Nosocomial Pneumonia

The **proposed indication** as it will appear in the labeling if approved is:

Nosocomial pneumonia caused by *Escherichia coli, Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.*

The sponsor has also appended the following statement to the draft labeling for this indication:

"As with other antibiotics, treatment of nosocomial infections due to *Pseudomonas aeruginosa* infections, may require combination therapy."

The **proposed dose** is alatrofloxacin 300 mg IV daily → trovafloxacin 200 mg PO daily for 10 – 14 days total.

In support of this indication, the sponsor has submitted one double-blind, comparative trial of the efficacy and safety of alatrofloxacin/trovafloxacin at the proposed dose compared to ciprofloxacin 400 mg IV BID → ciprofloxacin 750 mg PO BID for 10 – 14 days total (study 154-113), and one open, randomized trial of the efficacy and safety of alatrofloxacin/trovafloxacin at the proposed dose compared to ceftazidime 2 gm (maximum) BID IV → ciprofloxacin 750 mg BID for 10 – 14 days total (study 154-137).

Also contained within the electronic submission were documents related to the pharmacokinetics and microbiological properties of trovafloxacin and the requested indication. These were summarized in the MOR of AECB and will briefly be mentioned here.

Antimicrobial Agents Currently Approved for this Indication:

Zosyn®: moderate to severe nosocomial pneumonia caused by beta-lactamase producing strains of *Staphylococcus aureus.* "Initial presumptive treatment of patients with NP should start with Zosyn® at a dosage of 3.375 gm q 6 hours PLUS AN AMINOGLYCOSIDE. Treatment with the aminoglycoside should be continued in patients from whom *Pseudomonas aeruginosa* is isolated. If *Pseudomonas aeruginosa* is not isolated than the aminoglycoside may be discontinued at the discretion of the treating physician."

Ciprofloxacin: Mild/moderate/severe nosocomial pneumonia caused by *Haemophilus influenzae* or *Klebsiella pneumoniae* at a dose of 400 mg IV q8h.

***Medical Officer's Comment**: All other agents listed below are approved for the indication of LRTI (lower respiratory tract infections).*

Ciprofloxacin: (LRTI: mild to moderate): *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloace, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* and *Streptococcus pneumoniae.*)
Ceclor®: (LRTI and pneumonia: *Haemophilus influenzae, Streptococcus pneumoniae,* and *Streptococcus pyogenes.*
Cefizox®: (LRTI: *Klebsiella* spp., *Proteus mirabilis, Escherichia coli, Serratia* spp., *Enterobacter* spp., *Staphylococcus aureus, Haemophilus influenzae,* and *Streptococcus* spp. including *Streptococcus pneumoniae* but excluding *Enterococcus*)
Cefotan®: (LRTI: *Haemophilus influenzae, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis,* and *Serratia marcescens*)
Ceptaz®: (LRTI: *Pseudomonas aeruginosa,* other *Pseudomonas* spp., *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella* spp., *Enterobacter* spp., *Escherichia coli, Serratia* spp., *Citrobacter* spp., and *Staphylococcus aureus*)

Claforan®: (LRTI: *Haemophilus influenzae, Streptococcus pneumoniae,* other *Streptococcal* spp excluding Enterococci, *Klebsiella* spp., *Enterobacter* spp., *Escherichia coli, Serratia marscesens, Proteus* spp. and *Proteus mirabilis, Staphylococcus aureus, Pseudomonas* spp. including *aeruginosa.*)
Cleocin®: (LRTI: *Streptococcus pneumoniae* and other Streptococci excluding Enterococci, *Staphylococcus aureus*)
Flagyl®: (LRTI including pneumonia: *Bacteroides fragilis* group)
Fortaz®: (LRTI: *Pseudomonas aeruginosa,* other *Pseudomonas* spp., *Haemophilus influenzae Streptococcus pneumoniae, Klebsiella* spp., *Enterobacter* spp., *Escherichia coli, Serratia* spp., *Proteus mirabilis, Citrobacter* spp., and *Staphylococcus aureus.*)
Lorabid®: (Pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae).*
Spectobid®: (LRTI: *Haemophilus influenzae, Streptococcus pneumoniae,* beta-hemolytic Streptococci, and non-penicillinase producing Staphylococci)
Tazicef®: (LRTI: *Pseudomonas aeruginosa, Haemophilus influenzae Streptococcus pneumoniae, Klebsiella pneumoniae, Enterobacter* spp., *Escherichia coli, Serratia* spp., *Proteus mirabilis, Citrobacter* spp., and *Staphylococcus aureus.*)
Tazidime®: (LRTI: *Pseudomonas aeruginosa, Haemophilus influenzae Streptococcus pneumoniae, Klebsiella pneumoniae, Enterobacter* spp., *Escherichia coli, Serratia* spp., *Proteus mirabilis, Citrobacter* spp., and *Staphylococcus aureus.*)
Zinacef®: LRTI: *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella* spp., *Escherichia coli, Streptococcus pyogenes, Staphylococcus aureus,* and *Escherichia coli)*
Zithromax®:
Rocephin®: (LRTI: *Haemophilus influenzae, Haemophilus parainfluenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis,* and *Serratia marcescens.)*
Primaxin®: (LRTI: *Haemophilus influenzae, Haemophilus parainfluenzae, Acinetobacter* spp., *Enterobacter* spp., *Streptococcus pneumoniae, Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus,* and *Serratia marcescens.)*
Pipracil®: (LRTI: *Haemophilus influenzae, Pseudomonas aeruginosa, Acinetobacter* spp., *Enterobacter* spp., *Bacteroides* spp. and anaerobic cocci, *Klebsiella* spp., *Escherichia coli, Staphylococcus aureus,* and *Serratia* spp.*)*
Amoxil®: (indicated for the therapy of infections due to susceptible strains of the following Gram (+) cocci: *Streptococci* and *Streptococcus pneumoniae* and gram (-) organisms: *Haemophilus influenzae, Escherichia coli* and *Proteus mirabilis*).
Augmentin®: (LRTI: beta-lactamase producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*).
Azactam®: LRTI: *Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., *Proteus mirabilis, Pseudomonas aeruginosa* and *Serratia marcescens.)*
Ilosone/Ilotycin®: (LRTI: *Streptococcus* spp.)
Kefurox®: (LRTI: *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli,* and *Streptococcus pyogenes*)
Mandol®: (LRTI: *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella* spp., *Staphylococcus aureus, Proteus mirabilis* and beta-hemolytic Streptococci*)*
Mefoxin®: LRTI: *Streptococcus pneumoniae* and other Streptococci excluding *Enterococcus, Klebsiella* spp., *Escherichia coli, Haemophilus influenzae,* and *Bacteroides* spp.*)*
Mezlin®: (LRTI: *Haemophilus influenzae, Pseudomonas aeruginosa, Pseudomonas* spp., *Bacteroides* spp. including *fragilis, Klebsiella* spp., and *Escherichia coli)*
Nebcin®: (LRTI, serious: *Klebsiella* spp., *Escherichia coli, Enterobacter* spp., *Proteus mirabilis,* and *Staphylococcus aureus)*
Netromycin®: (LRTI including pneumonia and bronchitis: *Haemophilus influenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., *Proteus mirabilis, Proteus* spp., *Pseudomonas aeruginosa, Staphylococcus aureus* and *Serratia marscesens.)*
PCE Dispertab®: (LRTI: mild to moderate: *Streptococcus pneumoniae* and *Streptococcus* spp.)

