Medical officer review of CAP study 110

1. Per applicant

The synopsis of the applicant's final study report for study 110 is presented below; this is taken from the electronic submission, pages 9-15 of the Final Study Report (found in 8.G.1.A.1 of the NDA, under the 'Clinical Studies Relevant to the Claim Structure' section).

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

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Study Publication: Not Applicable

Study Dates: 19 January 1995 - 30 January 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ciprofloxacin and ampicillin followed by oral ciprofloxacin and amoxicillin in the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-110 was a randomized, multicenter, double-blind trial of alatrofloxacin (200 mg once daily) administered intravenously for 2-7 days followed by oral trovafloxacin (200 mg once a day) to complete 7-10 days of total treatment versus intravenous ciprofloxacin (400 mg twice daily) and ampicillin (500 mg every 6 hours) for 2-7 days followed by oral treatment with ciprofloxacin (500 mg twice daily) and amoxicillin (500 mg three times daily) to complete 7-10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia.

	Evaluation Groups[a]:			
	Alatrofloxacin ↓ Trovafloxacin		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin	
Entered Study[b]	198		202	
All Treated	196	(100%)	200	(100%)
Completed Treatment	147	(75%)	168	(84%)
Completed Study	177	(90%)	180	(90%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	196	(99%)	201	(>99%)
Clinically Evaluable	169	(85%)	181	(90%)
Bacteriological Intent-to-Treat	89	(45%)	94	(47%)
Bacteriologically Evaluable	76	(38%)	88	(44%)
Assessed for Safety				
Adverse Events	196	(100%)	200	(100%)
Laboratory Tests	192	(98%)	197	(99%)

a The daily doses of alatrofloxacin and trovafloxacin were each 200 mg. The daily doses of intravenous and oral ciprofloxacin were 400 mg BID and 500 mg BID, respectively. The daily doses of ampicillin and amoxicillin were each 500 mg, administered every 6 hours (ampicillin) or TID (amoxicillin).

b Subjects who were randomized.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and initial intravenous therapy were eligible to participate in this study.

Drug Administration: Study drug was in the form of intravenous solution (alatrofloxacin, ciprofloxacin, and ampicillin); and trovafloxacin tablets and ciprofloxacin and amoxicillin capsules which were packaged in blister packs, 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 and blood specimens). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, 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, the Cochran-Mantel-Haenszel test controlling for centers was done. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

Efficacy: 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: -8.3, 3.7 and -10.0, 4.0, respectively) and at the end of study (95% CI: -9.8, 5.5 and -8.8, 5.9, 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 tables.

Summary of the Sponsor's Assessment of Clinical Response (Clinically Evaluable Subjects)								
	End of Treatment				End of Study			
	Alatrofloxacin ↓ Trovafloxacin (N=169)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=181)		Alatrofloxacin ↓ Trovafloxacin (N=140)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=165)	
	Number and Percentage (%) of Subjects							
Number of Subjects Assessed	168	(100%)	179	(100%)	140	(100%)	165	(100%)
Success (Cure + improvement)	151	(90%)	165	(92%)	120	(86%)	145	(88%)
Distribution of Clinical Response:								
Cure	75	(45%)	74	(41%)	106	(76%)	130	(79%)
Improvement	76	(45%)	91	(51%)	14	(10%)	15	(9%)
Failure	17	(10%)	14	(8%)	17	(12%)	14	(8%)
Relapse	NA		NA		3	(2%)	6	(4%)
(Clinical Intent-to-Treat Subjects)								
	End of Treatment				End of Study			
	Alatrofloxacin ↓ Trovafloxacin (N=196)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=201)		Alatrofloxacin ↓ Trovafloxacin (N=196)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=201)	
	Number and Percentage (%) of Subjects							
Number of Subjects Assessed[a]	192	(100%)	198	(100%)	196	(100%)	201	(100%)
Success (Cure + improvement)	161	(84%)	172	(87%)	162	(83%)	169	(84%)
Distribution of Clinical Response:								
Cure	81	(42%)	75	(38%)	136	(69%)	144	(72%)
Improvement	80	(42%)	97	(49%)	26	(13%)	25	(12%)
Failure	31	(16%)	26	(13%)	31	(16%)	26	(13%)
Relapse	NA		NA		3	(2%)	6	(3%)

NA = Not Applicable

a Four subjects in the alatrofloxacin/trovafloxacin group and three subjects in the ciprofloxacin/ampicillin/amoxicillin group had missing assessments at the End of Treatment but were assessed at the End of Study.

Ref.: Tables 5.1.1 and 5.1.2

Summary of Sponsor-Defined Pathogen Eradication Rates (Bacteriologically Evaluable Subjects)								
	Alatrofloxacin ↓ Trovafloxacin (N=76)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=88)		Alatrofloxacin ↓ Trovafloxacin (N=64)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=75)	
	Number and Percentage (%) of Pathogens							
Pathogen[a]	End of Treatment				End of Study			
S. pneumoniae	35/39	(90%)	38/39	(97%)	30/33	(91%)	32/34	(94%)
H. influenzae	18/19	(95%)	20/21	(95%)	14/16	(88%)	20/21	(95%)
S. aureus	4/4		6/6		3/3		4/4	
K. pneumoniae	1/1		7/7		1/1		6/6	
C. pneumoniae	2/4		9/9		2/4		9/9	
L. pneumophila	2/2		4/4		2/2		4/4	
M. pneumoniae	8/8		8/9		8/8		7/8	
(Bacteriological Intent-to-Treat Subjects)								
	Alatrofloxacin ↓ Trovafloxacin (N=89)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=94)		Alatrofloxacin ↓ Trovafloxacin (N=89)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=94)	
	Number and Percentage (%) of Pathogens							
Pathogen[a]	End of Treatment				End of Study			
S. pneumoniae	39/46	(85%)	39/40	(98%)	36/41	(88%)	36/38	(95%)
H. influenzae	19/20	(95%)	22/23	(96%)	17/19	(89%)	21/22	(95%)
S. aureus	6/7		6/6		6/6		4/4	
K. pneumoniae	1/2		7/7		1/1		6/6	
C. pneumoniae	3/5		9/9		3/5		9/9	
L. pneumophila	2/2		4/4		2/2		4/4	
M. pneumoniae	8/8		8/9		8/8		8/9	

NA=Not applicable
a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline
Ref.: Tables 5.4.1 and 5.4.2

The subgroup of alatrofloxacin/trovafloxacin subjects with baseline *S. pneumoniae* had a greater proportion of subjects with baseline risk factors for poorer outcome (49% versus 33%) compared to the ciprofloxacin/ampicillin/amoxicillin subjects. Of the alatrofloxacin/trovafloxacin subjects with *S. pneumoniae*, 24% were ≥65 years, 27% were bacteremic, and 13% required high fractional oxygen or mechanical ventilation, versus 14%, 16%, and 5%, respectively, of subjects in the ciprofloxacin/ampicillin/amoxicillin group. This was associated with a numerically higher clinical failure rate (and associated microbiologic presumed persistence) in the alatrofloxacin/trovafloxacin subjects with baseline *S. pneumoniae*. Only a single subject with clinical *S. pneumoniae* failure had a repeat positive culture (with no change in MIC) and this was a subject with several high risk factors for poor outcome.

