Study 154 –137/Nosocomial Pneumonia:

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Study 154 –137/Nosocomial Pneumonia:

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Study 154 –137/Nosocomial Pneumonia:

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Medical Officer Review of Community Acquired Pneumonia Indication

JUL 15 1998

1. Overview of requested labeling and organisms.

Concerning study design, the IDSA states "Whenever possible, the study design should be randomized, prospective, and double-blinded." Recommended evaluation timepoints include a baseline assessment to determine study eligibility and enrollment; daily assessment while hospitalized; and an assessment within 5-7 days after completion of therapy (with a follow-up chest radiograph within 72 hours of completion of therapy, plus follow-up sputum cultures if clinical material is available).

The discussion of evaluability criteria in the IDSA Guidelines includes the following points:

A. all patients who receive at least 5 days of therapy and at least 80% of the prescribed medication should have an assessment of clinical response
B. an assessment of clinical *cure* requires *complete resolution* of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph.
C. clinical failure is defined as any of the following:
   I. persistence or progression of all signs and symptoms after 3-5 days of therapy;
   II. development of new pulmonary or extrapulmonary clinical findings consistent with active infection;
   III. persistence or progression of radiographic abnormalities;
   IV. death due to pneumonia; or
   V. inability to complete the study because of adverse effects.

3. Points To Consider document regarding Community Acquired Pneumonia (CAP).

The divisional Points To Consider (PTC) document contains the following discussion regarding community acquired pneumonia (CAP):

"One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product, and one open trial are suggested. The adequate and well-controlled trial should preferably be performed in the US... In this trial, the primary effectiveness endpoints should be clinical and radiographic endpoints; however, microbiologic evaluations should also be performed on each patient. Isolation of a pathogen from the baseline sputum culture should not be required for overall evaluability; however, rigid case definitions including specific entry sputum microscopy and radiographic findings... should be included in the trial design.

"Patients should be analyzed in two separate groups: those who were clinically evaulable (whether or not microbiologically evaluable) and those who were both clinically and microbiologically evaluable...

"Also suggested is a second study, which may be an open trial, involving at least 2 investigators in different geographic areas (no one center contribution more than 55% of the evaluable patients) in which 80 evaluable patients are studied. In this trial, the microbiologic etiology of the pneumonia should be confirmed for each patient.

"In situations where atypical microorganisms causing community-acquired pneumonia are evaluated or when different susceptibility patterns are expected for specific microorganisms in different populations, different comparative agents and/or different patient populations may be selected for the two trials that should corroborate one another in the establishment of effectiveness in treating this infection. In these circumstances, it should be appropriate to perform two studies that investigate outcomes in both the clinically evaluable patients and in the clinically and microbiologically (i.e., the pathogen is confirmed by an approved laboratory test methodology) evaluable subset of patients. Analyses of the data should confirm (by means of comparing the direction of the independent 95% confidence interval testing or by appropriate other analysis if the subgroups can be combined from the two separate studies) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients."

4. Divisional evaluability criteria (proposed):

The criteria in this document are comparable to the IDSA guidelines stated above. There are some differences that are noteworthy; these are italicised below:

"Inclusion criteria should include *at least two* signs and/or symptoms of acute infectious pneumonia (cough, purulent sputum production, ascultatory findings, dyspnea, tachypnea, hypoxemia, or the isolation of an organism from blood culture that is consistent with a respiratory pathogen)

and at least one of the following

fever (> 38° C orally or >39° C rectally or >38.5°C tympanically)
or
elevated peripheral WBC count (> 10,000/mL or >15% bands)

"Evaluation visits should include a pre-therapy (enrollment) assessment, an on-therapy assessment (the frequency of which depends on the severity of the pneumonia under study), an end-of-therapy evaluation (optional for evaluability purposes), and a test-of-cure evaluation that should be at least 7 days or 5 half-lives of the agent, whichever is the longer period, following completion of therapy."

5. Structure of claim

The sponsor has submitted a total of five clinical studies in support of the CAP indication. The general characteristics of these studies are outlined in the following table.

Clinical studies submitted as 'pivotal' to the CAP indication

Study # location	154-102 USA/Costa Rica	154-110 USA/Canada / South Africa	154-111 USA/Europe / Australia	154-112 USA/Europe / South Africa	154-134 USA/Canada
Design	Rand., Double--blinded, dose-ranging, comparative	Rand, DB, comparative IV → oral	Rand, DB, DD, comparative IV → oral	Rand, DB, DD, comparative	Rand, DB, DD, comparative
comparator	cefaclor	IV→PO cipro/ ampicillin	ceftriaxone→ ceftin (± erythro)	amoxicillin ± erythromycin	clarithromycin
Dates of conduct	12/93 → 11/94	1/95 → 1/96	2/95 → 3/96	12/94 → 6/96	11/94 → 11/95
N per arm at enrollment	Trova 200 = 50 Trova 300 = 52 Ceclor = 47	Trova = 196 Cipro = 200	Trova = 215 Ceftriaxone = 222	Trova = 150 Amox = 152	Trova = 178 Clarithromycin = 180

All of these studies (with the exception of study 102, which was conducted as a phase 2 study and had a dose-ranging component using a 300 mg qd dose of trovafloxacin as well as the standard 200 mg qu dose) utilized a 200 mg daily dose of trovafloxacin, in either the IV or oral mode of administration.