Abbreviations used in this section:

Ceftaz = Ceftazidime

URTI = upper respiratory tract infection
LRTI = lower respiratory tract infection
URT = upper respiratory tract
LRT = lower respiratory tract
COPD = chronic obstructive pulmonary disease
Cipro = ciprofloxacin
Trovafloxacin = trovafloxacin
V1 = visit one or baseline visit on study day 1
V2 = visit 2, window study days 3 –7
V3 = visit 3
V4 = visit 4
EOT = End of Therapy
EOS = End of Study
TOC = Test of Cure
AE = Adverse Event
PTC = Points to Consider
ELF = epithelial lining cells
MSSA = methicillin-sensitive *Staphylococcus aureus*
MRSA = methicillin-resistant *Staphylococcus aureus*
PMN = polymorphonuclear
AC = advisory committee
AE = adverse event
NP = nosocomial pneumonia
CAP = community acquired pneumonia
Bronch = bronchoscopy
VAP = ventilator associated pneumonia

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Materials Reviewed for this Indication:

Electronic submission/December 29, 1996
FAX/September 23, 1997 containing tables pertaining to studies 154-113 and 154-137

Background:

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The lower respiratory tract clinical syndrome of pneumonia can be divided into to broad categories: community-acquired pneumonias (CAP) and nosocomial pneumonias (NP).

Nosocomial pneumonia is a clinical syndrome, characterized by the presence of a new infiltrate on CxR, as well as at least 2 of the following: cough, the production of sputum or a change in the character of the sputum, ausculatory findings and/or evidence of pulmonary consolidation, dyspnea, tachypnea, fever, and leucocytosis. Additionally, an organism consistent with a respiratory pathogen must be isolated from an appropriately obtained specimen.

The term NP is utilized in patients who acquire this clinical picture while in the hospital setting (> 48 hours after admission), or in nursing home patients. This differentiation, based on time of acquisition, is necessary in order to separately evaluate those patients with CAP who not only may be treated as out-patients but additionally present with a different microbial etiologies. Additionally, this differentiation has prognostic significance because patients in a hospital setting have increased mortality.

Risk factors for the development of NP include advanced age, severity of the underlying disease, intubation, use of respiratory equipment, use of a naso-gastric tube, altered mental status, and previous antimicrobial usage. Approximately 60% of the cases of NP are associated with Gram (-) bacilli including *Klebsiella pneumoniae, Escherichia coli, Serratia marcescens, Enterobacter* spp., and *Pseudomonas* spp. *Haemophilus influenzae* is also thought to be a pathogen especially in patients who have been hospitalized for a brief duration.

Staphylococcus aureus accounts for approximately 20% of the cases in contrast to *Streptococcus pneumoniae* which accounts for only Anaerobic bacteria are often isolated (35%) but are thought to account for only 5% of the cases. *Legionella* spp. has also been reported as the cause of sporadic outbreaks.

Some debate exists over the most appropriate method for obtaining sputum samples and thus a microbiologic diagnosis. Methods that can be employed include expectorated sputum, transtracheal aspiration, bronchial brushings, biopsy materials, pleural fluid, blood cultures, and surrogate markers (detection of antigen or specific nucleic acid by non-culture methods)

There appears to be concurrence between the FDA Guidance document, the IDSA Guidelines as well as various medical texts, that the use of expectorated or endotracheally aspirated sputum is acceptable as long as the specimen is screened for suitability (presence of > 25 PMNs and < 10 squamous epithelial cells/low magnification field [x 10]).

An appropriate specimen and a microbiologic diagnosis should be made within 24 –72 hours of starting therapy. All isolates should be sensitive to both the test drug and the comparator.

General guidelines for the duration of therapy vary from 10 – 14 days. The type of therapy selected depends on several issues including the location of the patients within the hospital setting (ICU), the presence of a ventilator, the use of previous antimicrobial therapy which might have led to the selection of resistant pathogens, the site of the infiltrate, and many other factors. All of the above will ultimately help determine a microbial differential diagnosis and aid in the development of an empiric regimen. The use of an extended spectrum penicillin or a third generation cephalosporin is generally advocated. Unresolved issues include the need for the addition of anaerobic coverage or not, that is clindamycin or metronidazole as well as the addition of an aminoglycoside or aztreonam when *Pseudomonas aeruginosa* is suspected or documented. The emergence of MRSA has also led to the increasing use of vancomycin in the empiric treatment of this disease.

Above reference: Mandell, Douglas and Bennett's principles and Practice of Infectious Diseases, Fourth edition, pages 608 - 612.

The FDA PTC states that one well-controlled trial that establishes clinical efficacy (95%CI) or general equivalence (difference in success rate no greater than 5%) to an approved comparator is required for approval.

Current IDSA Guidelines for the evaluation of anti-infective drug products, Vol. 15, suppl. 1, Nov. 1992, pages S80 – S87, suggest the following:

The minimal diagnostic criteria permitting the inclusion of patients in clinical trials are:

- Patients must have signs and symptoms consistent with bacterial pneumonia as described above.
- Patients must have a new infiltrate on CxR within 48 hours of institution of therapy.
- Suitable specimens for microbiologic evaluation must be obtained. This includes purulent expectorated sputum, transtracheal aspirates, specimens obtained by bronchial lavage or biopsy, pleural fluid aspirates, blood cultures, and surrogate markers.
- Patients must be adults, > 18 years of age.

- Pregnant or lactating women as well as patients with severe underlying diseases must be excluded.
- Patients who received prior antimicrobial therapy for ≥ 24 hours should be excluded.
- The study design should be randomized, prospective, and double blind.

- A separate analysis of ventilator-associated pneumonia (VAP) should be provided.
- The duration of treatment varies but it may be desirable to treat until the patient has been afebrile for 7 – 10 days.
- Conversion from the intravenous to the oral route can occur after an evaluation between days 3 – 7 of the study.
- Clinical evaluation is based on the resolution or improvement of the clinical and laboratory signs of infection such as fever, leucocytosis, purulent sputum production, and radiographic lung infiltrates.
- Hospitalized patients should be assessed every day during treatment and within 5 – 7 days after completion.
- Sputum samples should be collected at entry and at regular intervals.
- A CxR should be obtained 3 days after initiation of therapy and at any other time the investigator deems necessary.
- A post-therapy evaluation is necessary to determine response.
- Patients who have received at least 5 days of therapy and at least 80% of the study medication will have an assessment of clinical response.

In addition to the above, patients who worsen or who do not improve after 2 - 3 days should be removed from the study and classified as clinical failures. The addition of an antimicrobial that is not a study drug should also result in the designation of clinical failure.

The definitions of clinical response are as follows:

- Clinical cure: the complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on CxR.
- Clinical failure: the lack of any resolution in the signs and symptoms of pneumonia or persistence or progression of these after 3-5 days of therapy; the development of new pulmonary or extrapulmonary clinical findings consistent with active infection; persistence or progression of radiographic abnormalities; death due to pneumonia; or an inability to complete the study because of adverse effects.
- Indeterminate: must be substantiated by stated reasons.

The definitions of microbiologic response include:

- Eradication
- Persistence
- Relapse
- Reinfection
- Superinfection.

The current guidance for evaluability criteria of the DAIDP recently addressed the indication of pneumonia (CAP and NP). Amongst the points that were stressed, were:

- The differentiation of a CAP as opposed to a NP, and within the category of NP, the subsetting of those patients with VAP.
- The need for those patients with NP to have both fever and leucocytosis as well as least 1 of the other symptoms (cough, purulent sputum, ausculatory findings, dyspnea, tachypnea, hypoxemia, and an organism consistent with a respiratory pathogen.)
- A CxR within 48 hours of initiation of therapy that reveals the presence of a new or progressive infiltrate.
- The lack of consensus in the literature on the criteria for interpretation of the culture and Gram stain results of specimens obtained from patients with VAP.
- The prerequisite of 80 – 120% of therapy for evaluability
- The "optional" EOT visit, as this visit cannot be used as the TOC
- The "required" TOC visit at least 1 week after completion of therapy
- Clinical outcome as the primary efficacy variable

The DAIDP advisory committee agreed to all of the above.