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

	Alatrofloxacin ↓ Trovafloxacin		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	140/196	(71%)	133/200	(67%)
Treatment-Related Adverse Events	53/196	(27%)	47/200	(24%)
Discontinuations Due to an Adverse Event[a]	26/196	(13%)	19/200	(10%)
Clinically Significant Laboratory Values	101/192	(53%)	108/197	(55%)

a For five subjects in the alatrofloxacin/trovafloxacin group and four subjects in the ciprofloxacin/ampicillin/amoxicillin group, the investigator indicated the study drug discontinuation on the adverse event page on 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

Six (6) subjects in the alatrofloxacin/trovafloxacin group and 14 subjects in the ciprofloxacin/ampicillin/amoxicillin group died during this study, of which two in the alatrofloxacin/trovafloxacin group and 10 in the ciprofloxacin/ampicillin/amoxicillin group occurred in the first 35 days. All deaths were considered by the investigator to be unrelated to study drug. Thirty-six (36) subjects in the alatrofloxacin/trovafloxacin group and 29 subjects in the ciprofloxacin/ampicillin/amoxicillin group had serious adverse events. With the exception of one subject in the alatrofloxacin/trovafloxacin group who had serious adverse events (nausea/vomiting) that were considered by the investigator to be related to study drug, all serious adverse events were attributed to other events or illnesses or to the disease under study.

Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy were statistically equivalent for clinical success rate at the end of treatment and at the end of study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable for the most frequently isolated baseline pathogens (*S. pneumoniae* and *H. influenzae*) between the two treatment groups at the end of treatment and at the end of study.

The percentage of subjects discontinued from treatment due to adverse events was 13% in the alatrofloxacin/trovafloxacin group and 10% in the ciprofloxacin/ampicillin/amoxicillin group. The overall percentage of all and treatment-related adverse events for subjects in the alatrofloxacin/trovafloxacin group was comparable to that of subjects in the ciprofloxacin/ampicillin/amoxicillin group (71% and 27% versus 67% and 24%, respectively). The most commonly reported treatment-related adverse events were headache in the alatrofloxacin/trovafloxacin group and diarrhea and dyspepsia in the ciprofloxacin/ampicillin/amoxicillin group. Injection site reactions were comparable between the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin groups (6% and 8%, respectively). Mortality (Day 1 - 35) was lower in the alatrofloxacin/trovafloxacin group compared to the ciprofloxacin/ampicillin/amoxicillin group (1% and 5%, respectively).

2. Per medical officer

A. Discussion of study design, execution, and analysis

This study was designed to comply with the IDSA Guidelines for the design and conduct of clinical trials which seek the CAP indication. In general, this study would appear to have been designed and conducted in such a manner. The inclusion and exclusion criteria for this study, as outlined by the sponsor, were as follows:

The following characteristics were to have been present:

a) New infiltrate(s) on chest x-ray;

and

b) At least one of the following
   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. Leukocytes (blood leukocyte count >10,000/mm^3 or >15% bands).

Medical officer comments: the IDSA guidelines call for at least TWO of the listed clinical signs or symptoms to be present, along with the presence of a new infiltrate on Chest X-ray.

The statement 'NEW infiltrate' implies the presence of a baseline CXR for each patient entered into the study. Although this would be the optimal situation, I do not believe that subjects should be considered unevaluable if there were not such a baseline film available to the investigator.

Although there is no mention of this issue anywhere in the Final Study Report, the issue of who shall interpret the baseline and follow-up CXRs is clearly delineated in the original study protocol: (section 7.1.2, page 15) "[baseline] Chest X-rays, both PA and lateral, will be obtained and reported by a qualified radiologist"; (section 7.3.2, page 18): "For the assignment of outcomes, all X-rays from a given patient will be read by a qualified radiologist and interpreted with respect to the baseline X-ray." The CRF files that will be audited will be checked for the presence of a radiologist report, at the very least for the baseline CXR used for entry into the study.

It should be noted that the above criteria are identical to those used for the previously reviewed CAP studies, both of which were oral only and designed for the study of outpatients. Although the listed inclusion criteria in section 3.3.1 state "... requiring hospitalization and initial intravenous therapy", this protocol makes no attempt to prospectively objectify differences between the patients enrolled in this study, as compared to those enrolled in the oral only studies. The enrolling investigators presumably had to justify the patient's admission within the context of that hospital's criteria for hospitalization; however, these criteria might vary considerably from hospital to hospital, from locality to locality. In conclusion, it is not readily discernable from this protocol that the patients will be necessarily sicker than the oral only studies.

Sequence of study evaluations:

At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for clinical diagnosis of community acquired pneumonia, as defined above, gave informed consent and met all additional inclusion criteria (see Section 3.3.1), and none of the exclusion criteria (see Section 3.3.2), were eligible for randomization. Baseline visit assessments were to include collection of demographic information, medical history and physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature). Clinical assessment of signs and symptoms of pneumonia were to include sputum characteristics, cough, dyspnea, chills/rigors, pleuritic chest pain, lung sounds, and chest x-ray (PA and lateral views). In addition, a standard panel of blood (including culture) and urine tests were to be performed. Initial serology testing for evidence of infection with *Legionella spp., C. pneumoniae, M. pneumoniae,* and *Chlamydia psittaci* was to be 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 to be 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, ciprofloxacin and ampicillin, was to be 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.