6. Medical officer comments:

In general, the above protocols comply with the IDSA Guidelines, as well as the Divisional Points To Consider and Evaluability Criteria documents. There is no shortage of studies, given that the PTC document calls for two studies in support of the indication.

It should be noted that although clarithromycin is indicated for the treatment of pneumonia, it is not labeled for the treatment of CAP per se, and is only labeled for pneumonia due to Mycoplasma pneumoniae or Streptococcus pneumoniae. Clarithromycin does, however, have activity against other organisms that might be encountered in CAP (for example, it is labeled for the treatment of both acute sinusitis and AECB due to Moraxella catarrhalis and Haemophilus influenzae, as well as due to Streptococcus pneumoniae). The sponsor discussed the appropriateness of clarithromycin as a comparator agent during the End of Phase 2 meeting with the Agency (24 August 1994), prior to initiating study 134. The Agency agreed at that time that clarithromycin was an appropriate selection as a comparator agent for this CAP study.

The IV to oral studies both recruited patients who were felt to be 'sufficiently ill to require initial hospitalization', although the entry criteria for each study appeared to be the same in both the PO and IV/PO protocols. (For example, there were no specific criteria such as pulse oximetry, respiratory rate, multilobar invlovement on CXR, etc. that would have standardized criteria for initial intravenous therapy across centers and across studies.) Nonetheless, as demonstrated in tables 5 and 9 of the Integrated Summary of Efficacy (section H.4, pages 840 and 851, volume 1.3 of NDA), there did appear to be approximately twice as many patients with co-morbid conditions

in the IV/PO studies as were enrolled in the PO studies. For example, 60% of trovafloxacin IV/PO subjects had at least one co-morbid condition listed vs. 35% of the PO subjects; 33% vs. 19% had COPD, 17% vs. 6% had CHF, and 17% vs. 8% had diabetes mellitus.

The requested organisms are also worthy of comment. Neither Staphylococcus aureus nor Pseudomonas aeruginosa are organisms usually considered to be etiologic agents in 'community acquired pneumonia'; to a somewhat lesser extent, neither is Klebsiella pneumoniae. The numbers subjects infected with each of these organisms will be closely reviewed; if adequate numbers of these agents are in fact present in these studies, it may indicate that a more severely ill patient population gained enrollment into these studies. Admittedly, the spectrum of illness between 'community acquired' and 'nosocomial' pneumonia is overlapping to a greater and greater extent as current trends in health care drive increasingly ill patients out of the hospital and into "the community", be it to home with in-house nursing assistance, or to an assisted living environment prior to actual return home. Thus it is not surprising to see that some organisms formerly associated exclusively with 'nosocomial' pneumonias may be showing up in protocols designed to study 'community acquired' pneumonia.

7. Review strategy

The following review strategy will be adopted: the five studies will be stratified according to the soundness of their design and the numbers of subjects enrolled. In this manner, when an adequate number of these studies have been reviewed and audited to justify the inclusion of this indication in the label, the review will be considered to be completed. Each of these studies will be sequentially audited to ascertain the validity of the data entered on the Patient Profiles; following this, and assuming that the sponsor's assertion of efficacy in this indication is felt to be justified, organism-specific investigations will be conducted to verify which requested organisms can be recommended for inclusion in the product labeling.

The five submitted studies will be reviewed in the following order: 134 (oral); 110 (IV→ oral); 111 (IV→ oral); 112 (oral); and finally, the phase 2 study 102 (oral, dose-ranging comparative). Of the submitted studies, 134 used the best single-agent comparator and thus could most successfully be conducted in the double blind, double-dummy manner in which it was designed. (In contrast, study 110 was also conducted in a DB, DD manner, but because of the design required subjects to ingest 12 tablets a day during the oral phase of the study. This raises concerns over compliance on the part of the subjects, many of whom would have just been discharged from hospital. Similarly, study 112 called for patients to take as many as 16 tablets and/or capsules daily.)

Medical Officer review of study 154-134

1. Per applicant

The synopsis of the applicant's final study report for study 134 is presented below; this is taken from pages 8-12 of the report, found in section

PROTOCOL 154-134: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN (CP-99,219) WITH CLARITHROMYCIN FOR THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA.

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Study Publication: Not Applicable
Study Dates: 28 November 1994 to 13 November 1995
Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin and clarithromycin in the treatment of subjects with community- acquired pneumonia appropriate for oral therapy.
Study Design: Study 154-134 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg once daily) versus clarithromycin (500 mg twice daily), administered orally for 7 or 10 days for the treatment of community-acquired pneumonia.

Evaluation Groups:

	Trovafloxacin (200 mg daily)		Clarithromycin (500 mg BID)	
Entered Study[a]	179		180	
All Treated	178	(>99%)	180	(100%)
Completed Treatment	147	(83%)	154	(86%)
Completed Study	157	(88%)	167	(93%)
Evaluated for Efficacy				
Clinical Intent-to-treat	163	(91%)	172	(96%)
Clinically Evaluable[b]	144	(80%)	156	(87%)
Bacteriologically Intent-to-Treat	64	(36%)	72	(40%)
Bacteriologically Evaluable[b]	59	(33%)	67	(37%)
Assessed for Safety				
Adverse Events	178	(100%)	180	(100%)
Laboratory Tests	173	(97%)	174	(97%)

a Subjects who were randomized.
b Based on End of Treatment assessment.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥16 years of age at the baseline assessment, with clinically and radiologically documented community-acquired pneumonia were eligible to participate in this study.

