiting, edema, rhinitis, herpes simplex, rash, and urticaria by 1 patient each).

A summary of all adverse events during treatment reported by ≥3% of patients in either treatment group is presented in Table 16.

Table 16 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.

All Adverse Events During Post-treatment (at least 4 days after the last dose of study drug)

During the post-treatment period, 50 (20%) patients in the CDTR-PI group and 49 (20%) patients in the PCN-VK group reported at least one adverse event. In the CDTR-PI group, headache was reported by 3% of patients, with all other adverse events having an incidence ≤ 2% during the post-treatment period. In the PCN-VK group, infection and headache each were reported by 3 % of the patients with all other adverse events having an incidence ≤ 2 % during the post-treatment period. Six (2 %) patients in the CDTR-PI group and no (0 %) patients in the PCN-VK group reported sinusitis during the post-treatment period, a statistically significant difference ($p = 0.030$). Two severe events (headache and pharyngitis) were reported in the CDTR-PI and three severe events (pain, anxiety, and laryngitis) were reported in the PCN-VK group during the post-treatment period.

Treatment-Related Adverse Events During Treatment

Fifty-one (20 %) patients in the CDTR-PI group and 56 (23 %) patients in the PCN-VK 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