Medical officer comment: ciprofloxacin is approved for the treatment of Lower Respiratory Infections due to several Gram-negative organisms, as well as those due to Streptococcus pneumoniae. *Because this agent is not considered optimal therapy for Gram positive and/or anaerobic respiratory pathogens, I agree with the decision to add ampicillin → amoxicillin to the comparator regimen. However, it should be noted that this regimen does not provide what would be considered optimal therapy for atypical pathogens, and ciprofloxacin is not labeled for treatment of such infections. For more aged subjects, particularly if the setting is nosocomial or nursing home-related pneumonia, atypical agents are low on the list of potential etiologies and a fluroquinolone + ampicillin regimen is appropriate. However, since this protocol allows for entry of anyone age 18 or above, and with pneumonia originating in the 'community', I would have questioned the use of such a comparator regimen for this study had I been involved with this drug's early development program. It is acknowledged, however, that the sponsor asserts in Appendix 4 to the cover letter of NDA 20-759:*

At Visit 2 (Day 4), a subject's need for continued intravenous therapy was to be assessed daily from Study Day 3 to 7. Subjects were to be 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.

At Visit 2 (Day 4) efficacy observations were to be performed including all clinical assessments of signs and symptoms of pneumonia to assess response to study therapy; bacteriologic response was to be assessed through sputum samples. Blood cultures were to be 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 (Day 11; end of treatment) efficacy observations were to be performed including all clinical assessments of signs and symptoms of pneumonia to assess response to study therapy; bacteriologic response was to be assessed through sputum samples. Blood cultures were to be repeated only if they had been positive at the previous visit; a chest x-ray was also to be performed. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory (hematology, biochemistry, and urinalysis) evaluations. The investigator was to provide an evaluation of clinical response.

At Visit 4 (Day 30; end of study), efficacy observations were to be performed including all clinical assessments of signs and symptoms of pneumonia to assess response to study therapy; bacteriologic response was to be assessed through sputum samples. Blood cultures were to be repeated only if they had been positive at the previous visit. If the Visit 3 chest x-ray had not resolved to the subject's baseline, a final x-ray was to be done at Visit 4. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, and adverse events. Laboratory evaluations were only to be performed if a clinically significant abnormality was present as Visit 3 (Day 11) or if the subject was experiencing a clinically significant adverse event. A final serology was to be performed and the investigator was to provide a final evaluation of clinical response.

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

Administration of study drug:

Study drug for intravenous administration was prepared using a double-dummy technique to maintain blinding. Intravenous alatrofloxacin or matching placebo for intravenous administration was provided in vials of 5 mg/mL (100 mg/20 mL) to be

diluted to 1 mg/mL with 5% dextrose (D5W). Intravenous ciprofloxacin or matching placebo was provided in vials of 10 mg/mL (200 mg/20 mL) to be diluted to 2 mg/mL (total 400 mg/200 mL) with D5W. Intravenous ampicillin was provided in vials of 500 mg ampicillin powder to be reconstituted in 50 mL of normal saline solution. Subjects assigned to alatrofloxacin/trovafloxacin group had a pharmacy blinded ampicillin placebo prepared containing 50 mL normal saline. Subjects received one of the following intravenous treatment regimens:

> Alatrofloxacin 200 mg in 200 mL of D5W once daily (2 x 100 mg vials) and 50 mL normal saline every 6 hours (ampicillin placebo).
> Ciprofloxacin 400 mg in 200 mL of D5W twice daily and ampicillin 500 mg in 50 mL normal saline solution every 6 hours.

Medical officer comment: During the conduct of this study, a total of 22 patients were treated with an inappropriately low dose of intravenous study drug. This situation is detailed in the following excerpt from the Final Study Report:

> Study drug administration deviations included 22 subjects who received only one vial of IV quinolone (100 mg of alatrofloxacin or 200 mg of ciprofloxacin) instead of two vials as specified in the protocol; these subjects received the correct doses of study drug during the oral dosing period and the ciprofloxacin subjects received the correct dose of IV ampicillin. The sponsor did not exclude these subjects from the classification of clinical evaluability because of this deviation in study drug administration as almost all of these subjects had a successful clinical response; see Section 8.3.1 for further discussion.

The medical officer agrees that it is not necessary to exclude these subjects from analysis. This type of dosing error was not particular to a single study center, but was distributed over a number of sites. It would therefore appear to have been something other than a systematic error that would have argued more strongly for exclusion of the subjects enrolled from that center.

All subjects were to receive intravenous study medication every 6 hours in combinations of active drug and placebos for active drug.
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. Study drug for oral administration was in the form of tablets and 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 tablet)
>
> Ciprofloxacin 1000 mg/day in two equally divided doses (2 x 250 mg capsule per dose) and amoxicillin 1500 mg/day in three equally divided doses (3 x 250 mg capsule)

All subjects were to receive oral study medication in the morning, afternoon and evening in combinations of active drug and placebos for active drug.
Subjects with more severe pneumonias at baseline (respiratory compromise or bacteremia) may have received up to a total of 14 days of combined IV and oral therapy.

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 comment: during this oral therapy phase of the study, subjects were taking a total of 12 tablets/capsules per day. One can only speculate on whether this formidable number of pills might have had a negative impact on patient compliance.

Data analysis:

All Randomized Subjects

The all randomized subjects subset included all subjects who were randomized 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 active double-blind study medication. This subset was used for all safety tables.

Clinical Intent-to-Treat Subjects

The clinical intent-to-treat subjects subset included those subjects in the all randomized subjects subset who had a baseline diagnosis of the disease or condition under investigation determined by protocol specific inclusion criteria (subject had a medical history and clinical radiological findings consistent with community-acquired bronchopneumonia or lobar pneumonia of severity that required hospitalization and initial intravenous therapy; including a new infiltrate on chest x-ray and at least one of the following signs or symptoms: cough or increasing severity of cough, 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, auscultatory findings such as rales or evidence of pulmonary consolidation, and/or leukocytosis [blood leukocyte count >10,000/mm^3 or >15% bands]). Some subjects in this subset may never have received any study medication. Subjects found to have tuberculosis or pneumocystis pneumonia were excluded from the clinical intent-to-treat subset.

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 (See Section 4.2).

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 with at least one pathogen identified at baseline by culture or appropriate serology, unless one or more of the criteria for non-evaluability applied (see Section 4.3).