Drug Administration: Study drug was in the form of trovafloxacin tablets and clarithromycin blinded tablets and was packaged in blister cards, using a double-dummy technique to maintain blinding.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens and blood cultures at baseline). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis) and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Treatment groups were compared using the confidence interval approach. Confidence intervals (95%) were produced for the difference in success rates between treatments using the normal approximation method. Additionally, a chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment was used to account for investigator differences. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

Efficacy Results: Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -3.3, 6.5 and -6.0, 7.4, respectively) and at the end of study (95% CI: -5.0, 10.5 and -6.0, 10.1, respectively).

Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects and pathogen eradication rates for bacteriologically evaluable and intent-to-treat subjects are presented in the following table.

Summary of the Sponsor's Assessment of Clinical Response
(Clinically Evaluable Subjects)

	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=144)	Clarithromycin 500 mg BID (N=156)	Trovafloxacin 200 mg (N=135)	Clarithromycin 500 mg BID (N=144)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	143 (100%)	155 (100%)	135 (100%)	144 (100%)
Success (Cure + improvement)	137 (96%)	146 (94%)	120 (89%)	124 (86%)
Distribution of Clinical Response:				
Cure	56 (39%)	59 (38%)	108 (80%)	113 (78%)
Improvement	81 (57%)	87 (56%)	12 (9%)	11 (8%)
Failure	6 (4%)	9 (6%)	6 (4%)	9 (6%)
Relapse	NA	NA	9 (7%)	11 (8%)

(Clinically Intent-to-Treat Subjects)

	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=163)	Clarithromycin 500 mg BID (N=172)	Trovafloxacin 200 mg (N=163)	Clarithromycin 500 mg BID (N=172)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	162 (100%)	170 (100%)	163 (100%)	172 (100%)
Success (Cure + improvement)	145 (90%)	151 (89%)	137 (84%)	141 (82%)
Distribution of Clinical Response:				
Cure	59 (36%)	62 (36%)	122 (75%)	127 (74%)
Improvement	86 (53%)	89 (52%)	15 (9%)	14 (8%)
Failure	17 (10%)	19 (11%)	17 (10%)	20 (12%)
Relapse	NA	NA	9 (6%)	11 (6%)

Summary of Sponsor-Defined Pathogen Eradication Rates
(Bacteriologically Evaluable Subjects)

	Trovafloxacin 200 mg (N=59)	Clarithromycin 500 mg BID (N=67)	Trovafloxacin 200 mg (N=56)	Clarithromycin 500 mg BID (N=59)
	Number of Pathogens[a]			
Pathogen	End of Treatment		End of Study	
H. influenzae	12/12	15/16 (94%)	10/10	13/16 (81%)
S. pneumoniae	10/11	14/15 (93%)	11/12	13/15 (87%)
C. pneumoniae	6/6	10/10	5/6	5/6
M. pneumoniae	17/18 (94%)	18/18 (100%)	16/17 (94%)	17/17 (100%)

(Bacteriologically Intent-to-Treat Subjects)

	Trovafloxacin 200 mg (N=64)	Clarithromycin 500 mg BID (N=72)	Trovafloxacin 200 mg (N=64)	Clarithromycin 500 mg BID (N=72)
	Number of Pathogens[a]			
Pathogen	End of Treatment		End of Study	
H. influenzae	14/15 (93%)	15/17 (88%)	12/13	13/17 (76%)
S. pneumoniae	12/13	16/18 (89%)	12/13	15/18 (83%)
C. pneumoniae	6/6	11/11	5/6	10/12
M. pneumoniae	17/18 (94%)	18/18 (100%)	17/18 (94%)	18/18 (100%)

a ≥10 isolates of a given pathogen at any evaluation period; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline
NA=Not applicable
Ref.: Tables 5.1.1, 5.1.2, 5.4.1, and 5.4.2

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 200 mg		Clarithromycin 500 mg BID	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	100/178	(56%)	120/180	(67%)
Treatment-Related Adverse Events	57/178	(32%)	71/180	(39%)
Discontinuations Due to an Adverse Event[a]	18/178	(10%)	12/180	(7%)
Clinically Significant Laboratory Values	39/173	(23%)	48/174	(28%)

a For two subjects in the clarithromycin group, the investigator indicated study drug discontinuation on the adverse event page of the CRF (Table 6.1); however, study drug discontinuation was not checked off on the subject summary page of the CRF (Table 4.1).

Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, and 7.1

Eleven subjects in the trovafloxacin group and 13 subjects in the clarithromycin group had serious adverse events. With the exception of the one subject in the clarithromycin group who had a serious adverse event that was considered to be related to study drug, all serious adverse events were attributed to other illnesses or to the disease under study. There were three deaths that occurred greater than 30 days after the last treatment dose; all deaths were unrelated to study drug.

