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**INVESTIGATIONAL NEW DRUG  
CLINICAL PROTOCOL  
NEW DRUG A  
PROTOCOL NO. NDP - 1003**

**A Multicenter, Prospective, Randomized Study to Evaluate the Safety and Efficacy of Drug  
A versus Cefuroxime in the Treatment of Community-Acquired Pneumonia in Adults**

**IND # 27930**

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**Drug A Protocol Summary**  
**Protocol No. NDP- 1 003**

- 1. Project Status:** Phase III
- 2. Purpose:** To evaluate the safety and efficacy of Drug A versus cefuroxime in the treatment of community acquired pneumonia
- 3. Design:** Multicenter, prospective, randomized Phase III study
- 4. Number of Subjects:** Approximately 450 outpatient subjects to yield 400 subjects that met the criteria, minimum of 200 subjects in each of two treatment groups. 20 subjects will be enrolled from each site
- 5. Types of Subjects:** Male and female subjects with clinical symptoms of community-acquired pneumonia who are appropriate candidates for oral therapy
- 6. Key Inclusion Criteria:** Subject must be at least 18 years old with clinical signs and symptoms of acute pneumonia
- 7. Key Exclusion Criteria:** Subjects infected with a known resistant organism; acute allergic reaction to any non-antimicrobial, or a severe reaction to penicillin or any cephalosporin; renal failure; neutropenia; pregnant or nursing mothers; prior use of an investigational agent within 30 days; or previous treatment under this protocol
- 8. Comparative Agent:** Cefuroxime axetil
- 9. Dosage & Duration:** Drug A - 500 mg PO q12h x 7-14 days Cefuroxime axetil - 500 mg PO q12h for 7-14 days
- 10. Safety Parameters:** Safety evaluations will be based on changes in the physical exam and laboratory tests from pre- to post-therapy and reporting of any adverse events.
- 11. Efficacy Parameters:**
  - a. Microbiological response (2-4 days post-therapy) will be based on eradication of the pathogens isolated at admission.
  - b. Clinical response (2-4 days post-therapy) will be based on resolution of signs/symptoms and changes in radiological findings reported at admission.
- 12. Location:** Multicenter; 20-25 sites are expected to participate
- 13. Data Analysis:**

- a. Safety - adverse events and changes in physical examinations and clinical laboratory tests from pre- to post-treatment will be summarized
- b. Efficacy- the microbiological eradication rates and clinical response rates will be compared for Drug A and Cefuroxime axetil

## **1. BACKGROUND AND RATIONALE**

Drug, A is an investigational compound in the quinolone class of antibiotics. It- has been used in Europe for 5 years for treating patients with community-acquired bacterial pneumonia, with success rates around 90%.

Although Drug A is more active in vitro than other members of its class, toxicity profiles in animal studies are similar. Accordingly, Drug A is expected to offer an opportunity to enhance the efficacy profile of quinolones without an incremental increase in adverse events.

It is anticipated that Drug A could be used once daily for many infections including mild to moderate skin, lower respiratory, and pelvic infections, as well as UTIS. Severe or life-threatening infections could be treated with a twice-daily dosing schedule.

To date, approximately 150 subjects have received Drug A in Phase I and Phase II trials in the United States. Adverse reactions were judged probably or possibly drug-related in 14.8% of courses; drug treatment had to be stopped prematurely in 3.5%. The most frequent reactions were gastrointestinal complaints (chiefly nausea, diarrhea, and vomiting), metabolic disorders (elevated SGOT, SGPT, serum creatinine or blood urea nitrogen), nervous system effects (dizziness, restlessness, tremor, and headache), and rash.

In animal toxicologic trials, Drug A and other quinolones appear to have similar safety profiles. The absorption, distribution, metabolism, and excretion appear to be similar as well, both in animals and in humans. Based on these studies, it is anticipated that the fate of administered Drug A will be comparable to that of other long acting quinolones both with respect to human safety and tolerance.

Over 40 million people have been treated with various quinolones. They have generally been well tolerated. The events considered likely to be drug-related in clinical trials in subjects receiving multiple doses were nausea, headache, dizziness, and diarrhea.

## **2. Study Design**

### **2.1 OBJECTIVE**

The objective of this study is to evaluate the safety and efficacy of Drug A compared to orally administered cefuroxime axetil in the treatment of community-acquired pneumonia due to susceptible organisms in adults.