Criteria for Clinical Evaluability

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

1. Insufficient Therapy: A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement (≥5 days) was not evaluable.

Medical officer comment: The IDSA guidelines for Infectious Pneumonia state that "inability to complete the study because of adverse effects" should be considered a reason for declaring a subject to be a clinical failure. This fundamental point is a major item of difference between the sponsor's analysis of the study results and those suggested by the IDSA guidelines.

2. Prior Antibiotic Usage: A subject was not evaluable if the subject had been treated with any systemic antibiotic for 24 hours or longer within 72 hours prior to enrollment without documented evidence of resistance or the subject was a clinical failure and had a culture positive baseline pathogen in the evaluable baseline window.

3. Concomitant Antibiotics Given for Intercurrent Illness: A subject who was prescribed a concomitant antibiotic (at any time before the End of Treatment assessment) that was potentially effective against the condition under study was not evaluable if the concomitant antibiotic was given for an adverse event or intercurrent illness. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the clinically evaluable subjects subset. For the purpose of subject evaluability, prior antibiotic use that ended on Day 1 was not considered to be concomitant.

Medical officer comment: this aspect of the study analysis is subject to considerable bias. How does one distinguish between an intercurrent infectious illness and study drug failure? Does it matter whether the 'intercurrent infection' is a process for which the sponsor also seeks approval in the trovafloxacin label? For example: subjects 5135-0172, 5224-0282, 5430-0371, and 5501-0236 were all placed on additional antimicrobials following completion of trovafloxacin therapy, all for reasons described as "exacerbation of chronic obstructive pulmonary disease" or "acute bronchitis". In a study of community acquired pneumonia, such 'intercurrent illnesses' are difficult to distinguish from a clinical failure of the study drug to successfully treat the originally diagnosed pneumonia. The rationale behind such subject outcomes will be carefully scrutinized.

4. Intercurrent Illness: A subject who developed an intercurrent illness whose clinical course confounded the clinical evaluation of the disease or condition under investigation was not evaluable. The Pfizer Clinical Group determined intercurrent illnesses that caused a subject to be not evaluable for this reason.

5. No Post-Baseline Clinical Assessments: A subject with no post-baseline investigator clinical assessments was not evaluable unless given an antibiotic for insufficient response any time during study, up to and including the last day of the End of Study analysis window.

6. No Post-Baseline Assessment in the Evaluable Analysis Window: In order to be evaluable a subject must have had an assessment in at least one evaluable timepoint window, unless

    - the investigator's clinical response was a failure before the beginning of the End of Treatment window (Days 5-20), or

- the subject was given an antibiotic for insufficient response at any time during study, up to and including the last day of the End of Study analysis window (Days 21-40).

A subject was included in the analysis at the End of Study assessment if either the subject was:

- clinically evaluable for the End of Treatment visit, and
- was not given any antibiotics for intercurrent illness before the assessment at the End of Study visit, and
- had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study, up to and including the last day of the End of Study analysis window,

or the subject was:

- clinically evaluable for the End of Treatment visit, and
- the sponsor-defined clinical response was failure or relapse (Section 4.5).

Criteria for Bacteriological Evaluability

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

1. No Baseline Pathogen: No baseline causative pathogen was isolated.

2. Baseline Culture Outside Baseline Visit Window: The baseline culture was done more than 2 calendar days before the first dose of double-blind study medication.

3. No Post-Baseline Cultures: Post-baseline cultures were not obtained, except in the instance of no suitable culture material due to clinical cure or improvement based on the investigator-defined clinical response, in either the evaluable End of Treatment or End of Study analysis windows unless:

   - subject was given an antibiotic for insufficient response, at any time up to and including the last day of the evaluable End of Study analysis window, 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.

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 study, up to and including the last day of the End of Study analysis window.

Subjects 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.

Primary and Secondary Endpoints for Efficacy

Primary efficacy endpoints were:

- Sponsor-defined subject clinical response at the End of Treatment visit and;
- 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 comment: the end of study endpoint will be considered to be of primary importance. The Divisional Draft Evaluability Criteria state that "a test-of-cure evaluation... should be at least 7 days or 5 half-lives of the agent, whichever is the longer period, following completion of therapy." Admittedly, this document was not available to the sponsor at the time this protocol was submitted to the IND and, subsequently, implemented. It should nonetheless be intrinsically obvious that one cannot accurately assess the clinical and bacteriologic outcome of a course of therapy until all traces of the administered antimicrobial have been eliminated from the patient, and any residual infectious agent(s), if present, are permitted some time period to make their continued presence clinically manifest.

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 occurrence of any of the following conditions were to supersede the investigator's assessment.

1. 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.

2. Failure: If a subject was given a concomitant antibiotic for insufficient clinical response during double-blind therapy plus one day then the Sponsor Defined Subject Clinical Response was a failure at the End of Treatment and all subsequent assessments. If a subject was given a concomitant antibiotic for insufficient clinical response at any time before the assessment plus one day, the Sponsor Clinical Response was failure at that assessment and all subsequent assessments. If a subject did not have an assessment in a particular window and was given an antibiotic for insufficient response in that assessment window then the Sponsor Defined Clinical Response was a failure at that timepoint and all subsequent assessments.

3. 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 (Intent-to-Treat Analysis only).

4. 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 an 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 clinical intent-to-treat subject subset, a 'last observation carried forward' strategy was used for subjects who were 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 was treated as missing data.
Confidence intervals (95%) for differences in clinical success (cure + improvement) between treatments were calculated as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.
The definition of equivalence, as suggested by some regulatory agencies, is that the 95% confidence interval for the difference in response rates is within 10% when the true satisfactory response rate of the reference drug is 90% or better. Assuming the clinical response rate of the reference drug is 90%, the number of subjects for each treatment group required to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy does not exceed 10% is 142 subjects per treatment group.

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 within the End of Treatment analysis window, the last outcome assigned to each baseline pathogen was used. If multiple visits occurred within the End of Study window, the worst case outcome was used. Selection of worst case outcome followed the order: Persistence or Relapse, Presumed Persistence, Presumptive Eradication, Eradication.

1. Eradication: Baseline pathogen was 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. If the subject was lost to follow-up, the eradication was carried to subsequent implied visits.

2. Presumptive Eradication: No culture was obtained (either not done, or absence of adequate culturable material), and sponsor-defined subject clinical response was cured or improved.

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. If the subject was lost to follow-up, persistence was carried to subsequent implied visits.