Summary and Conclusion: Trovafloxacin 200 mg once daily for 7 or 10 days was statistically equivalent to clarithromycin 500 mg BID for 7 or 10 days for the treatment of community-acquired pneumonia. The percentage of subjects discontinued from treatment due to adverse events was 10% in the trovafloxacin group and 7% in the clarithromycin group. The overall percentage of adverse events was lower (56%) in the trovafloxacin group compared to the clarithromycin group (67%); treatment-related adverse events were reported in 32% and 39% of subjects, respectively. The most commonly reported treatment-related adverse events in the trovafloxacin group were nausea (12%) and dizziness (10%). The most commonly reported treatment-related adverse events in the clarithromycin group were taste perversion (19%), nausea (8%) and diarrhea (7%).

2. Per Medical Officer

The design of this study is in keeping with the parameters set forth in the IDSA Guidelines and the two Divisional documents (Points To Consider and the draft Evaluability Criteria). Since the five studies submitted in support of the CAP indication are very similar in their overall design (except for the comparators used and whether they are strictly PO studies vs. IV→ PO), an overview of this design will be presented here so that it may be referred back to in subsequent reviews of the remaining studies under this indication.

The following text is excerpted from the sponsor's text of protocol 154-134:

Numbers

Up to 320 subjects will be randomized into this study. Each study site should attempt to enroll at least 10 subjects.

Recruitment will cease when the appropriate number of subjects have been enrolled even if some centers have not reached their agreed recruitment targets.

Inclusion criteria

1. Subjects aged 16 years or more

Women of childbearing potential (i.e., not surgically sterile or less than one year post-menopausal) must have a negative gonadotrophin pregnancy test (urine or serum) immediately prior to entry in the study and must use adequate contraception (for women on oral contraceptives additional barrier contraception must be used) both during and for one month after the end of treatment.

2. Subjects with a medical history, and clinical and radiological findings consistent with an uncomplicated community acquired pneumonia and appropriate for oral therapy.

The following criteria must be met:

a. New infiltrate(s) on chest X-ray

AND

b. At least one of the following signs or symptoms:
   1). Cough or increasing severity of coughing
   2). Acute changes in the quality of sputum
   3). Oral temperature >38°C (100.4°F) or <36.1°C (97°F) or documented fever or hypothermia within the last 24 hours.
   4). Auscultatory findings such as rales or evidence of pulmonary consolidation.
   5). Leukocytosis (blood leukocyte count >10,000/mm^3 or > 15% bands)

3. Written informed consent from the patient and the patient's parent or legal guardian if less than 18 years old.

Exclusion criteria

1. Pregnant women, nursing mothers or women of childbearing potential not practicing adequate contraception.

2. Known or suspected hypersensitivity to any quinolone or macrolide.

3. Treatment with any systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline visit

4. Subjects with any of the following conditions:
   a) Pneumonia whose severity is sufficient to warrant initial intravenous antibiotic therapy.

b) Suspected pulmonary infection (such as abscesses or empyemas) that may require antibiotic treatment for a period greater than 10 days.
c) Known Acquired Immunodeficiency Syndrome (AIDS) or suspected Pneumocystic carinii pneumonia.
d) Neutropenia, defined as a total white blood cell count less than 2500 leukocytes/mm^3 or absolute neutrophil count less than 1000/mm^3.
e) Immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including treatment with greater than 10mg/day of systemic prednisone or equivalent).
f) Cavitary lung disease by chest X-ray, or known lung cancer, or aspiration pneumonia.
g) Cystic fibrosis
h) Significant gastrointestinal or other conditions which may affect study drug absorption.
i) A history of any form of epilepsy or seizure.

5. Treatment with another investigational drug within four weeks prior to the baseline visit.

6. Prior enrollment in this protocol.

7. Evidence of recent drug or alcohol abuse or dependence.

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8. Subjects receiving treatment with terfenadine or who may require treatment during the duration of treatment.

STUDY TREATMENTS

Allocation to study treatment

The investigator will be provided with a masked randomization schedule consisting of a list of numbers to which the study drugs have been randomly allocated. The investigator will assign study numbers sequentially to the subjects as they are determined to be eligible for treatment. The study number will be entered onto the patient's case report form and the patient should receive study medication assigned to the corresponding number.

Drug presentation

All oral medication has been blinded by double-dummy technique and will be provided in blister packs with matching placebos. Drug supplies and the patient randomization number will be provided as follows:

CP-99,219	200mg daily as a single dose for 7 or 10 days.
Clarithromycin	500mg two times daily for 7 or 10 days.

Blister pack contains blinded oral CP-99,219 or matching placebo and blinded oral clarithromycin and matching placebo. Subjects will take two 100mg tablets of CP-99,219 or its matching placebo once a day and one 500mg blinded tablet of clarithromycin or its matching placebo twice a day.

Blister packs will be labelled:

"morning" (am) dose containing:
2 tabs 100 mg CP-99,219 or matching placebo.

1 tab 500 mg clarithromycin or matching placebo

"evening" (pm) dose containing:
1 tab 500 mg clarithromycin or matching placebo

Drug administration

On the first day of therapy, subjects will be instructed to take three tablets from the blister pack ("morning" dose) regardless of the time of day; a further single tablet will be taken 12 hours later if appropriate to time of day ("evening" dose). If first ("morning") dose is late in the day, the "evening" dose may be skipped for Day 1. Day 2 will begin with the "morning" dose regardless of Day 1 dosing. This daily administration schedule will be repeated until the second visit (day 3 to 5). At this visit the investigator will decide whether the patient requires a total of 7 days or 10 days of therapy. This decision will be based on resolution of pyrexia, improving clinical symptomatology and the presence of other comorbid conditions. Subjects who are afebrile and clinically improving may only need 7 days of therapy.