Previous Recent Regulatory History:

Ofloxacin: NDA 19-735/S-029 and NDA 20-087/S-009: submitted in February 1993 for the indications of NP and severe CAP. The applicant submitted the data from 1 controlled and 1 uncontrolled study in support of this indication. Ceftazidime was the comparator agent in both trials. In the controlled trial, the efficacy of ofloxacin was inferior to that of the comparator. Multiple problems existed with the submission including: the lack of the specification of the timing of the acquisition of the NP in hospitalized patients, thus making the differentiation between patients with NP and those with CAP difficult. Additionally, the duration of therapy ranged from 7 – 14 days which again made the evaluation of the patients difficult. A severity scoring system was not provided and although sputum samples were collected, no guidelines as to the characterization of an acceptable specimen were provided, thus making the differentiation between colonization and true infection impossible. This application was denied.

Ciprofloxacin: NDA 19-847/S-008, NDA 19-857/S-008, NDA 19-858/S-008: submitted January 1993 for the indication of severe LRTI including NP. The applicant submitted one well designed, controlled, third party blinded, randomized trial comparing the efficacy and safety of ciprofloxacin with intravenous imipenem in patients with severe pneumonia. Additionally, data from supportive studies was also submitted. The MO utilized clinical response as the primary efficacy variable as compared to the applicant who used bacteriologic response. All other parameters in this submission were similar to those of the current submission. Clinical cure rates at the EOS were 59.2% for the ciprofloxacin-treated patients and 39.5% for the imipenem-treated patients. The MO recommended approval for this indication, but only for *Haemophilus influenzae* (14/19 eradicated) and *Klebsiella pneumoniae* (8/9 eradicated). Approval was not recommended for the requested pathogens: *Staphylococcus aureus* (8/14 eradicated) and *Pseudomonas aeruginosa* (18/29 eradicated) in severe disease although there was pre-existing approval for *Pseudomonas aeruginosa* in mild to moderate disease.

Medical Officer's Comment: *The original RMO determined that there was concurrence from all sources as to the criteria utilized in the diagnosis of NP as well as in the design and implementation of clinical trials to assess the efficacy and safety of new agents for this entity. Additionally, the RMO found that the sponsor had adhered to the FDA Guidance document in the design and implementation of these clinical trials for the indication of NP.*

The MO made the following determinations with regards to evaluability criteria:

- *The diagnosis of NP must be well established. This included the development of the signs and symptoms consistent with NP at least 48 hours after admission to the hospital for a non-respiratory diagnosis. The exception to this was the acceptance of non-ambulatory nursing home patients admitted for a possible Gram (-) pneumonia.*

The sponsor has adequately provided this information. A review of the CRFs revealed that the investigators not only had to verify the presence of increased cough, sputum production, increased purulence, dyspnea, fever, and leucocytosis, but additionally had to obtain a CxR to verify the presence of a new infiltrate as well as a sputum culture to assess not only for purulence but also for a predominant organism. Blood cultures were also obtained on all patients.

- *The MO carried forward any patient who received any additional antimicrobials not prespecified in the protocol, during the study as an evaluable failure. The only exception to this was in patients who received an antimicrobial that was clearly utilized for another infectious process and that had no activity against the designated pathogen. Failure was determined after 1 full day of therapy. This was consistent with the sponsor's evaluation of the data which was done in a blinded ad hoc manner because the duration of therapy necessary before a patient could be called a failure was not pre-determined by protocol. Although the MO determined that 1 day of therapy was not enough to fairly categorize a patient as a failure attributable to the study drug, the MO decided to re-evaluate this issue if it appeared that there were significant numbers of patients that fell into this category from either treatment arm.*

- *The MO did not consider evaluable those patients who received an alternative antimicrobial within 24 hours of the start of the study, unless the prerequisite clinical and microbiologic criteria were present (that is the isolation of a predominate pathogen on culture in association with the clinical picture of NP).*

- *The MO provided separate analyses of clinical response for those patients with ventilator-associated pneumonia and requested that the sponsor provide similar analyses of their data.*

- *The MO adhered to the categories of clinical and microbiologic assessment as described above in the IDSA Guidelines. This included the use of the primary efficacy variable of clinical response as a determinate of microbiologic outcome for each pathogen. That is, a patient who was cured was assumed to have "eradication/presumed eradication" of the primary pathogen or alternatively, a patient who failed was assumed to have "persistence/presumed persistence" of the primary pathogen.*

- *The MO assessed cure and improvement together in order to provided a dichotomous "cure/fail" analysis.*

- *The MO determined that the TOC should be applied to the EOS visit. This determination differs from that of the sponsor where the primary efficacy variable, clinical response, was applied to the EOT. The logical continuation of this argument was that a patient who was not seen at the later follow-up visit was not evaluable. If, however, the sponsor excluded a patient because they were not seen at the EOT but were seen at the later visit, the MO determined that this patient was evaluable. All failures were carried forward.*

- *Patients were eligible for classification as clinical cures if they received of the study drug.*

- *The windows of evaluability provided for by the sponsor were not changed for the EOS (days 28 –35) as the MO TOC was at the EOS and therefore sufficiently far out from therapy that the presence of active drug or post-antibiotic effect could be excluded.*

- *In both the double-blind trial (154-113) and the open trial (154-137), where ciprofloxacin and ceftazidime/ciprofloxacin were the respective comparator agents, the sponsor allowed for the use of either clindamycin or metronidazole, at the investigator's discretion, to provide broader anaerobic coverage. The MO elected to accept this concomitant antimicrobial usage. Additionally, both studies allowed for the addition of vancomycin in the presence of MRSA. If Pseudomonas aeruginosa was isolated, study 113 allowed for the addition of aztreonam and study 137 for the addition of gentamicin. The MO requested that the sponsor provide a separate analysis of the data with regards to these patients who received additional Gram (-) coverage.*

The MO reviewed the sponsor's evaluability criteria and general approach in this introduction. Both studies (154-113 and 154-137) were similar with only minor differences between them and these were pointed out in this section. Subsequent to the introduction, each study was reviewed separately and the MO referred back to this introductory section.

Microbiology:

In support of the effectiveness of trovafloxacin against the requested pathogens, the sponsor submitted, (microbiology section of the electronic submission), the results of microbiology studies of trovafloxacin versus the requested pathogens. These MIC-90 results are summarized below:
(Copied from page 10, section H.3.A of the Esub)

Pathogen	MIC_{90} (µg/mL)
Streptococcus pneumoniae (including penicillin resistant)	0.12
Staphylococcus aureus	0.06
Haemophilus influenzae	0.015
Moraxella catarrhalis	0.03
Escherichia coli	0.06
Klebsiella pneumoniae	0.12
Pseudomonas aeruginosa	1.0
Enterobacter cloacae	1.6
Proteus mirabilis	0.5
Enterococcus faecalis	2.0
Serratia marcescens	1.0
Morganella morganii	0.5
ATYPICAL	
Legionella pneumoniae	0.008
Mycoplasma pneumoniae	0.25
Chlamydia pneumoniae	1.0
ANAEROBES	1.0

Pharmacokinetics:

The MO reviewed the 2 studies submitted by the sponsor assessing the penetration of orally administered trovafloxacin into the bronchial tree (studies 154-016: an open study to assess concentrations of trovafloxacin in bronchial washings and serum after administration of a single dose to subjects undergoing bronchoscopy and 154-020: an open study to assess the concentration of trovafloxacin in bronchial mucosa, epithelial lining fluid, and alveolar macrophages compared to that of serum after administration of single and multiple oral 200 mgm doses to subjects undergoing fiber-optic bronchoscopy), in the MOR pertaining to AECB.