4. Presumed Persistence:

   - Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day as, 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 then the presumed persistence was carried to subsequent implied visits. Absence of microbiological data was defined as 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 presumed persistence if the organism 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.

In addition, organisms not present at baseline were classified as follows:

1. Superinfection: A pathogen, other than one identified at baseline, that was 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 necessitating antibiotic therapy.

2. Colonization: Any organism, other than one identified at baseline, that was 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 infection necessitating antibiotic therapy.

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

- Presumed Persistence. A serologically defined atypical pathogen, and sponsor-defined subject clinical response was failure.
- Presumed Eradication. A serologically defined atypical pathogen (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella)*, and the sponsor-defined subject clinical response was cure or improvement.

Confidence intervals (95%) for differences in pathogen eradication rates between treatments were calculated. The Cochran-Mantel-Haenszel test controlling for centers was also done.

B. Medical officer comments on sponsor's analysis of study, and random audit of CRFs

This study was conducted in three countries: US, Canada, and South Africa. The great majority of study sites enlisted were in the US (N=52) compared to Canada and South Africa (4 each). In terms of enrolling study sites, 36 were in the US, 2 in Canada, and 4 in South Africa. Randomized subjects were predominantly American: there were 338 Americans, 53 South Africans, and 9 Canadians randomized into this study.

The following table presents the names and locations of the ten leading centers that enrolled subjects into this study:

Investigator	ID#	location	N	# subinvestigators	subjects per investigator
Dowell	5501	WY	39	1	19.5
Dekock	5992	S. Africa	28	4	5.6
Bittner	5224	NE	26	12	2.0
Grossman	5231	SC	25	2	8.3
Baird	5222	OH	23	0	23.0
Plouffe	5239	OH	18	0	18.0
Honsinger	5556	NM	16	3	4.0
Mandell	5430	Canada	14	1	7.0
Weiss	5462	FL	13	5	2.1
Dunbar	5500	LA	12	3	3.0
Kilian	5629	S. Africa	12	1	6.0
Ho	5233	TX	12	4	2.4

The geographic distribution of the enrollees appears to be adequate. With the exception of two single investigators in Ohio and one investigator in Wyoming who listed one co-investigator, the number of enrollees per investigator appears to be lower than most of the investigators listed in study 112.

CRF and Patient Profile audit

A random listing of 10% of the PIDs from study 110 was generated by the reviewing statistician. These 40 CRFs were carefully compared with the data as presented in the sponsor-generated Patient Profiles, to verify the authenticity of the data from which the sponsor's data tables were generated.

Ciprofloxacin + ampicillin/amoxicillin patients

PID	Investigator	Location	OK?	Comments
51350430	Nelson	MO	✓	
52220186	Baird	OH	✓	
52280333	Farrukh	UT	✓	
52330469	Ho	TX	✓	
52350067	Jauregui	OH	✓	
52390138	Plouffe	OH	✓	
52390299	"—"		✓	
52390442	"—"		✓	
52470215	Sherman	PA	✓	
54240166	Brown	CA	✓	*Patient profile lists investigator EOT assessment as "Not Assessable", but CRF shows it to be "Cure". Appropriately called "Failure" by sponsor at both EOT and EOS.*
54270144	Gammon	AL	✓	
55010330	Dowell	WY	✓	
55050232	Reinoso	TX	✓	
55560037	Honsinger	NM	✓	*Diagnosis of* Chlamydia pneumoniae *byfour-fold rise in serum IgA titer.*
55560040	"—"		✓	
59910386	Schleicher	S.Africa	✓	*Called clinical cure after 6 days of therapy, and thus Rx stopped. Had appropriate length of f/u (to day 31), no additional antibiotics, thus I do not* (b)(4) *LFTs may have played a role in clinical decision to stop therapy at day 6.*
59920391	Dekock	S.Africa	✓	

Alatrofloxacin → trovafloxacin patients

PID	Investigator	Location	OK?	Comments
51350362	Nelson	MO	✓	*Called 'cure' but given Bactrim for days 33-42 for 'COPD Exacerbation'. Culture day 33 shows* H. influenzae. *See comments pages 26-7, below.*
51350364	"—"		✓	
51890353	Geckler	MD	✓	
52220188	Baird	OH	✓	*No micro specimen sent to reference lab.*
52220347	"—"		✓	
52340342	Jackson	WA	✓	
52390297	Plouffe	OH	✓	*Got 8 days of therapy; no explanation given.*
52390300	"—"		✓	
52400189	Renston	OH	✓	*Dizziness reported at day 5; was actually day 2 of oral trovafloxacin. May coincide with increased ambulation post-removal of IV.*
52400190	"—"		✓	
52430106	Rumans	KS	✓	
52430108	"—"		✓	*Patient had serum creatinine rise No mention of this as AE by investigator.*
52470216	Sherman	PA	✓	
54710275	Occhipinti	GA	✓	
55000126	Dunbar	LA	✓	
55010236	Dowell	WY	✓	*Given antibiotics day 17-29 for 'other infection' (acute bronchitis); called cure by investigator, not assessable by sponsor at EOS eval day 28. See discussion on pages 26-7, below.*
55010329	"—"		✓	
55050305	Reinoso	TX	✓	*Multiple crossouts/corrections!!*
59910398	Schleichter	S. Africa	✓	
59920407	De Kock	S. Africa	✓	
59920501	"—"		✓	
59920502	"—"		✓	
59930498	Beale	S. Africa	✓	

General comments:

1. No radiology reports were included in the CRFs for any patient in this study. When queried about this in reference to study 134, the sponsor was able to produce the baseline chest x-ray interpretations for all requested patients. It was not felt to be necessary to repeat this request for the patients in this study as well. The protocol for this study also stated, "For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and interpreted with respect to the baseline X-ray." Thus it remains unclear to this medical officer why such reports were not felt to be important elements of the data collected on each enrolled patient (and therefore worthy of inclusion in the CRF, along with Gram stain and culture reports).

2. As with the other CAP studies audited, the lab results for each patient never included a percentage reading for the WBC differential, even though >15% bands was included in the entry criteria for the study.

3. The diagnosis of pneumonia due to the 'atypical' agents is appropriately made via serology, as was performed in this study. However, a number of subjects (4 ciprofloxacin and 2 trovafloxacin) were diagnosed with Chlamydia pneumoniae pneumonia on the basis of a ≥ four-fold rise in serum IgA titers.