After visit 2 subjects will be instructed to continue treatment as outlined above, such that the patient completes a total of 7 or 10 days of therapy.

Mineral supplements, calcium-, aluminium-, or magnesium-based antacids should not be taken within (before or after) two hours of dosing. All study medications may be taken without regard to food.

PATIENT evaluation VISITS

Visit 1 DAY 1 (Baseline)

The following procedure will be undertaken within 48 hours prior to the start of therapy.

Clinical

The baseline visit assessment includes collection of demographic information, concurrent disease, antibiotic therapy within the last seven days, concomitant medication use, targeted physical examination and vital signs (pulse, respiration, blood pressure and body temperature).

Clinical assessment of signs and symptoms of pneumonia will include sputum characteristics, cough, dyspnea, pleuritic chest pain, chills or rigors and lung sounds. In addition a blood and urine sample for laboratory safety testing (see Section 9.3) will be obtained and sent to the central laboratory for testing. Women of childbearing potential will also provide a urine or serum sample for pregnancy testing.

Chest X-ray

Chest X- rays, both PA and lateral will be obtained. An AP chest X-ray is acceptable if the subject's medical condition does not allow a PA and lateral to be obtained.

Bacteriology

Sputum

Freshly expectorated purulent sputum samples must be examined macroscopically for consistency and color and microscopically to determine the suitability for culture (presence of

>25 polymorphonuclear leukocytes and < 10 squamous cells per low power field of a Gram stained specimen defined as an "adequate sputum"). Suitable adequate specimens must be cultured at a local approved laboratory, preliminary sensitivities determined, and isolates sent to the central testing laboratory for final sensitivity determination.

If a satisfactory specimen of expectorated sputum cannot be obtained, the investigator may carry out induction of sputum with nebulized saline or physiotherapy. Should this technique also prove unsuccessful and, if medically indicated, the investigator may attempt to obtain other lower respiratory secretions such as transtracheal aspiration, bronchial brushings or biopsy material (obtained by bronchoscopy).

All sputum and other respiratory isolates will be sent to the central laboratory for testing.

Blood

Blood samples for culture must be obtained from all subjects . If the blood culture subsequently proves to be positive for a pathogen, therapy may be continued, at the discretion of the investigator, only if there is evidence of clinical improvement. If there is no such improvement study therapy must be discontinued and evaluated as a treatment failure. It is important that follow-up blood cultures be obtained. The procedure outlined in Section 9.4, must be followed for all discontinuations.

Isolates from blood must also be sent to the central laboratory for testing.

Susceptibility testing

Information on susceptibility testing with CP-99,219 is provided in Appendix D.

No baseline pathogen or resistant pathogen

Subjects need not be discontinued from the study drug if they do not have a pathogen isolated at baseline or because the pathogen is resistant to any of the study medications. If the patient needs to be discontinued because of failure to improve clinically, then the patient should be discontinued (see Section 9.4) and evaluated as a treatment failure and appropriate therapy instituted. The appropriate therapy should be recorded under the concomitant medication section of the CRF. The patient must however be followed up for safety assessment.

Serology

Serum will be obtained at the baseline visit for the determination of antibodies to Mycoplasma pneumoniae, Legionella spp., Chlamydia pneumoniae and Chlamydia psittaci, and sent to the central laboratory for testing. Urine for Legionella antigen will also be obtained and sent to the central laboratory.

Visit 2 Day 4 (day 3 to 5)

Clinical

All signs and symptoms identified at the baseline visit should be assessed . New signs or symptoms since the first assessment should also be reported.

Other procedures to be performed at visit 2 are recording of vital signs, concomitant medication, study drug dosing, and adverse events volunteered by the patient or observed by the investigator.

The battery of blood safety tests performed at baseline should be repeated.

Bacteriology

If possible an "adequate" sputum sample must be obtained and sent for culture as defined for visit 1. All sputum isolates will be sent to the central laboratory for testing.

The absence of an adequate sputum specimen and reason must be documented as inability to produce sputum will be considered equivalent to a negative culture providing the patient is clinically improved or cured.

Blood culture is to be repeated if the baseline culture was positive. Isolates from blood must also be sent to the central laboratory for testing.

~~Visit 3 Day~~ 11 (day 9 to 14) - the end of study therapy period

At the end of study therapy or at the time of premature discontinuations due to lack of efficacy the patient's response to treatment must be assessed by performing the following procedures:

Clinical

All signs and symptoms identified at the first and second visit as well as new signs or symptoms since the second visit should be assessed.

Other procedures to be performed at visit 3 are recording of vital signs concomitant medication, study drug dosing, adverse events volunteered by the patient or observed by the investigator.

Blood and urine samples should be obtained and the battery of blood and urine safety tests performed at baseline should be repeated.

At this visit the investigator is to provide an evaluation of clinical response, as described in Section 8.1.

Chest X-ray

A repeat chest X-ray must be undertaken and reported.

For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and intrepreted with respect to the baseline X-ray.