The results of these studies are provided below (copied from the electronic submission):

154-016	26	Bronchial epithelial cells/macrophages	2.9 (4-6 hr postdose) 7.3 (18-24 hr postdose)
154-020	5	Lung mucosa (single dose)	1.1 (6 hr postdose)
	9	Lung mucosa (multiple dose)	1.1 (6 hr postdose)
154-020	5	Lung epithelial lining fluid (single dose)	2.3 (6 hr postdose)
	7	Lung epithelial lining fluid (multiple dose)	5.8 (6 hr postdose)
154-020	5	Alveolar macrophages (single dose)	13.3 (6 hr postdose)
	8	Alveolar macrophages (multiple dose)	24.1 (6 hr postdose)

Medical Officer's Comment: *These results showed that trovafloxacin was well distributed to bronchial mucosal tissue, ELF and macrophages following single and multiple 200 mg doses. In addition, the concentrations obtained were well above the MIC-90s of pathogens responsible for lower respiratory tract infections, including those associated with NP. The sponsor stated that:*
(Copied from page 10, section H.3.A of the Esub)

The mean peak blood levels (C_{max}) of the 200 mg trovafloxacin oral dose (used for community-acquired pneumonia and sinusitis) and 300 mg alatrofloxacin IV dose (trovafloxacin equivalent dose; used for nosocomial pneumonia) are 2.5 ug/mL and 4.5 ug/mL, respectively, with a half life of 10-12 hours. Trovafloxacin has been found to be well distributed to bronchial mucosa, epithelial lining fluid (ELF) and alveolar macrophages following single and multiple 200 mg doses. Lung levels of trovafloxacin are 2-8 fold higher than serum levels giving levels in the lung and blood with once daily oral dosing that are many fold higher than the respiratory pathogen MIC_{90}s. Animal experiments (including models of meningitis) have confirmed potent *Streptococcus pneumoniae* activity in experiments where common quinolones have failed. In *in vitro* and animal models of legionellosis, trovafloxacin is more potent than any of the currently marketed azalides, macrolides, or quinolones.

Medical Officer's Comment: *The MO defers to the PK reviewer for further comment.*

General Approach to Evaluation:

Copied below from page 9 of section H.3.A, is the sponsor's table of the studies performed in support of this indication:

Nosocomial Pneumonia					
154-113	Alatrofloxacin 300 mg[d] QD IV → trovafloxacin 200 mg QD PO (10 to 14 days total)	129	Ciprofloxacin 400 mg BID IV → ciprofloxacin 750 mg BID PO (10 to 14 days total)	138	Phase III DB
154-137	Alatrofloxacin 300 mg[d] QD IV → trovafloxacin 200 mg QD PO (10 to 14 days total)	135	Ceftazidime 2 gm (max.) BID IV → ciprofloxacin 750 mg BID (10 to 14 days total)	140	Phase III Open Randomized

Medical Officer's Comment: *Study 154-137 was identical to 113 with the exception that it was an open study due to the difficulties in blinding ceftazidime because of its color.*

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Definitions:

The sponsor's definition of NP has been copied below from page 11, section H.3.A of the Esub:

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- new infiltrate on chest x-ray;
- at least one of the following: cough or increasing severity of coughing, acute changes in the quality of sputum, oral temperature >38°C (100.4°F) or <36.1°C (97°F) or documented fever or hypothermia within the last 24 hours, ausculatory findings such as rales or evidence of pulmonary consolidation, or leukocytosis (blood leukocyte count >10000/mm^3 or >15% bands);
- requirement for hospitalization and initial intravenous therapy;
- absence of cavitary lung disease, known lung cancer, cystic fibrosis, and suspected *P. carinii* pneumonia.
- nosocomial pneumonia was acquired at least 48 hours after a hospitalization for reasons other than respiratory infection.
- Nonambulatory, institutionalized (nursing home) subjects being admitted to a hospital for suspected gram negative pneumonia may also have been enrolled.

Medical Officer's Comment: *The MO agreed with this definition and points out the concurrence between this definition and that found in the FDA Guidance document. The characterization of purulent sputum as sputum which on Gram stain shows > 25 PMNs and < 10 squamous epithelial cells per low power field, is well established.*

Systemic Antibiotic Usage (copied from page 12 of section H.3.A):

Prior systemic antibiotic usage for more than 24 hours within 72 hours of baseline was prohibited unless there was documented bacterial resistance, or the subject was a clinical failure or developed new infiltrate on the antibiotic.

Medical Officer's Comment: *The MO agreed with this definition.*

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Data Analysis:

Copied below from page 14, section H.3.A, are the sponsor's definitions of subject subsets:

- **All Randomized (Double-Blind Studies) or Enrolled (Non-Randomized Open Studies) Subjects**
  The all randomized or enrolled subjects subsets included all subjects who were randomized or enrolled to a treatment group, regardless of whether or not a particular subject received any study medication.
- **All Treated Subjects**
  The all treated subjects subset included all subjects who received one or more doses of study medication (active double-blind study medication for the double-blind studies).

- **Clinical Intent-to-Treat Subjects**
  The clinical intent-to-treat subjects subset included those subjects in the all randomized or enrolled subjects subset who had a baseline diagnosis of the disease or condition under investigation determined by protocol specific inclusion and exclusion criteria (not applicable to protocol 154-101, which had a check box on the case report form for underlying disease rather than inclusion/exclusion criteria). Some subjects in this subset may never have received any study medication.

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- **Clinically Evaluable Subjects**
  The clinically evaluable subjects subset included all subjects in the clinical intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied.

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- **Bacteriological Intent-to-Treat Subjects**
  The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline. Some subjects in this subset may never have received any study medication.

- **Bacteriologically Evaluable Subjects**
  The bacteriologically evaluable subjects subset included all subjects in the clinically evaluable subjects subset, unless one or more of the criteria for non-evaluability applied.

Medical Officer's Comment: The MO's evaluable population was compromised of a subset of the sponsor's clinically evaluable subset. That is all patients who did not have an EOS visit were excluded from the analysis.

Evaluability Criteria (copied from pages 15- 16 of section H.3.A):

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Clinical:

If any of the following were present, the subject was considered non-evaluable for clinical efficacy:

- insufficient therapy (subject discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement);

Medical Officer's comment: The sponsor's representative, Dr. Debra Williams verified that all failures were carried forward. However, the above statement infers that if a patient was discontinued on day 4 because of an AE, this patient would not be labeled as a failure. The MO elected to evaluate these patients separately in order to determine outcome.

- prior antibiotic usage (for >24 hours within 3 days before Day 1 of the study); unless, , the subject had a culture positive baseline pathogen in the evaluable baseline window (as determined by exclusion criteria);

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- use of a concomitant antibiotic, given for intercurrent illness or adverse event, that was potentially effective against the condition under study (unless given for insufficient response);
- or intercurrent illness that could confound clinical evaluation of the condition under study.

Subjects in Phase III studies were also non-evaluable for clinical efficacy if the following applied:

- no post-baseline assessment in the evaluable analysis window, unless the investigator's clinical response was failure before the beginning of the end of treatment window,
- or the subject was given an antibiotic for insufficient response at any time during the study.

A subject was included in the analysis at the end of study assessment if the subject:

- was clinically evaluable at the end of treatment visit, and
- was not given any antibiotics for intercurrent illness before the assessment at the end of study visit (unless given for insufficient response), and
- had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study,

or the subject was:

- clinically evaluable at the end of treatment visit, and
- the sponsor-defined clinical response was failure or relapse at end of treatment.

Medical Officer's Comment: The MO agreed with the sponsor's evaluability criteria. All failures were carried forward and the EOS visit was necessary to apply the TOC. The MO did not consider the EOT visit necessary.