Trovafloxacin patients:

PID	acute/convalescent	IgG	IgM	IgA
52240357	acute			
	convalescent			
55340447	acute			
	convalescent			

Ciprofloxacin patients:

PID	acute/convalescent	IgG	IgM	IgA
52240319	acute			
	convalescent			
55010225	acute			
	convalescent			
55560037	acute			
	convalescent			
55560118	acute			
	convalescent			

* these values appear in table 5.3a of the Final Study Report; however, there are no laboratory reports in the CRF for this patient to document these results, so that the IgM and IgG results are not found.

There is no mention of the utility of an isolated rise in serum IgA in the diagnosis of Chlamydia pneumoniae infection in the most current edition of Mandell's Principles and Practice of Infectious Diseases. In a reference called Use and Interpretation of Tests in Medical Microbiology by J.B. Peter, MD, the author states: "The best evidence of an acute C. pneumoniae infection is a fourfold or greater rise in antibody titers between acute and convalescent serum samples, and the presence of C.pneumoniae - specific IgM by microimmunoflourescence of ≥ 1:16. A single C.pneumoniae - specific IgG titer of ≥ 1:512 or a single C.pneumoniae - specific IgM titer of ≥ 1:16 is suggestive of acute infection."

From this definition, then, both of the trovafloxacin subjects have serologies that are suggestive but not diagnostic of acute C. pneumoniae pneumonia. Neither text referenced above mention the utility of a serum IgA titer in the diagnosis of this disease. Thus it can be concluded that patients so diagnosed in this and the other CAP studies should be eliminated from consideration when tallying numbers of subjects with specific pathogens, for the purpose of product labeling.

4. Use of concomitant and/or follow-up antibiotics for 'concomitant infections'.

The following table, taken from the sponsor's Final Study Report for study 110, details all subjects for whom the sponsor altered clinical responses from those that had been provided by the individual investigators:

Table A. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Treatment			
5231-0201	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5231-0202	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 3)
5231-0290	Improvement	Failure	Concomitant antibiotic due to inadequate response (empyema ([pneumonia failure]) (Day 6)
5231-0311	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 5)
5248-0257	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 6)
5466-0113	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5992-0390	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 6)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

TABLE F Continued on Next Page

Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Study			
5046-0328	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 7)
5135-0172	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for chronic obstructive pulmonary disease (Day 18)
5222-0185	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for surgical prophylaxis (Day 27)
5222-0346	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics (Day 6); subject discontinued treatment early due to adverse events
5222-0487	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics (Day 7); subject discontinued treatment early due to adverse events
5224-0282	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for chronic obstructive pulmonary disease - (Day 14)
5224-0360	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic lung disease (Day 18)
5228-0072	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 7)
5231-0160	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics (Day 15)
5231-0201	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5231-0202	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 3)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

TABLE F Continued on Next Page

Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Study			
5231-0290	Cure	Failure	Concomitant antibiotic for empyema (Day 6)
5231-0291	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for meningitis[a] (Day 16)
5231-0311	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 5)
5235-0068	Cure	Failure	Concomitant antibiotic for concern of septic shock (Day 4)
5235-0198	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for sinus infection (Day 27)
5243-0477	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for persistent pleural effusion (Day 14)
5245-0049	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for bronchitis (Day 28)
5247-0213	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for sore throat (Day 13)
5248-0257	Not Assessed	Failure	Concomitant antibiotic due to inadequate response (Day 6)
5425-0087	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for prophylaxis secondary to bronchial obstruction (Day 15)

a When meningitis was diagnosed, this subject, who had no baseline pathogen, had a full workup and bacterial meningitis was excluded.

Ref: Appendix I, Table 2.4 and Appendix V, Table 16

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Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Study			
5430-0371	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic obstructive pulmonary disease (Day 31)
5466-0113	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5471-0273	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 8)
5501-0236	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for acute bronchitis (Day 17)
5992-0382	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 6)
5992-0390	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 6)
Ciprofloxacin/Ampicillin → Ciprofloxacin/Amoxicillin: End of Treatment			
5239-0138	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 7)
5239-0298	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 9)
5250-0129	Not Assessed	Failure	Concomitant antibiotic due to worsening of pneumonia (Day 1)
5424-0166	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 3)
5501-0226	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 8)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

TABLE F Continued on Next Page

Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Ciprofloxacin/Ampicillin → Ciprofloxacin/Amoxicillin: End of Study			
5135-0361	Cure	Failure	Failure (Day 7) carried forward
5222-0187	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for prophylaxis of urinary tract infections (Day 10)
5224-0183	Not Assessed	Relapse	Concomitant antibiotics due to inadequate response (Day 24)
5224-0281	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic obstructive pulmonary disease (Day 28)
5228-0333	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for *S. viridans* bacteremia (Day 16)
5233-0156	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 4)
5233-0469	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic obstructive pulmonary disease (Day 16)
5234-0089	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for *E. coli* sepsis (Day 29)
5239-0138	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 7)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

TABLE F Continued on Next Page

Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Ciprofloxacin/Ampicillin → Ciprofloxacin/Amoxicillin: End of Study			
5239-0298	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 9)
5239-0442	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 8)
5248-0164	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for abdominal abscess (Day 25)
5250-0129	Not Assessed	Failure	Concomitant antibiotics due to worsening of pneumonia (Day 1)
5424-0166	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 3)
5466-0521	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 6)
5471-0274	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for a virus (Day 21)
5501-0205	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for unrelated upper respiratory tract acute infection (Day 17)
5501-0226	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 8)
5505-0229	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 17)
5992-0403	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for otitis media (Day 18)
5992-0424	Improvement	Failure	Failure (Day 11) carried forward
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

To summarize the 'directionality' of these changes, the following table was compiled by the medical officer:

Sponsor overrides at End of Study evaluation timepoint, Study 154-110, as enumerated in Table F of sponsor's Final Study Report

Investigator's interpretation	Sponsor's interpretation	Trovan (N = 27)	Cipro (N = 21)
Cure	Fail	7	4
Improved	Fail	4	1
Not assessed	Fail	1	6
Cure	Not assessed	10	6
Improved	Not assessed	5	3
Not assessed	Relapse	0	1

It would appear from this analysis that the sponsor has not biased these changes in a manner that is advantageous to trovafloxacin. There are no overrides that confirmed a better outcome than that assigned by the investigator. The only category in the above table that is of note is that which changed an investigator's 'not assessed' to 'fail'; there were 6 of these in the ciprofloxacin arm versus only one in the trovafloxacin arm. Review of each of these cases found the change to be appropriate; the investigator had deemed a patient not assessable because of the addition of concomitant antimicrobials due to 'inadequate response to study medication'.