Bacteriology

If possible an "adequate" sputum sample must be obtained and sent for culture as defined for visit 1. All sputum isolates will be sent to the central laboratory for testing.

The absence of an adequate sputum specimen and reason must be documented as inability to produce sputum will be considered equivalent to a negative culture providing the patient is clinically improved or cured.

Blood culture is to be repeated if previous blood sample (visit 2) was positive. Isolates from blood must also be sent to the central laboratory for testing.

Visit 4 Day 30 (day 28 to 35) - the final assessment.

The final assessment of the patient's response to treatment must be assessed by performing the following procedures. If the patient was assessed as a failure at the previous visit and discontinued then the activities relating to the assessment of efficacy should not be undertaken but activities associated with safety (e.g., adverse events and safety bloods) must be undertaken.

Clinical

All signs and symptoms identified at all the previous visits as well as new signs or symptoms since the last visit should be assessed.

Other procedures to be performed at visit 4 are recording of vital signs, concomitant medication, adverse events volunteered by the patient or observed by the investigator.

The battery of blood and urine safety tests performed at baseline need to be repeated only if an abnormality was present at visit 3 (day 9 to 14), or if subject is experiencing a clinically significant adverse event.

At this visit the investigator is to provide a final evaluation of clinical response, as described in Section 8.1.

Chest X-ray

A final chest X-ray needs to be undertaken only if the visit 3 (day 11) radiograph had not cleared (i.e., signs of infiltration remained) or the patient's clinician condition has deteriorated. For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and intrepreted with respect to the baseline X-ray.

Bacteriology

If clinically indicated an "adequate" sputum sample must be obtained and sent for culture as defined for visit 1. All sputum isolates will be sent to the central laboratory.

The absence of an adequate sputum specimen and reason must be documented as inability to produce sputum will be considered equivalent to a negative culture providing the patient is clinically improved or cured.

Serology

Serum will be obtained for the determination of antibodies to the pathogens mentioned in Section 7.1.4.

STUDY EVALUATIONS

Clinical

The overall clinical response will be determined by the investigator at the end of study treatment (visit 3, day 11) and at the last follow-up assessment (visit 4, day 30) or at the time of discontinuation.

Clinical response will be classified by the investigator as cure, improvement, failure as defined in Appendix C . Clinical evaluation of response will be based on the global assessment of the clinical presentation of the patient and compared to the baseline assessment. Clinical assessment will be based upon resolution or improvement of radiological, clinical signs of infection such as resolution of fever, disappearance or diminution in purulent sputum production, improvement or resolution of dyspnea, cough and leukocytosis, as well as improvement in general physical condition.

Bacteriological

The bacteriological response will be determined by the sponsor from the culture results of visit 2, (day 4), at the end of treatment (visit 3, day 11) and at the end of the study (day 30) or at the time of discontinuation due to lack of efficacy.

Bacteriological response will be classified by the sponsor as indicated in Appendix C . Repeat cultures of sputum, if obtainable, will be done at visits 2, 3 and 4. Only "adequate" sputum specimens determined by Gram stain should be sent for culture. The absence of adequate sputum specimens at follow-up assessments will be considered equivalent to a negative culture if the clinical response is improved or cure. However, the investigator must document the fact that there was an inadequate sputum production

Standardized susceptibility testing will be performed on all pathogens (see Section 7.1.3). Collection of specimens that require semi-invasive techniques (e.g., bronchoscopy) should only be repeated if there is a suboptimal clinical response.

Radiological assessment

Consecutive chest X rays will be evaluated and their evolution will be graded as:

Resolution: disappearance of all radiological signs of infection

Marked improvement: Significant improvement in the radiological signs of infection compared to baseline.

Radiological failure: no change or worsening in the radiological signs of infection compared to baseline.

Serological

Serological assessments will be undertaken at baseline and day 30.

SAFETY ASPECTS

Adverse events will be monitored up to visit 4 (day 30). Serious adverse events will be monitored throughout the study and for 30 days after the last dose of study drug.

Adverse events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study drug will be recorded on the Adverse Event page(s) of the case report form. Please note that adverse events are not limited to suspected adverse drug reactions but also include illnesses with onset during the study, or exacerbations of pre-existing illnesses which should therefore also be recorded.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a Serious Adverse Event requiring immediate notification to the Pfizer appointed monitor (see Section 9.2). Follow-up of the adverse event, even after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the Pfizer appointed monitor.

Serious Adverse Events

All Serious Adverse Events which occur during the study until the last follow-up visit required by the protocol and for 30 days after the last dose of study drug, whichever comes later, regardless of treatment group or suspected relationship to drug, must be reported immediately by telephone to the Pfizer appointed monitor.

Serious Adverse Events include those that suggest a significant hazard, such as events which:

- are fatal
- are life-threatening
- result in permanent disability
- require in-patient hospitalization or prolongation of a hospital stay
- involve cancer, a congenital anomaly or drug overdose

It should be emphasized that, regardless of the above criteria, any additional adverse experience which the investigator considers serious should be immediately reported.

Any serious adverse event occurring either during the clinical trial and for 30 days after the last dose of study drug must be reported immediately independent of the circumstances or suspected cause.

All deaths should be immediately reported, regardless of elapsed time between last dose in a clinical trial and the death and thus extends beyond the 30 day post study limit.