Bacteriological:

For subjects with no baseline atypical pathogen, if any of the following were present the subject was considered non-evaluable for bacteriological efficacy:

- no baseline pathogen or baseline culture outside baseline visit window (>2 days before the first dose of study medication).
- no post-baseline culture, except in the instance of no suitable culture material due to clinical cure or improvement based on the investigator-defined clinical response,
- or the subject was given an antibiotic for insufficient response or the investigator's clinical response was failure (at any time up to and including the last day of the evaluable end of study analysis window.
- Subjects with a serologically defined baseline atypical pathogen were bacteriologically evaluable if they were clinically evaluable.

For all protocols and for subjects with no baseline atypical pathogens, bacteriologically evaluable subjects were excluded from the analysis at the end of study visit if:

- they were excluded from the clinical analysis at the end of study visit, or
- they did not have a culture result in the end of study window, unless given an antibiotic for inadequate response or the investigator's clinical response was failure any time during the study, up to and including the last day of the end of study analysis window.

Subjects in protocols with a serologically defined baseline atypical pathogen were included in the bacteriological analysis at end of study if they were included in the clinical analysis at end of study.

Medical Officer's Comment: The MO agreed with these criteria. The MO's bacteriologically evaluable population was a subset of the clinically evaluable. As the MO TOC was applied to the EOS visit, the presence of a culture result in the EOS window was necessary within the context of making a presumptive

versus a definite determination of outcome. However, as stated above, as the main determinant of efficacy was clinical, the MO accepted a presumptive determination in correlation with the clinical.

Primary and Secondary Endpoints for Efficacy (copied from page 16 of section H.3.A):

The primary efficacy endpoints were:

- Sponsor-defined subject clinical response at the end of treatment visit;
- Pathogen eradication rates at the end of treatment visit.

Secondary efficacy endpoints were:

- Pathogen eradication rates at the end of study visit;
- Investigator-defined subject clinical response at the end of treatment visit, and sponsor-defined and investigator-defined subject clinical response at the end of study visit. –

Medical Officer's Comment: In accordance with regulatory precedence as well as the DAIDP's guidance document and the AC recommendations, the MO elected to assess outcome, clinical and bacteriological, at the EOS as opposed to the EOT visit. Any patient without an EOS visit was not considered evaluable and any patient excluded by the sponsor because they did not have an EOT visit but did have an EOS visit was considered evaluable. Information submitted by the sponsor on September 23, 1997 revealed that 16 trovafloxacin patients and 24 ciprofloxacin patients would be excluded from the MO's evaluable population in study 113. 2 ciprofloxacin patients who had an EOS visit but no EOT visit were considered evaluable by the MO. Thus, the MO's population consisted of 72 trovafloxacin and 70 ciprofloxacin patients as compared to 88 and 101 per arm respectively, as per the sponsor's analysis.

The respective numbers in study 137 were 18 trovafloxacin patients without an EOS visit and 3 without an EOT visit, thus leaving 85 MO evaluable patients as compared to 100 as per the sponsor. On the ceftazidime arm, there were 20 patients without an EOS visit and 2 without an EOT visit; thus 89 patients were initally evaluable as per the MO as compared to 107 as per the sponsor.

Additionally, if there was no bacteriologic response documented at the EOS, the EOT response was carried forward from the EOT to the EOS by the MO as a presumptive response.

Definitions of Response (copied from pages 17,18, and 19 of section H.3.A.A):

Sponsor-Defined Subject Clinical Response:

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the global evaluations made by the investigator at the end of treatment and end of study visits.

The investigator classified the clinical response of the subject as cure (resolution of all signs and symptoms of the disease under study to the level that existed before baseline), improvement (incomplete resolution of signs and symptoms), or failure (lack of resolution of any of the signs and symptoms of infection).

The occurrence of the following conditions superseded the investigator's assessment:

- **Failure.** If the investigator defined subject clinical response was failure at any visit, then the sponsor-defined subject clinical response was failure at all subsequent visits.

- **Failure.** If a subject was given a concomitant antibiotic for insufficient clinical response or failure then the sponsor-defined subject clinical response was failure at that visit and at all subsequent visits.

- **Failure:** If a subject had no post-baseline assessment, that subject was classified as a clinical failure at both the end of treatment and end of study visits (ITT only).

- Relapse:

- If a subject was a clinical cure or improvement at the end of treatment visit, and was assessed by the investigator to be a failure at a subsequent visit, then that subject was classified as a clinical relapse at the end of study visit.

- If a subject was a clinical cure or improvement at the end of treatment visit, but required additional antibiotic therapy for the primary disease before the end of study visit, then the subject was classified as a clinical relapse at the end of study visit.

For the analysis of the Clinically Intent-to-Treat Subject subset, a 'last observation carried forward' strategy will be used for subjects who are lost to follow-up before the End of Study visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment will be treated as missing data.

Sponsor-Defined Pathogen Outcome

For both evaluable and intent-to-treat subjects, the sponsor classified each baseline organism as a pathogen or as a non-pathogen. Each baseline organism classified as a pathogen was assigned a sponsor-defined pathogen outcome. Multiple baseline pathogens identified in culture samples from the same subject were assigned separate outcomes. Baseline pathogens were assigned a separate outcome for the end of treatment and end of study visits. If multiple visits occurred in the end of treatment analysis window, the last outcome assigned to each baseline pathogen was used. If multiple visits occurred in the end of study window, the worst case outcome was used. Selection of the worst case outcome followed the order persistence or relapse, presumed persistence, presumptive eradication, eradication.

The sponsor-defined pathogen outcomes were defined as follows:

1. Eradication: Baseline pathogen absent from a culture from the same site. If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this negative culture, the eradication was carried forward to all subsequent visits, regardless of subsequent culture results.

2. Presumptive eradication: Absence of adequate culture material for evaluation and the sponsor-defined subject clinical response was cure or improvement.

3. Persistence: Baseline pathogen present in a culture sample from the same site (or any relevant site, including blood). If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this positive culture, the persistence was carried forward to all subsequent visits, regardless of subsequent culture results.

4. Presumed Persistence:

- Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day, or within 3 days after, a positive or negative culture, in the absence of prior microbiological data in the same evaluable analysis window resulted in a

sponsor-defined pathogen outcome of presumed persistence at that visit and all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up, the presumed persistence was carried forward to subsequent implied visits. Absence of microbiological data was either no visit in the window or culture not done at all visits in the window.

- No culture was obtained (either not done or absence of adequate culturable material) and the sponsor-defined subject clinical response was failure.

- The baseline pathogens of subjects who were lost to follow-up (i.e., no visit) at either the end of treatment or end of study visits were assigned the outcome of presumed persistence if the pathogen was persistent at any previous visit.

5. Relapse: The original baseline pathogen was present at the end of study visit in a culture from the same site after the end of treatment culture was negative.

Organisms not present at baseline were classified as superinfection or colonization, defined as follows:

6. Superinfection: A pathogen, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and associated with emergence or worsening of clinical and laboratory evidence of infection.

7. Colonization: Any organism, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and not associated with signs or symptoms of active infections.

Each atypical pathogen, identified by serology test, was assigned a sponsor-defined pathogen outcome as follows:

1. Presumed persistence: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and sponsor-defined subject clinical response was failure.

2. Presumed eradication: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and the sponsor-defined subject clinical response was cure or improvement.

Medical Officer's Comment: *The MO agreed with the sponsor's definitions of bacteriologic outcome for those cases where the change in the TOC did not affect the response.*

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Evaluability Windows:

As per the original protocols, the sponsor-designated evaluable for analysis windows were study days 12 – 16 for the EOT and study days 28 – 35 for the EOS. As per the electronic submission as well as verbal communication with Dr. Debra Williams, these windows were changed during the data analysis to EOT: days 7 – 20 and EOS: days 21 - 40. The rationale for these changes was, as in previously reviewed indications, to capture as many patients as possible. As stated above, as the MO applied the TOC to the EOS visit, there was no disagreement in the analysis window set by the sponsor for that visit as it routinely represented at least 1 week post-therapy.