The determination of what, in fact, constitutes an 'inadequate response' of the underlying disease being treated (in this case being community-acquired pneumonia) to the study drug, as opposed to the onset of a concomitant but 'unrelated' infectious illness, is a potential source of considerable bias. For example, here is a partial list of reasons provided by the investigator for the administration of concomitant antimicrobials during or following adminstration of study drug (this listing is only of those subjects who were rendered 'not assessable' by the sponsor):

'Cure' or 'Improvement' per investigator to 'Not Assessable' changes by sponsor Study 154-110

	Trovafloxacin (N=15)	Ciprofloxacin (N=9)
concomitant antibiotics for other respiratory infectious processes:		
COPD exacerbation	4	2
bronchitis/upper resp. infection	2	1
otitis media	0	1
sinus infection	1	0
sore throat	1	0
persistent pleural effusion	1	0
prophylaxis:		
pre-surgical	1	0
bronchial obstruction	1	0
abdominal abscess	0	1
urinary tract infection	0	1
meningitis	1	0
bacteremia/sepsis	0	2
"a virus"	0	1
no reason specified	1	0
Study drug discontinued due to adverse event	2	0

Determining what constitutes a failure to treat the underlying pneumonia, as opposed to what constitutes an episode of bronchitis or 'exacerbation of COPD', is very difficult clinically. In such instances, the adequacy of the blind of the study becomes paramount. In general, the above numbers do not appear to indicate any sort of systematic bias on the part of the sponsor.

The two trovafloxacin discontinuations due to adverse events were on days 6 and 7 of therapy. The first, PID 52220346, had pruritus that was considered 'not study drug related' yet was switched to cephalexin on day 6, and followed up to day 31 of study. The second, PID 52220487, developed oropharyngeal thrush on therapy which resulted in the discontinuation of trovafloxacin and initiation of clarithromycin. Since both of these subjects received more than 5 days of study drug, they should be clinically evaluable and thus one could argue both should be clinical failures of trovafloxacin therapy. After all, trovafloxacin patient PID 59910386 was considered a 'cure' by the sponsor after having received only 6 days of therapy (see medical officer audit, page 17 of review).

These two cases lead to the question of how drug discontinuations due to adverse events should be handled in the assessment of outcomes. The IDSA guidelines call for "inability to complete the study because of adverse effects" to be one of the definitions of clinical failure. The sponsor has opted to ignore this aspect of the IDSA guidelines, along which all studies for this indication are ostensibly designed and executed.

Medical officer conclusions regarding efficacy results, study 110:

1. The overall design and conduct of this study was acceptable. There did not appear to be any systematic errors or biases in the interpretation of results that were unacceptable to the medical officer. The issues discussed in the above 'General Comments' do not invalidate the results of this study. The double-blind design of this study minimalizes the effect of some of the sources of bias discussed above.
2. The results of this study support the sponsor's assertion that trovafloxacin, given intravenously followed by orally, is as efficacious as ciprofloxacin (IV→ PO) plus amoxicillin/ampicillin in the treatment of CAP. At the EOS clinically evaluable assessment, the cure rates for trovafloxacin and ciprofloxacin were 106/140 (76%) and 130/165 (79%), respectively.
3. The number of subjects withdrawn during treatment, for any cause, was considerably higher in the trovafloxacin arm of this study (49/196 or 25%) than in the comparator arm (32/200 or 16%). Of those 49 withdrawn trovafloxacin patients, 23 were felt to be study drug related, and 13 of those were adverse events. Total number of patients having adverse events leading to study drug discontinuation (regardless of causality) were 21/196 (11%) in the trovafloxacin arm and 15/200 (8%) in the ciprofloxacin/ampicillin arm.
4. The use of change in serum IgA titers led to the diagnosis of *Chlamydia pneumoniae* pneumonia in two trovafloxacin-treated subjects in this study; these diagnoses will be discounted when tabulating total number of such subjects for the purposes of organism-specific labeling.

Medical Officer Review of CAP study 154-111

1. Per Applicant

The synopsis of the applicant's final study report for study 111 is presented below, as excerpted from the electronic version of the NDA (section 2.H.2):

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN (CP-116,517) FOLLOWED BY ORAL TROVAFLOXACIN (CP-99,219) WITH INTRAVENOUS CEFTRIAXONE FOLLOWED BY ORAL CEFPODOXIME WITH OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Principal Investigators:

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Daniel Kett, MD	Daniel Musher, MD	Ronald Fergusson, MD
Edward Britt, MD	Rodney Wishnow, MD	Iain Gould, MD/ C. Christopher Smith, MD
Frank Byrne, MD/ Brian Zehr, MD	Gregory Kane, MD	Andrew Greening, MD
Timothy Kotschwar, PharmD	Phillip Masters, MD	Robert Masterton, MD
Ralph Steele, MD	Martin Tauber, MD	Robert Monie, MD
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Susan Pingleton, MD	Howard Koffler, MD	Robin Macmillan, MD
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David Grossman, MD	Eric Fournier, MD	Bruce Hall, MD
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James Taylor, MD	Antoni Torres Marti, MD	Franz Daschner, MD
David Wisinger, MD	Ramon Estruch, MD	Raul Marques, MD

Study Publication: Not Applicable
Study Dates: 8 February 1995 - 22 March 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ceftriaxone followed by oral cefpodoxime, with optional erythromycin, for the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-111 was a randomized, multicenter, double-blind, double-dummy trial of alatrofloxacin administered intravenously for 2 to 7 days followed by oral trovafloxacin to complete 7 to 10 days of total treatment versus intravenous ceftriaxone for 2 to 7 days followed by oral cefpodoxime to complete 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

	Evaluation Groups[a]:			
	Alatrofloxacin ↓ Trovafloxacin		Ceftriaxone ↓ Cefpodoxime	
Entered Study[b]	218		225	
All Treated	215	(100%)	222	(100%)
Completed Treatment	170	(79%)	172	(77%)
Completed Study	182	(85%)	183	(82%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	212	(97%)	221	(98%)
Clinically Evaluable	180	(83%)	187	(83%)
Bacteriologically Intent-to-Treat	92	(42%)	102	(45%)
Bacteriologically Evaluable	80	(37%)	85	(38%)
Assessed for Safety	215	(100%)	222	(100%)
Adverse Events	203	(94%)	205	(92%)
Laboratory Tests				

a The daily doses of alatrofloxacin and trovafloxacin were each 200 mg. The daily dose of ceftriaxone was 1000 mg and the daily dose of cefpodoxime was 400 mg (200 mg administered twice daily).

b Subjects who were randomized.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and initial intravenous therapy were eligible to participate in this study.