For all serious adverse events, the investigator is obligated to pursue and provide information as requested by the Pfizer appointed monitor in addition to that on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Pfizer appointed monitor. The investigator should ensure that information on such cases is reported by telephone or other means and information entered in the case report form is accurate and consistent.

For Canadian studies, in order to conform with Canadian Regulatory requirements as well as U.S. Regulatory requirements, such reactions originating from investigational drug studies conducted in Canada must also be reported IMMEDIATELY to the Director of Drug Regulatory Affairs, Pfizer Canada, Montreal (514-695-0500).

Laboratory safety tests and abnormal laboratory results

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Since clarithromycin may raise theophylline levels, all subjects on concommitant theophylline should have theophylline levels monitored periodically at the local laboratory.

The clinical laboratory tests, outlined below, will be performed at baseline (visit 1), during therapy (visit 2, day 4 - no urinalysis) and at the end of therapy (visit 3, day 11). Additional safety tests, i.e., at day 30 need only to be undertaken if clinically indicated (e.g., post therapy, clinically significant adverse event) or if a clinically significant abnormality was present at visit 3.

The laboratory safety tests will be conducted by a central laboratory appointed by Pfizer. Transfer of laboratory data from the central laboratory to the investigator and to Pfizer will be by hard copy and where possible by electronic means. The results of all known laboratory tests required by the protocol will be held/recorded in the patient's Case Report Forms (CRFs).

Hematology

Hemoglobin, hematocrit, red blood cells, white blood cells, differential count and platelets.

Biochemistry

AST, ALT, total bilirubin, LDH, alkaline phosphatase, urea, creatinine, total protein, albumin, sodium, potassium, bicarbonate, chloride and random blood glucose.

Urinalysis

Microscopy and urine chemistry (protein, glucose, ketones, bilirubin, pH, urobilinogen, blood and nitrate).

Clinically significant laboratory tests

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the Pfizer appointed monitor.

Further procedures for specific laboratory abnormalities are given in Appendix B .

Discontinuation from study (withdrawals from study)

The reason for a patient discontinuing from the clinical trial must be recorded in the case report form. A discontinuation occurs when an enrolled patient ceases participation in the clinical trial, regardless of the circumstances, prior to completion of the protocol. A discontinuation must be reported immediately to the Pfizer appointed monitor if it is due to a Serious Adverse Event. The investigator is encouraged to contact the Pfizer appointed monitor to discuss

any patient he is considering withdrawing from the trial. However, the final decision as to withdrawal rests with the investigator.

The final efficacy evaluation required by the protocol and microbiology (see Section 7.4.) will be performed at the time of study drug discontinuation. However, subjects must be followed for safety until visit 4. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the patient's condition. Any medication started after the discontinuation but before visit 4 must also be recorded on the concomitant medication section of the case record form.

Medical Officer comments:

In general, this study is a well designed, DB,DD trial against an appropriate comparator agent. The trial design basically follows the recommendations of the IDSA guidelines.

Although a total of 71 investigators (68 US and 3 Canadian) were listed as contributing to this study, only 51 of them (including 2 Canadian investigators who enrolled a total of 6 subjects) eventually contributed enrolled subjects. The following 9 of these investigators contributed at least 10 subjects to this study:

Investigator	ID#	location	N	#subinvestigators	subjects per investigator
Sullivan	5139	Alabama	44	1	22.0
Gezon	5017	Utah	32	7	4.0
Herrod	5209	Utah	28	26	1.1
Upchurch	5140	Oregon	20	1	10.0
Hartford	5129	Idaho	18	12	1.5
Miller	5051	Oregon	15	5	2.5
Follett	5252	Wyoming	14	5	2.3
Schultz	5251	Iowa	11	13	0.8
Pearl	5214	Utah	11	9	1.1

The number of subinvestigators and the ratio of enrolled subjects per investigator is listed to provide an index of the intensity of enrollment per listed investigator. Since the dates of this study are listed as November 1994 to November 1995, it can be seen that Dr. Sullivan and his co-investigator (Dr. Flippo), each saw 22 patients with CAP at a single practice site (Parkway Medical, Birmingham AL) over the course of one respiratory season in Alabama.

The geographic distribution of the largest recruiting centers in this study appears to be predominantly the western portion of the US, with the sole exception of Alabama. The states represented above are not among those with the highest degree of emerging penicillin resistance in pneumococci. Interestingly 71/358 enrolled subjects (20%) in this study ended up being from the state of Utah.

Clarithromycin patients

PID	Investigator	Location	OK?	Comments
50170192	Gezon	UT	✓	
50240505	Martel	Canada	✓	
51290465	Hartford	ID	✓	
51390403	Sullivan	AL	✓	
51390416	"—"		✓	
51400020	Upchurch	AL	•	No CRFs in CANDA
51400104	"—"		✓	
51400387	"—"		✓	
51560125	Saddoris	OR	✓	
52090194	Herrod	UT	✓	Baseline radiologist interpretation negative
52520305	Follett	WY	✓	
52560235	Weerasinghe	NY	✓	
52580226	Applestein	CA	✓	
52620259	Bias	KY	✓	
52630276	Freiberg	MN	✓	
54620479	Weiss	FL	✓	
58070449	Markel	CO	✓	Baseline CXR read as "no interval change; no acute pneumonia or CHF." Amended to read "possible lingular infiltrate"
58070450	"—"		✓	