It is once again noted that a "failure" could be designated as such from day 1 and as per the sponsor's analysis, a "cure" could be designated as such as of day 7. The MO however, required a minimum of 80% of therapy, or 8 days of therapy before a patient could be designated as a "cure."

Study 154-113

TITLE:

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN (CP-116, 517) FOLLOWED BY ORAL TROVAFLOXACIN (CP-99, 219) WITH INTRAVENOUS CIPROFLOXACIN FOLLOWED BY ORAL CIPROFLOXACIN FOR THE TREATMENT OF NOSOCOMIAL PNEUMONIA.

Study Dates: February 3, 1995 – June 13, 1996

Objective: the objective of this Phase III study was to compare the safety and efficacy of intravenous alatrofloxacin, followed by oral trovafloxacin (with optional aztreonam and/or vancomycin), compared to intravenous ciprofloxacin followed by oral ciprofloxacin (with optional aztreonam, vancomycin, clindamycin and/or metronidazole), for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

List of Principal Investigators:

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United States	5017	John Gezon, MD
	5050	Charles VanHook, MD
	5079	W. Travis Ellison, MD
	5106	Charles Ballow, PharmD
	5108	Edward Britt, MD
	5111	Daniel Herr, MS, MD
	5112	Timothy Kotschwar, PharmD
	5115	Michael Niederman, MD
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	5118	Claude Tellis, MD
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	5123	Dennis Mikolich, MD
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	5211	Andrew Quartin, MD
	5249	David Smith, MD
	5368	Jeffrey Timby, MD
	5384	Martin Tauber, MD
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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
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	5984	John Samies, MD
	5985	David McEniry, MD
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	5780	Dr. Werner Bachmann
	5903	Dr. Walther Grau
	6111	Dr. H. Landgraf
	6112	Dr. Peter-Henning Althoff
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	6404	Dr. Hans Schulz
	6477	Dr. Franz Hartmann
	6543	Dr. Thomas Muller
United Kingdom	5395	Dr. Ian Gould
		Dr. David Noble
	5396	Dr. Ian Grant
		Dr. Robert Masterton
	5407	Dr. Peter Duncan
	5408	Dr. Robin Macmillan
	5409	Dr. Martin Street
	5410	Dr. Graham Sunderland
	6115	Dr. Shane O'Neill
	6339	Dr. John Colvin
France	5441	Dr. Rene Pariente
	5508	Dr. Yann Curran
	5511	Dr. Fabrice Pierre Brunet

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
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	5423	Michael Alexander, MD
	5986	Mark Miller, MD
Spain	5623	Dr. Antoni Marti
	5627	Dr. Jose Martin
	5835	Dr. Joaquin Duran
Belgium	5510	Dr. Vincent D'Orio
	5834	Dr. Jean Petermans
Portugal	5543	Dr. Raul Marques
	5600	Dr. Jorge Pimentel
Costa Rica	5034	Guillermo Rodriguez, MD

Study Design: Study 154-113 was a randomized, double-blind, double-dummy, multicenter trial of alatrofloxacin administered intravenously daily for 2 to 7 days, followed by oral trovafloxacin to complete 10 to 14 days of total treatment, compared to intravenous ciprofloxacin for 2 to 7 days followed by oral ciprofloxacin to complete 10 to 14 days of treatment of patients with nosocomial pneumonia requiring initial intravenous therapy. In subjects with documented *Pseudomonas aeruginosa* infection or MRSA, aztreonam or vancomycin respectively, may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added in a blinded manner to the ciprofloxacin arm only.

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Protocol Overview:

Copied below from the electronic submission, appendix A of the original protocol is the sponsor's schedule of visits and procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number Study day: Allowable Window	1 Day 1 (-24 hours)	2 Day 4 (Day 3-7)	3 Day 14 (Day 12-16)	4 Day 30 (Day 28-35)
Treatment Period Follow-up period	Day 1 to	Day 10 to Day 14	Day 15 to	Day 35
Informed consent	X			
Demographic Information	X			
Targeted Physical Exam	X			
Apache II Score	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record		X	X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X		X	abn
Microbiology				
sputum Gram stain	X	X	X	X2
culture & sensitivity	X	X	X	X2
blood culture	X	X3 X4		
Serology	X			X
Safety laboratory tests				
haematology	X	X	X	abn
biochemistry	X	X	X	abn
urinalysis	X		X	abn
Pregnancy test1	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's assessment of clinical response5			X	X

abn = abnormal at previous visit or clinically significant adverse event

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1 to be done by local site for women of child bearing potential

2 to be done if clinically indicated

3 to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure

4 to be done if a positive culture was obtained at visit 2

5 to be done at the time of discontinuation, if applicable

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As can be appreciated from the above schedule, at the baseline assessment (Visit 1, Day 1), all subjects were to have had a medical history and clinical and radiological findings consistent with nosocomial pneumonia. The NP must have been acquired at least 48 hours after hospitalization for reasons other than respiratory infection, and the patients must have required initial intravenous therapy. Nonambulatory nursing home patients who were admitted to a hospital for suspected gram-negative pneumonia were also eligible for enrollment.

The following characteristics were to have been present:

- New infiltrate on chest x-ray;

and

- At least one of the following:

  - Cough or increasing severity of coughing.
  - Acute changes in the quality of sputum.
  - Body temperature >38°C (100.4°F) or <36.1°C (97°F) or documented fever or hypothermia within the last 24 hours.
  - Auscultatory findings such as rales or evidence of pulmonary consolidation.
  - Leukocytosis (blood leukocyte count >10,000/mm^3 or >15% bands).

All subjects who met the criteria for the clinical diagnosis of NP at V1, and who gave informed consent and met all additional inclusion criteria and none of the exclusion criteria were eligible for randomization.

V1 assessments included collection of demographic information, medical history and physical examination (including APACHE II score), concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature). Clinical assessment of signs and symptoms of pneumonia included sputum characteristics, cough, dyspnea, chills/rigors, pleuritic chest pain, lung sounds, and CxR (PA and lateral views). In addition, a standard panel of blood (including culture), and urine (including culture), tests were performed. Initial serology testing for evidence of infection with *Legionella* spp. was performed. Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per low power field [LPF], squamous epithelial cells per LPF) of sputum were performed. If a satisfactory specimen could not be obtained the investigator could have induced sputum with nebulised saline solution or physiotherapy. If this technique was unsuccessful the investigator could have used such techniques as transtracheal aspiration, bronchial brushings or biopsy material obtained by bronchoscopy.

Susceptibility to the study drugs, trovafloxacin and ciprofloxacin, was determined for all potentially significant organisms isolated from sputum specimens, that were considered adequate. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. If no pathogen was detected on baseline culture or if a pathogen was resistant to study medication, study therapy could continue, at the discretion of the investigator.

At Visit 2 (V2: Day 4), a patient's need for continued intravenous therapy was assessed (daily from study days 3 to 7). Subjects were switched to oral therapy if the following conditions applied:

- resolution of fever (based on daily maximum temperature);
- improvement of symptoms;
- no progression of x-ray changes.

Efficacy observations were performed at this visit, including clinical assessment of signs and symptoms of pneumonia to assess response to study therapy. Bacteriologic response was assessed through sputum samples. Blood cultures were repeated only if they had been positive at the previous visit. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory (hematology and biochemistry) evaluations.

At Visit 3 (V3: Day 14: EOT) efficacy observations were performed including clinical assessment of signs and symptoms of pneumonia to assess response to study therapy. Bacteriologic response was assessed through sputum samples. Blood cultures were repeated only if they had been positive at the previous visit; a chest x-ray was also performed. In addition to efficacy observations, safety was assessed through the recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory

(hematology, biochemistry, and urinalysis) evaluations. The investigators provided an evaluation of clinical response.