## **DESCRIPTION OF STUDY**

This is a multicenter, prospective, randomized, Phase III study to evaluate the safety and efficacy of Drug A compared with cefuroxime axetil in the treatment of community-acquired pneumonia in adults.

Investigators will collectively enroll approximately 450 outpatient subjects with community-acquired pneumonia to ensure clinically evaluable data from 400 subjects. The study will be terminated when 200 clinically evaluable subjects per treatment group have been prospectively enrolled. The study may be amended if necessary to ensure enrollment of sufficient numbers of subjects with infections due to critical pathogens. The data will be pooled across investigators for safety and efficacy analyses. A subject is eligible for study entry if the infection was acquired in a community setting.

Subjects who meet all the inclusion criteria and exhibit none of the exclusion criteria may be enrolled. A Potential Subject Roster, which will document the initials of each patient considered for study entry, the date of assessment, severity of diagnosis and the reasons for not enrolling any potential study subject, will be maintained at each site. As subjects qualify for the study, subject numbers will be assigned in strict sequential order at each site. Subjects will receive one of two treatment regimens according to a computer-generated randomization schedule prepared by the CCRP Pharmaceuticals, Inc. and kept at the individual investigational sites. This randomization schedule will provide for equal numbers of subjects in the two regimens. The random study group assignment will be provided for each subject in individually sealed envelopes. As a qualified subject enters the study, the next available randomization envelope in the sequence will be opened to reveal the appropriate therapy regimen. The following two regimens will be used:

- 1. Drug A 500 mg PO q12h**
- 2. Cefuroxime axetil 500 mg PO q12h**

Total therapy duration will be 7 to 14 days, as clinically indicated. A minimum of five days of therapy will be required for analysis of microbiologic response, unless subjects have failed clinically and have taken sufficient drug to be considered evaluable within this time. If, in the opinion of the investigator, a subject requires more than 14 days of therapy (e.g., *Legionella pneumophila*, slowly resolving pneumonia, etc.) the medical monitor should be contacted.

All subjects will be assessed for possible adverse events during the course of the study. All adverse events will be documented on the case record form. Safety will also be assessed by the physical examinations and laboratory tests performed pre-therapy and post-therapy.

Efficacy will be assessed by microbiological and clinical response. Microbiological data will be obtained from cultures of respiratory secretions.

Clinical response will be evaluated by assessing physical exam signs and symptoms, laboratory results, and chest X-ray findings by the investigator after the completion of therapy.

## 2.2 SUBJECT SELECTION

### A. Study Population

To ensure clinically evaluable data from 400 subjects (a minimum of 200 subjects in each of two treatment groups), approximately 450 outpatient subjects with community-acquired pneumonia will be admitted to the study.

### B. Inclusion Criteria

Subjects may be included in the study if they satisfy all of the following criteria:

1. Age: 18 years of age or older
2. Sex: male or female
3. Clinical picture consistent with pneumonia, including at least two of the following clinical signs or symptoms of pneumonia:
  - cough
  - fever (101°F or greater)
  - production of purulent sputum
  - rales
  - pleuritic chest pain
4. Chest x-ray infiltrate compatible with acute infection
5. If female, subject must be using an acceptable form of birth control and have a negative pregnancy test prior to being enrolled; or be post-menopausal
6. Must be able to give informed consent

### C. Exclusion Criteria

1. Subjects infected with a resistant organism known prior to starting therapy
2. Previous allergic or serious adverse reaction to any members of the quinolone class of antimicrobials, or a severe reaction to penicillin or any cephalosporin
3. Severe renal failure (creatinine clearance < 20 ml/min)
4. Presence of neutropenia (< 500 WBC's/mm<sup>3</sup>)
5. Pregnant women or nursing mothers
6. Use of an investigational agent within 30 days prior to entry into the study
7. Previous treatment under this protocol

## **D. Patient Recruitment and Screening Procedures**

Subjects who meet all the inclusion criteria and exhibit none of the exclusion criteria may be enrolled. A Potential Subject Roster, which will document the initials of each patient considered for study entry, the date of assessment, severity of diagnosis and the reasons for not enrolling any potential study subject, will be maintained at each site.