Trovafloxacin patients

PID	Investigator	Location	OK?	Comments
50170382	Gezon	UT	✓	WBC count 14.7 K (baseline) to 3.5 K (day 3)
50170384	"—"		✓	
50170486	"—"		✓	
50220481	Payne	TX	•	no CRFs found for this patient in CANDA
50500313	VanHook	CO	✓	
51390177	Sullivan	AL	✓	*this patient was afebrile, had a normal WBC count, no purulent sputum, and a handwritten CXR interpretation of "possible abnormality of LLL". Symptoms listed were 2+ cough and 2+ increased sputum production, which was inadequate by Gram stain criteria and never cultured. It is this type of patient for whom a radiologist's report would be valuable to validate that, at a minimum, there was objective evidence of pneumonia.*
51400102	Upchurch	OR	✓	
51400197	"—"		•	no CRFs found in CANDA
51490090	Ruoff	MI	✓	*CXR report included, documenting radiologist reading of "normal chest" and subsequent withdrawal of subject from study*
51520049	Alwine	PA	✓	*subject has duplicate inclusion/exclusion criteria sheets, in different handwriting but same date and PID number.*
51520118	"—"		•	CRF includes seven pages of 'data clarification' sheets, indicative of multiple corrections/changes to CRF forms.
51540065	Estess	MS	✓	
51600126	Saddoris	OR	✓	
52090399	Herrod	UT	✓	
52520307	Follett	WY	✓	
52580227	Applestein	CA	✓	WBC (b)(4) [redacted]
52620258	Bias	KY	✓	
52660230	Sanders	OK	✓	

General comments:

1. No radiologist reports were included in any of the CRFs, despite the protocol statement that:

> "A repeat chest X-ray must be undertaken and reported.
>
> For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and intrepreted with respect to the baseline X-ray."

The sponsor was asked to present radiology reports on the audited subjects listed above. The following communication was transmitted to the sponsor on 9 October 1997 via electronic mail:

> The CAP studies are designed in such a way that the only piece of objective clinical data that is required for entry is a CXR showing a 'new' infiltrate. (This of course implies the presence of a baseline

radiograph, but that is a pre-enrollment requirement that is in my opinion overly restrictive. That is not the point of this communication.)

Four of the five CAP studies (102 is the only one that does not) specify that the interpretation of xrays will be done by a radiologist.

I was disappointed to find that these interpretations were not included in the primary dataset that is included in the case record forms for each enrolled subject.

(The sole exception appears to be study 112, which includes some radiology reports in the CRFs.)

As I mentioned, this is the only piece of objective clinical evidence that is required for study entry in these studies.

I do not want to request that all such documentation be provided at this point. However, I would like to review a sample of one study's radiology reports as a check on the correlation between the information provided in the CRF (which varies from an apparrent verbatim transcription of a radiology report, to nothing other than checking off the boxes on the CRF) and the official interpretation of the admission CXR.

Here is a 10% random sample of subjects enrolled in study 154-134. I have selected this study because it is (in my opinion) the best designed in terms of blinding and comparator, and is domestic. Please provide all radiologist reports on all entry radiographs taken on the following study subjects:

The sponsor's response:

2. None of the laboratory reports in the CRFs for this study reported a differential WBC count that included the number or percent immature forms (i.e., 'bands'). This is not of major concern, although this is a generally recognized parameter of acute infection that is helpful in making the diagnosis of an acute bacterial infectious process. It is also part of the entry criteria [page 8 of original protocol, item 5.2.b.5: "leukocytosis (blood leukocyte count > 10,000/mm^3 or >15% bands)].

3. Of the CRFs examined, practically all of the treated subjects received 10 days of therapy. In the study report (table 3 in appendix) , 16 subjects in the trovafloxacin arm and 16 in the clarithromycin arm received 7 days of therapy, compared to 129 and 133, respectively, who received 10 days. The proposed labeling requests a 7-14 day duration of therapy in the table presented in the DOSAGE AND ADMINISTRATION section. This study does not support a lower limit of 7 days of therapy for this indication.

4. The results of the CRF audit, in general, reveal no other inconsistencies of major concern. There were two CRFs in the trovafloxacin subjects and one clarithromycin subject for whom no CRFs were imaged in the "CRF Casebook" section of the CANDA. Although not of major concern, this represents 3/36 or 8% of the audited CRFs.

Medical Officer conclusions regarding efficacy results, study 134:

1. This double-blinded study supports the clinical efficacy of trovafloxacin in the treatment of community-acquired pneumonia. The sponsor's evaluation using the clinically evaluable EOS endpoint demonstrates equivalence with the approved comparator, clarithromycin. The bacteriologically (and clinically) evaluable subset at EOS did not demonstrate any remarkable organism-specific differences in outcome between the two treatment arms.
2. The results of subjects who were considered failure or relapse did not reveal any discrepancies; both study arms had 11 culture negative failure/relapses. Of the remaining subjects who were culture positive at baseline, the clarithromycin failure/relapses had 3 *M. catarrhalis* and 3 *H. influenzae* failures, whereas there were none of either of these organisms listed as failure/relapses in the trovafloxacin arm (out of a total of 13 isloates for *H. influenzae*, and 4 for *M. catarrhalis*).