At Visit 4 (V4: Day 30: EOS), efficacy observations were performed including clinical assessment of signs and symptoms of pneumonia to assess response to study therapy. Bacteriologic response was assessed through sputum samples. If the V3 CxR had not resolved to the patient's baseline, a final x-ray was obtained. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, and adverse events. Laboratory evaluations (hematology, biochemistry, and urinalysis) were only performed if a clinically significant abnormality was present as V3 (Day 14) or if the subject was experiencing a clinically significant adverse event. A final serology was performed and the investigator provided a final evaluation of clinical response.

Medical Officer's Comment: The MO determined that the study was well designed and in accordance with current guidelines. Efficacy evaluations were performed at V3 and V4. However, per the sponsor, only V3 was obligatory for evaluability.

Compliance:

This study was conducted in compliance with a local or central Institutional Review Board (IRB) and informed consent regulations.

Concomitant Illnesses and Medications:

At each visit, the investigator obtained information about concomitant illnesses and any therapeutic interventions (e.g., drug therapy, surgery, etc.) that had occurred. Included, was the diagnosis and dates of onset and remission of all illnesses, as well as the name and start date of medications (including self-prescribed medication), date(s), and description of surgery, etc.

If any antibiotic was taken during the study period, the reason for its use was documented. If the antibiotic was taken for a different infection, then, in order to ensure that such subjects remained evaluable, final efficacy assessments were performed prior to starting new antibiotic treatment.

Medical Officer's Comment: As stated in the introduction, the MO agreed to accept as evaluable patients, those patients who received another anti-microbial for a clearly documented different infection and only where the concomitant anti-microbial could have had no activity against the primary pathogen. If there was no primary pathogen however, the MO determined that these patients should be excluded from the analysis.

Discontinuation of Study Therapy:

The investigator discontinued study therapy in the event of limiting side effects or significant laboratory abnormalities (including marked liver function abnormalities), independent of their suspected causal relationship to study drug. Discontinuations due to serious adverse events were reported to the Pfizer monitor immediately. The reasons for discontinuation of any subject were recorded on the case report form.

In the event of discontinuation of study therapy, appropriate non-study therapy was initiated and the subject was followed for safety observations throughout the remainder of the study (V 4). Untoward events leading to discontinuation of study therapy were followed until they returned to normal or had stabilized; the frequency of follow-up was at the discretion of the investigator. For subjects discontinued from study therapy because of clinical failure, the final clinical and microbiological efficacy evaluation required by the protocol was performed at the time of study drug discontinuation

Protocol Amendments:

The protocol was amended three times (October 20, 1994, November 16, 1994, and October 5, 1995).

The October 20, 1994 and November 16, 1994 amendments were prior to the study start and concerned the addition of optional vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, and simplified placebo dosing.

The October 5, 1995 amendment was primarily to allow the addition of clindamycin or metronidazole to the ciprofloxacin arm of the study and to allow a total of 14 days of intravenous study drug dosing for subjects unable to take oral study drugs.

Precautions:

Subjects were instructed not to donate blood during and for 30 days after the end of study.

Study Population:

It was expected that up to 320 subjects were to be randomized to one of two treatment groups, with each center enrolling approximately 8 patients.

Inclusion and Exclusion Criteria:
(Copied from page 9 of the original protocol)

Inclusion criteria

1. Aged 18 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 a nosocomial pneumonia acquired <u>at least</u> 48 hours after a hospitalisation for reasons other than respiratory infection. Nonambulatory, institutionalised (nursing home) subjects being admitted to a hospital for suspected gram negative pneumonia may also be enrolled.

   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) Body temperature > 38°C (100.4°F) or < 36.1°C (97°F)
      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 subject or the appropriate third party (parent, guardian, legal representative, or next of kin) if the subject is not competent to give consent.

Exclusion criteria

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

2. Known or suspected hypersensitivity or intolerance to any quinolone

<October 20, 1994 Amendment>
antibiotic, or aztreonam, *or vancomycin.*

3. Treatment with any potentially effective systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline assessment unless patient is a clinical failure for a nosocomial pneumonia or has a new infiltrate which developed on the antibiotic.

4. Concurrent treatment with any potentially effective systemic antibiotic.

5. Subjects with any of the following conditions:

   a. Known Acquired Immunodeficiency Syndrome (AIDS) or suspected *Pneumocystis carinii* pneumonia.
   b. Neutropenia, defined as a total white blood cell count less than 2500 leukocytes/mm³ or absolute neutrophil count less than 1000/mm³.
   c. Immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including chronic treatment with greater than 10 mg/day of systemic prednisone or equivalent). Subjects may be treated during the study with medically necessary steroid therapy.
   d. Cavitary lung disease by chest X-ray; or known lung cancer.
   e. Cystic fibrosis.
   f. A history of all forms of epilepsy or seizure.

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

7. Prior enrolment in this protocol.

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

Medical Officer's Comment: *As stated in the introduction, the MO agreed with the inclusion and exclusion criteria.*

Randomization and Blinding:

The investigator sequentially assigned study numbers to the patients as they were determined to be eligible for treatment. This number was entered onto the CRF and the subject received the study medication assigned to the corresponding number.

The primary study drugs (trovafloxacin and ciprofloxacin) were blinded by a double-dummy technique.

Dosage Form and Administration:
(Copied from pages 21 and 22 of the study report)

Study drug for intravenous administration was prepared using a double-dummy technique to maintain blinding. Intravenous alatrofloxacin (equivalent to 300 mg trovafloxacin) or matching placebo (sterile water) for intravenous administration was provided in vials of 5 mg/mL (100 mg/20 mL) to be diluted to 1.5 mg/mL with 5% dextrose in water (D5W). Intravenous ciprofloxacin or matching placebo (sterile water) was provided in vials of 10 mg/mL (200 mg/20 mL) to be diluted to 2 mg/mL with D5W.

Subjects received one of the following intravenous treatment regimens:

Alatrofloxacin 300 mg (3 x 100 mg vials) in 200 mL of D5W administered once daily as a 60-minute infusion in the morning; 200 mL D5W (ciprofloxacin placebo; 2 vials) administered as a 60-minute infusion once daily in the evening.

Ciprofloxacin 400 mg (2 x 100 mg vials) plus alatrofloxacin placebo (1 vial) in 200 mL of D5W administered in the morning and ciprofloxacin 400 mg (2 x 100 mg vials) in 200 mL of D5W in the evening, each as a 60-minute infusion.

When the investigator had determined a subject's resolution of fever with an improvement of symptoms and no new x-ray findings, the subject was switched from intravenous to oral therapy. Intravenous dosing could have been extended to 14 days in subjects unable to take oral medication. Doses of study medication for subjects that needed to continue intravenous dosing beyond 10 days were to be pharmacy blinded using unblinded vials of alatrofloxacin or ciprofloxacin to prepare the blinded supplies.

Study drug for oral administration was in the form of trovafloxacin tablets and ciprofloxacin capsules and was packaged in blister packs, using a double-dummy technique to maintain blinding. After 2 to 7 days of intravenous treatment with randomized study medication subjects received one of the following treatments orally:

Trovafloxacin 200 mg/day as a single active dose (2 x 100 mg tablets) administered in the morning and three capsules (ciprofloxacin placebo) administered twice daily, once in the morning and once in the evening.

Ciprofloxacin 1500 mg/day in two equally divided doses (3 x 250 mg capsules) administered once daily in the morning and once in the evening and two tablets (trovafloxacin placebo) administered once daily in the morning.