## **E. Randomization**

As subjects qualify for the study, subject numbers will be assigned in strict sequential order at each site. Subjects will receive one of two treatment regimens according to a computer-generated randomization schedule prepared by the CCRP Pharmaceuticals, Inc. and kept at the individual investigational sites. This randomization schedule will provide for equal numbers of subjects in the two regimens. The random study group assignment will be provided for each subject in individually sealed envelopes. As a qualified subject enters the study, the next available randomization envelope in the sequence will be opened to reveal the appropriate therapy regimen. The following two regimens will be used:

- 1. Drug A 500 mg PO q12h**
- 2. Cefuroxime axetil 500 mg PO q12h**

Total therapy duration will be 7 to 14 days, as clinically indicated. A minimum of five days of therapy will be required for analysis of microbiologic response, unless subjects have failed clinically and have taken sufficient drug to be considered evaluable within this time. If, in the opinion of the investigator, a subject requires more than 14 days of therapy (e.g., *Legionella pneumophila*, slowly resolving pneumonia, etc.) the medical monitor should be contacted.

## **V. PROCEDURES**

The schedule of study procedures is diagrammed in the Flow Chart (Appendix 1).

### **A. Visit #1 - Baseline Visit**

At the baseline visit, the following will be performed:

1. Sign informed consent form
2. Pertinent medical history
3. Pertinent physical examination, including vital signs
4. Chest x-ray (PA & lateral)
5. Respiratory secretions must be obtained within the 48 hours prior to study entry for routine culture and Gram stain. Deep expectorated or auctioned sputum, transtracheal aspirates, bronchial brushings, washings, biopsies, or pleural fluid are

all acceptable. Specimens should also be cultured for *M pneumoniae*, *L. pneumophila*, and *C pneumoniae* when indicated and if the microbiology laboratory has the capability to perform these cultures.

Disk and MIC susceptibilities for all study drugs are to be performed on all aerobic pathogens isolated (except *M pneumoniae*, *L. pneumophila*, and *C pneumoniae*). Genus and species identification is required on all pathogens isolated.

6. Obtain venous blood samples and process blood at local institution:
  - a. Hematology:
    - hemoglobin
    - hematocrit
    - RBC
    - platelet count
    - WBC, including differential
  - b. Serum chemistry:

-glucose	-total bilirubin
-creatinine	-inorganic phosphorous
-BUN	-alkaline phosphatase
-total protein	-calcium
-albumin	-uric acid
-sodium	-chloride
-potassium	-CO <sub>2</sub>
-SGOT	-LDH
-SGPT	
  - c. Pharmacokinetics (these will be shipped and analyzed at a central laboratory, see Appendix II for instructions)
7. Urinalysis, including pH, specific gravity, and microscopic examination of sediment for RBC, VIBC, and non-amorphous crystals
8. Urine pregnancy test
9. Evaluate subject for signs and symptoms of pneumonia
10. Complete confidential follow-up form
11. Assign subject number
12. Pharmacist to open randomization envelope and dispense/prescribe appropriate drug

**B. Visit #2 - On-Therapy Evaluations (Study Days 5-7)**

The investigator should assess the overall clinical progress of the subject and adverse events.

1. Physical exam, including vital signs
2. Evaluate subject for signs and symptoms of pneumonia
3. Assess adverse events
4. Pharmacokinetics (see Appendix II for instructions)
5. Assess drug compliance

**C. Visit #3 - Post-Therapy Evaluation (Study Days 2-4 After Completion of Therapy)**

The investigator should assess the subject's overall clinical progress and assess adverse events.

Clinical response will be determined by comparing a subject's post-therapy signs and symptoms to those observed on admission as well as by comparing post-therapy chest x-ray findings with those on admission, as follows:

Cure:	Resolution of signs and symptoms associated with active infection along with resolution of chest x-ray findings
Improved:	Incomplete resolution of signs, symptoms, and chest x-ray findings
Failure:	No response to therapy
Unable to Evaluate:	Due to the administration of non-study antimicrobials, I insufficient course of therapy, subject not returning for post-therapy evaluation, etc.

**The following will be performed:**

1. Physical examination, including vital signs
2. Evaluate subject for signs and symptoms of pneumonia
3. Culture and Gram stain of respiratory secretions
4. Obtain venous blood samples and urine studies listed for baseline visit
5. Repeat chest x-ray
6. Assess adverse events
7. Instruct subjects to contact the investigator immediately if they experience a return of symptoms
8. Urinalysis