Drug Administration: Study drug was in the form of intravenous solution (alatrofloxacin and ceftriaxone); trovafloxacin tablets and cefpodoxime capsules, which was packaged in blister packs, 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 and blood specimens). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, 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, the Cochran-Mantel-Haenszel test controlling for centers was done. 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: -3.6, 9.5 and -6.5, 8.1, respectively) and at the end of study (95% CI: -4.1, 11.9 and -5.2, 10.0, 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 tables.

Summary of the Sponsor's Assessment of Clinical Response (Clinically Evaluable Subjects)								
	End of Treatment				End of Study			
	Alatrofloxacin ↓ Trovafloxacin (N=180)		Ceftriaxone ↓ Cefpodoxime (N=187)		Alatrofloxacin ↓ Trovafloxacin (N=159)		Ceftriaxone ↓ Cefpodoxime (N=169)	
	Number and Percentage (%) of Subjects							
Number of Subjects Assessed	178	(100%)	184	(100%)	159	(100%)	169	(100%)
Success (Cure + improvement)	160	(90%)	160	(87%)	136	(86%)	138	(82%)
Distribution of Clinical Response:								
Cure	102	(57%)	108	(59%)	128	(81%)	128	(76%)
Improvement	58	(33%)	52	(28%)	8	(5%)	10	(6%)
Failure	18	(10%)	24	(13%)	19	(12%)	25	(15%)
Relapse	NA		NA		4	(3%)	6	(4%)
(Clinically Intent-to-Treat Subjects)								
	End of Treatment				End of Study			
	Alatrofloxacin ↓ Trovafloxacin (N=212)		Ceftriaxone ↓ Cefpodoxime (N=221)		Alatrofloxacin ↓ Trovafloxacin (N=212)		Ceftriaxone ↓ Cefpodoxime (N=221)	
	Number and Percentage (%) of Subjects							
Number of Subjects Assessed[a]	207	(100%)	214	(100%)	212	(100%)	221	(100%)
Success (Cure + improvement)	171	(83%)	175	(82%)	171	(81%)	173	(78%)
Distribution of Clinical Response:								
Cure	109	(53%)	115	(54%)	158	(75%)	153	(69%)
Improvement	62	(30%)	60	(28%)	13	(6%)	20	(9%)
Failure	36	(17%)	39	(18%)	37	(17%)	41	(19%)
Relapse	NA		NA		4	(2%)	7	(3%)

NA = Not Applicable

a Five subjects in the alatrofloxacin/trovafloxacin group and seven subjects in the ceftriaxone/cefpodoxime group had missing assessments at the End of Treatment but were assessed at the End of Study.

Ref.: Tables 5.1.1 and 5.1.2

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

	Alatrofloxacin ↓ Trovafloxacin (N=80)		Ceftriaxone ↓ Cefpodoxime (N=85)		Alatrofloxacin ↓ Trovafloxacin (N=68)		Ceftriaxone ↓ Cefpodoxime (N=79)	
	Number and Percentage (%) of Pathogens							
	End of Treatment				End of Study			
Pathogen[b]								
S. pneumoniae	28/31	(90%)	22/23	(96%)	25/27	(93%)	19/20	(95%)
H. influenzae	16/16	(100%)	23/26	(88%)	13/15	(87%)	22/24	(92%)
S. aureus	4/4		7/8		3/3		6/7	
M. catarrhalis	5/5		3/3		3/3		3/3	
P. aeruginosa	5/5		1/2		2/2		0/2	
C. pneumoniae	4/4		9/9		2/2		7/8	
L. pneumophila	8/11		8/10		7/10		8/10	
M. pneumoniae	12/12		5/6		9/10		4/6	

(Bacteriologically Intent-to-Treat Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=92)		Ceftriaxone ↓ Cefpodoxime (N=102)		Alatrofloxacin ↓ Trovafloxacin (N=92)		Ceftriaxone ↓ Cefpodoxime (N=102)	
	Number and Percentage (%) of Pathogens							
	End of Treatment				End of Study			
Pathogen[b]								
S. pneumoniae	31/37	(84%)	24/25	(96%)	29/34	(85%)	21/22	(95%)
H. influenzae	18/19	(95%)	23/26	(88%)	15/17	(88%)	23/25	(92%)
S. aureus	5/5		8/9		3/3		7/8	
E. coli	4/5		4/6		3/3		3/5	
M. catarrhalis	5/5		3/3		5/5		3/3	
P. aeruginosa	5/5		1/2		6/6		0/2	
C. pneumoniae	4/4		9/9		4/4		8/9	
L. pneumophila	8/11		9/11		8/11		9/11	
M. pneumoniae	12/12		6/7		11/12		5/7	

NA=Not applicable
a Eradication rates = number of eradicated + presumed eradicated pathogens / number of pathogens.
b Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline. Non-eradicated pathogens were either persistent (confirmed microbiologically) or presumed persistent. For bacteriologically ITT, pathogens for subjects lost to follow-up were considered persistent.
Ref.: Tables 5.4.1 and 5.4.2

No subject in the alatrofloxacin/trovafloxacin group with a clinical outcome of failure had a microbiologically confirmed persistent pathogen.

Of the 11 subjects in the alatrofloxacin/trovafloxacin group and 20 subjects in the ceftriaxone/cefpodoxime group who died during this study, three subjects in the alatrofloxacin/trovafloxacin group and eight subjects in the ceftriaxone/cefpodoxime group died while receiving treatment or within 30 days following last treatment dose due to worsening of the disease under study. Two (2) alatrofloxacin/trovafloxacin subjects and five ceftriaxone/cefpodoxime subjects who died while receiving treatment or within 30 days following last treatment dose due to worsening of the disease under study were clinically evaluable treatment failures.