Subjects were to receive the appropriate oral therapy to complete a total maximum treatment duration of 10 to 14 days.
Subjects with *Pseudomonas* infection, methicillin-resistant *Staphylococcus aureus*, and/or anaerobic infection may have received optional antibiotic therapy, as follows:

Optional Aztreonam
For subjects with documented *Pseudomonas* infection at baseline, treatment with open-label aztreonam, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in either treatment regimen. Treatment with aztreonam was to continue for a maximum of 14 days.

Optional Vancomycin
For subjects with documented methicillin-resistant *Staphylococcus aureus* at baseline, treatment with open-label vancomycin, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in either treatment regimen. Treatment with vancomycin was to continue for a maximum of 14 days.

Optional Clindamycin / Metronidazole
For subjects randomized to ciprofloxacin who had suspected anaerobic pneumonia at baseline, treatment with clindamycin or metronidazole, at medically appropriate and approved doses was to be initiated. The study pharmacist was to break the blind on a particular subject when such a request was made. For subjects randomized to ciprofloxacin, the prescribed dose of clindamycin or metronidazole was to be prepared in a blinded fashion. For subjects randomized to alatrofloxacin/trovafloxacin, an identical placebo dose was to be prepared to the same final volume in the same diluent. Clindamycin or metronidazole or matching placebo were to be administered at a frequency prescribed by the physician. Only the pharmacist was to have knowledge of or access to the randomization assignment.

At intervals during treatment or at the time of premature discontinuation of study therapy, appropriate entries for tablets/capsules taken and returned were completed on the case report form (CRF) and the Pfizer Drug Inventory Record (PDIR). If doses were missed, the reason was to be recorded on the CRF.

Medical Officer's Comment: The study pharmacist was unblinded in the case of prolonged intravenous therapy or when clindamycin or metronidazole were utilized for additional anaerobic coverage. Per the original protocol and the study report, the investigator remained blinded.

The MO points out the necessity of a documented culture result for Pseudomonas aeruginosa or Staphylococcus aureus prior to the initiation of aztreonam or vancomycin on either arm. The MO determined that this prerequisite, maintained not only the blind but also the equal treatment of patients on both arms, thereby avoiding not only bias but the use of alternative effective agents during active therapy as much as possible.

APPEARS THIS WAY ON ORIGINAL

Compliance:

The patients were informed that compliance with taking all tablets and capsules was imperative.

Inpatients received all medications under supervision. Outpatients were instructed to bring used blister packs to V2 and V3. All missed doses and the reasons they were missed were recorded on each patient's medication log.

Microbiologic Methods:

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Criteria for determining susceptibility to the study drugs are summarized below:
(Copied form page 24 of the study report)

Criteria	Trovafloxacin		Ciprofloxacin		Aztreonam	
	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (30 µg Disk)
Susceptible	≤2	≥15	≤2	≥15	≤2	≥21
Intermediate	4		4		4	
Resistant	≥8	≤10	≥8	≤10	≥8	≤13

Note: Trovafloxacin 5 µg disks were never approved for clinical trial use and were subsequently replaced with 10 µg disks. Results using the 10 µg disks were not available during the study report period.

Susceptibility breakpoints for trovafloxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and zone diameter (mm) for ciprofloxacin and aztreonam are based on NCCLS criteria.

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Clinical Response:
(Copied from page 23 of the study report)

Clinical response was determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from the study.

Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical

condition. Subjects were to be assessed for signs and symptoms, as detailed below, and these assessments were recorded on the case report form.

1. Cough, dyspnea, chills/rigors, pleuritic chest pain, and increased sputum volume were each to be assessed at baseline (Day 1) and at every clinic visit thereafter by the investigator and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. In addition, fever and abnormal focal or diffuse lung sounds were to be recorded by the investigator as present or absent at these timepoints.

2. Chest x-ray was to be obtained at baseline (Day 1) and Visit 3 (Day 14) and at any other timepoint deemed necessary by the investigator (e.g., previous x-ray had not cleared). Consecutive chest x-rays were to be evaluated and graded as resolution (disappearance of all radiological signs of infection), marked improvement (significant improvement in the radiological signs of infection compared to baseline), or radiological failure (no significant change in radiological signs of infection compared to baseline or worsening as compared to baseline).

Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia and a need for additional antibiotic).

Medical Officer's Comment: As previously stated, the final determination of clinical response was made by the sponsor. As per the sponsor's representative, Dr. D. Williams, the sponsor never overrode an assessment of failure made by the investigator. In other words, once a failure, always a failure.

Although a severity scoring system was utilized, this system was not additive but rather, each parameter was evaluated separately and the scoring system served as merely as a guide to outcome assessment.

The sponsor applied the TOC to the EOT (V3) visit, but also to the EOS. However, sponsor evaluability was not contingent upon the evaluation of a patient at the final timepoint.

APPEARS THIS WAY ON ORIGINAL

Bacteriologic Response:

(Copied from page 24 of the study report)

Bacteriological response was determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study.

Bacteriologic response was t classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Only "adequate" specimens, as defined in the Protocol and determined by Gram stain, were to be cultured. The absence of "adequate" sputum specimens was to be considered equivalent to a negative culture if the subject was cured or improved.

Sputum samples were first sent to the local laboratory for culture. Isolates were sent to the central laboratory (SciCor) where disk susceptibility and minimum inhibitory concentrations (MIC) for all drugs were determined using standard techniques. Each time an organism was isolated, susceptibility to the study drugs was re-established. Susceptibility to both study drugs was recorded on the subject's case report form for all isolates. Local susceptibility data obtained at some sites were used in the analyses only when a SciCor value was missing for a particular pathogen.

Legionella spp. serology was performed at baseline (Day 1) and at Visit 4 (Day 30).

Medical Officer's Comment: Only the sponsor determined bacteriologic efficacy. This determination was based on culture data as described above. The MO determined that the bacteriologic assessment of the patients was appropriately performed and consistent with the methods utilized in past submissions that have received approval.

Safety Assessments:

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the case report form. Following resolution of the adverse event or at the end of study, the investigator's judgment of causality of the adverse event was recorded.

Serious Adverse Events:

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the Pfizer-appointed project clinician immediately by telephone. All deaths were immediately reported, regardless of elapsed time between the last dose in a clinical trial and death, and thus extended beyond the 30-day post-study timepoint. In the case of death, a summary of available autopsy findings was submitted as soon as possible to the sponsor.

Clinical Laboratory Tests:

Hematology, serum chemistry, and urinalysis determinations were performed at baseline (V1), and at V2 (excluding urinalysis) and V3 (Days 4 and 14, respectively). In addition, blood cultures were obtained at baseline; if positive, or if the subject was discontinued due to clinical failure, they were obtained again at V2 (Day 4) and/or at V3 (Day 14). At V4 (Day 30), hematology, serum chemistry, and urinalysis were only performed if a clinically significant abnormality was present at V3.

Other Safety Parameters

Physical examination was performed at baseline (V1). Concomitant medication use and vital signs (pulse, respiration, blood pressure, and body temperature) were evaluated at V1 and at V2, V3 (EOT), and V4 (EOS).

Data Analysis:

See the introduction to the MOR (page 382) for an overview of the sponsor's subject subsets.

Clinical Evaluability Criteria:

See the introduction to the MOR (page 383) for a review of the sponsor's criteria.

Criteria for Bacteriological Evaluability:

See the introduction to the MOR (page 384), for a review of the sponsor's criteria.

Primary and Secondary Endpoints for Efficacy:

See the introduction to the MOR (page 384) for a review of the sponsor's endpoints and the Reviewer's comments.

Medical Officer's Comment: As noted in the introduction, the primary efficacy variable was clinical response at the EOT, as determined by the sponsor, unless the patient was determined to be a failure by the investigator. The MO agreed with the use of clinical response as the primary efficacy variable and points out that this is in accordance with both the FDA guidance document as well as with IDSA guidelines.