9. Evaluate clinical response

**D. Visit #4 - Post-Study Evaluation (Study Days 21-28 After Completion of Therapy)**

1. Physical exam, including vital signs
2. Evaluate subject for signs and symptoms of pneumonia
3. Culture and Gram stain of respiratory secretions, if still positive at Visit #3 (Study Days 2-4 After Completion of Therapy)
4. Repeat chest x-ray, if pneumonia not resolved at Visit #3 (Study Days 2-4 After Completion of Therapy)
5. Clinical response will be assessed by comparing the subject's pre-study signs and symptoms (including pre-study chest x-ray findings) to those observed post-therapy:
  - Cure - resolution of signs and symptoms associated with active infection, along with resolution of chest x-ray findings
  - Improved - continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period
  - Failure - no response to therapy
  - Relapse - resolution or improvement of signs and symptoms at the post-therapy evaluation with reappearance or deterioration of signs and symptoms of infection.
  - Unable to Evaluate - due to the administration of non-study antimicrobials, subject not returning for post-study evaluation, etc.
6. Assess adverse events

**E. Early Withdrawal from the Study**

In the event a subject withdraws from therapy prematurely, the same procedures as in Visit #3 (Study Days 2-4 After Completion of Therapy) should be performed at the time of study withdrawal. The reason for early therapy withdrawal should be documented on the appropriate case record form. Schedule follow-up visit, if appropriate.

To date approximately 150 subjects have been given Drug A. The most frequently reported side effects are outlined in the table below:

Possible Risk/Side Effect	How often has it	How serious is it?
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	<b>occurred</b>	
Nausea	It is expected to occur	Can be easily treated
Diarrhea	It is expected to occur	Can be easily treated
Vomiting	It is uncommon	Can be treated
Changes in certain levels in your blood chemistry	It is uncommon	Very Serious
Dizziness	It occasionally occurs	Can be treated
Restlessness	It occasionally occurs	Can be treated
Tremors	It occasionally occurs	Can be treated
Headache	It is expected to occur	Can be easily treated
Rash	It occasionally occurs	Can be treated

**Allergic reaction to any antibiotic in the past should be documented or noted by the investigator or the study coordinator because the study subject may have an allergic reaction to antibiotics used in this study. These allergic reactions may be life threatening.**

The risks of drawing blood from a vein includes discomfort at the site of the needle stick, possible bruising and swelling around the site of the needle stick, rarely an infection, and uncommonly feeling faint from the procedure.”

The risks of Drug A and Cefuroxime axetil to an unborn child are unknown. Therefore, if the study subject is capable of giving birth to or fathering a child, he/she should use adequate birth control measures while on the study. These measures may include abstinence, oral contraceptives (birth control pills), IUD, diaphragm, Norplant, approved hormone injections, condoms, or documentation of medical sterilization.

This research study involves exposure to radiation from chest x-rays. The amount of radiation exposure from this procedure(s) is equivalent to a uniform whole body exposure of 10 millirems. This is equivalent to 5 % of the amount of natural environmental radiation the average person receives annually. The risk from radiation exposure of this magnitude is too small to be detected in this population.

Severe and Unanticipated Adverse Events:

A severe unanticipated adverse effects are any that is severe and not stated above.

A serious Adverse event is any that is

## **VI. STUDY DRUG ADMINISTRATION**

Equal numbers of subjects will be assigned to each treatment regimen according to a computer-generated randomization schedule prepared by the sponsor. The following two regimens will be utilized:

1. Drug A 500 mg tablets PO q12h for 7-14 days

2. Cefuroxime axetil 500 mg tablets PO q12h for 7-14 days

**A. Dosage Adjustment**

Dosages of both drugs should be adjusted for subjects with a calculated creatinine clearance less than or equal to 50 ml/min. These subjects should receive an initial loading dose of 500 mg po and then subsequent doses as follows:

<u>Creatinine Clearance</u>	<u>Drug Dose</u>	<u>Dose Interval</u>
20-50 ml/min	500 mg	48 hours

When only serum creatinine data are available, the following formula (based on sex, weight, and age of the subject) may be used to estimate the creatinine clearance. The serum creatinine should represent a steady state of renal function.

**Males:**  $\frac{\text{weight (kg)} \times (140 - \text{age [in years]})}{72 \times \text{serum creatinine (mg/100 ml)}}$

**Females:** 0.85 x above value

**Study Measurements and weights**

All clinical data will be collected on standardized case report forms.

The Case Report Form will be used to collect all patient data and assessments that will be used for evaluation of the patient's response to treatment. It is the responsibility of the PI to ensure the completeness and accuracy of case report forms. One set of case report forms should be completed for each subject participating in the trial. The Case Report Forms should be completed within two (2) days of the patient's visit for review by Clinical Research Monitors, Inc., CCRP Pharmaceutical's agent for monitoring the trial. Case Report Forms will be monitored following guidelines established by CCRP Pharmaceuticals at the study onset. Investigators will permit inspection of the study files and patient medical charts by authorized representatives of Clinical Research Monitors & CCRP Pharmaceuticals and responsible government agencies.

Data will be entered at the site by the Principal Investigator (PI) and/or his/her designee. After all data has been entered and all queries are resolved for a patient, the patient's data will be locked. Once the data is locked, the PI will review the patient's data and will attach an electronic signature to the e-crf indicating that he/she has reviewed all data and to the best of his/her knowledge, the data has been accurately captured. It will be necessary for the PI to have on file at the FDA a certification statement that his/her electronic signature is 'intended to be the legally binding equivalent of traditional handwritten signatures.'

All proposed publications and presentations by investigators must be submitted to CCRP Pharmaceuticals for review and approval. A copy of each proposed publication and presentation

shall be submitted at least sixty (60) days prior to submission for publication or presentation. This provision is in recognition of CCRP Pharmaceutical's rights and responsibility to provide peer input regarding the content and conclusions of such publications and to ensure that none of its confidential information will be disclosed or inappropriately utilized.

### **Maintaining of Records**

Investigators shall maintain the records of drug disposition, Case Report Forms and other study records and worksheets for a period of 5 years following the date the Product License Application is approved by the FDA or, if the application is not filed or is withdrawn for 5 years after the Food and Drug Administration has been notified by CCRP Pharmaceuticals that the investigational program has been discontinued. To avoid error, investigators should contact CCRP Pharmaceuticals before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, CCRP Pharmaceuticals should be contacted if the investigator plans to leave the institution so that arrangements can be made for transfer of records.

Upon completion or termination of the study, investigators should submit a final written report to the sponsor as required by the U.S. IND regulations. The report should be submitted to CCRP Pharmaceuticals within 30 days of completion or termination of the study. This report should include:

1. Introduction: a brief description of the study.
2. Methods: a description of the methods employed and any deviations from the protocol.
3. Study Population: a statement of the number of patients evaluated; of the number of dropouts and reasons for them; and description of the initial nature and severity of medical conditions for which the patients were evaluated.
4. Results and Discussions: a clinical assessment of the effect of the investigational agent on the medical conditions evaluated and a description of adverse reactions observed or reported with an indication, to the extent possible, of their relationship to the investigational agent.
5. Conclusion: a summary statement of the investigator's opinion of the efficacy of the study agent in the patients enrolled in his/her study.

## **VIII. STATISTICAL METHODS**

The microbiological eradication rates and clinical response rates will be compared for Drug A and Cefuroxime axetil. A Chi-square analysis will be performed to compare the rates of eradication and response between the two drugs. Using an alpha level of 0.05 and power of 85% will require a sample size of 200 subjects in each of the two groups.



APPENDIX I  
STUDY FLOW CHART

Procedure/Test	Visit #1 (Baseline)	Visit #2 (Study Days 5-7)	Visit #3 (Study Days 2-4 after therapy)	Visit #4 (Study Days 21-28 after therapy)	Early Withdrawal
Medical History	X				
Physical Exam	X	X	X	X	X
Chest X-ray	X		X	X*	X*
Culture & Gram stain	X		X	X*	X*
Blood Samples	X		X		X
Pregnancy Test	X				
Pharmacokinetics	X	X			
Urinalysis	X		X		X
Signs and Symptoms	X	X	X	X	X
Adverse Events		X	X	X	X
Clinical Response			X	X	X

\* Repeat only if positive at Visit #3 (Study Days 2-4 After Completion of Therapy)

## APPENDIX II

### CENTRAL LABORATORY FNSTRUCTIONS

Pharmacokinetic samples will be shipped to:

Redi Lab  
Attn: Receiving Department  
100 Main Street  
Tampa, FL 3322S

All pharmacokinetic samples must be processed according to the following guidelines. Draw blood into the provided purple top tube. Allow to clot for 30 minutes. Centrifuge for 10 minutes, pipette serum into small plastic container (provided) and IMMEDIATELY freeze. Ship the samples, on dry ice, for next day delivery using provided shipping boxes and containers.

Please fax the Pharmacokinetic requisition to Redi Lab on the day of shipment: Fax #305-555-7890

Any questions may be directed to the receiving department at Redi Lab: Phone # 305-555-1234.