

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 (N=215)		Ceftriaxone ↓ Cefpodoxime (N=222)	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	177/215	(82%)	172/222	(77%)
Treatment-Related Adverse Events	70/215	(33%)	57/222	(26%)
Discontinuations From Treatment Due to an Adverse Event ^a	22/215	(10%)	18/222	(8%)
Clinically Significant Laboratory Values	121/203	(60%)	114/205	(56%)
<p>a With the exception of eight subjects in the alatrofloxacin/trovafloxacin group and eight subjects in the ceftriaxone/cefpodoxime group who were discontinued due to unrelated adverse events, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related.</p> <p>Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, 7.1, and Appendix I, Table 3.1</p>				

Eleven (11) subjects in the alatrofloxacin/trovafloxacin group and 20 subjects in the ceftriaxone/cefpodoxime group died during this study. With the exception of one death in the ceftriaxone/cefpodoxime group that occurred >30 days post-therapy and was considered by the investigator to be treatment related (upper gastrointestinal bleeding and pneumonia), all deaths were considered by the investigator to be unrelated to study drug. Thirty-four (34) subjects in the alatrofloxacin/trovafloxacin group and 47 subjects in the ceftriaxone/cefpodoxime group had serious adverse events. Two subjects in the alatrofloxacin/trovafloxacin group and two subjects in the ceftriaxone/cefpodoxime group who had serious adverse events that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or concomitant treatment.

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 ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were statistically equivalent for the sponsor-defined clinical success rate at the end of treatment for both intent-to-treat and evaluable subjects. Of the 11 subjects in the alatrofloxacin/trovafloxacin group and 20 subjects in the ceftriaxone/cefpodoxime group who died during this study, three alatrofloxacin/trovafloxacin subjects and eight ceftriaxone/cefpodoxime subjects died

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while receiving study medication or within 30 days of last treatment dose due to worsening pneumonia.

Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and at the end of study for baseline isolates of *S. pneumoniae* and *H. influenzae*. All subjects who had penicillin-resistant ($\text{MIC} \geq 0.1 \mu\text{g/mL}$) *S. pneumoniae* isolated at baseline (10 in the alatrofloxacin/trovafloxacin group and one in the ceftriaxone/cefepodoxime group) were clinical cures or improvements at the end of treatment and the end of study. No subject in the alatrofloxacin/trovafloxacin group with a clinical outcome of failure had a microbiologically confirmed persistent pathogen.

The percentage of subjects discontinued from treatment due to adverse events was 10% in the alatrofloxacin/trovafloxacin group and 8% in the ceftriaxone/cefepodoxime group. Nine (9) subjects in the alatrofloxacin/trovafloxacin group and two subjects in the ceftriaxone/cefepodoxime group were discontinued from treatment due to treatment-related adverse events. The most frequently occurring treatment-related adverse events that lead to discontinuation were those related to the intravenous insertion site (insertion site reaction, paresthesia, pruritus, thrombophlebitis, phlebitis) among subjects in the alatrofloxacin/trovafloxacin group and colitis and diarrhea among subjects in the ceftriaxone/cefepodoxime group. The overall percentage of all and treatment-related adverse events in the alatrofloxacin/trovafloxacin group was comparable to that of subjects in the ceftriaxone/cefepodoxime group (82% and 33% versus 77% and 26%, respectively). The most commonly reported treatment-related adverse events were dizziness (5%) and nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and diarrhea (7%) for subjects in the ceftriaxone/cefepodoxime group.

2. Per Medical Officer

APPROPRIATE
ON OPINION

A. Comments on comparator regimen

The chosen comparator regimen for this study is appropriate for use in the treatment of community-acquired pneumonia. Current labeling for ceftriaxone reads in part,

“Lower Respiratory Tract Infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus mirabilis*, or *Serratia marcescens*” at a dose of 1-2 grams given once daily or in equally divided doses twice daily depending on the type and severity of infection. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

For cefepodoxime: “acute Community Acquired Pneumonia caused by *Streptococcus pneumoniae* or non-beta-lactamase-producing *Haemophilus influenzae* ... at a dose of 200 mg bid for 14 days”.

The protocol-specified duration of 7-10 days for the comparator regimen is clearly less than the labeled duration of therapy for cefepodoxime, yet it exceeds the minimal duration of ceftriaxone specified in the labeling. The protocol does allow for a 14-day regimen to be given if the patient was felt to be adequately ill (defined as with bacteremia or requiring mechanical ventilation or high fractional O_2 [$>35\%$ to maintain PO_2 at >60]). A careful note will be made regarding the duration of therapy in the comparator arm and how it conforms to these labeling parameters.

Although these cephalosporins are not active against the agents of 'atypical' pneumonias, this protocol allowed for the addition of erythromycin, IV followed by tablets, if an atypical agent was suspected. Matching placebo was to be provided to the alatrofloxacin/trovafloxacin subjects.

B. Comments on study design and analysis

The design of this study is essentially identical to that of study 110, reviewed previously, aside from the difference in comparator regimen. The comments regarding design and analysis that were made in that portion of the Medical Officer review are appropriate for this study as well.

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

ceftriaxone → cefpodoxime subjects

PID	Investigator	Location	OK?	Comments
50790075	Ellison	SC	✓	
50790105	"_"		✓	
50790235	"_"		•	<i>Called double infection with Klebsiella pneumoniae and Legionella pneumophila. Four-fold rise in titer documented but admission urinary antigen negative. X-ray shows lobar consolidation; patient smoker with purulent gram stain. Unlikely to be true co-infection; more likely to be false positive serology for legionellosis. See discussion below regarding issue of multiple pathogens in setting of positive serology for atypical agents.</i>
50791076	"_"		✓	
51080057	Britt	MD	✓	
51191051	Truab	MA	•	<i>Local lab claims sputum grew Strep pneumo; reference lab grew Serratia marcescens. Gram stain report shows Gram Positive Cocci, consistent with local lab diagnosis. Called clinically and microbiologically evaluable by sponsor.</i>
51220043	Grossman	OH	✓	
51710164	Ericsson	TX	✓	
51710177	"_"		✓	
51760015	Levine	MI	✓	
51760205	"_"		✓	
52000017	Pullman	MT	✓	
52060175	Leggett	OR	✓	<i>Called 'cure' at EOT (day 10), having been given cephalosporin but no erythromycin for what is serologically diagnosed as Chlamydia pneumoniae pneumonia. Lab result showing day 31 titer of 1:256 has "not clinically significant" written on it by investigator.</i>
53971162	Monie	UK	✓	
55150604	Daschner	Germany	✓	
56210729	Maestu	Spain	✓	
56210732	"_"		✓	
58330810	Bonnet	Belgium	✓	
59470926	Phillips	Australia	✓	
63401167	Dhillon	UK	✓	

alatrofloxacin → trovafloxacin subjects

PID	Investigator	Location	OK?	Comments
50790073	Ellison	SC	✓	
50791074	"—"		✓	
51161057	Pingleton	KS	✓	
51210141	Zervos	MI	•	<i>Patient received 13 days of trovafloxacin (6 IV then 7 PO) for blood culture positive Streptococcus pneumoniae infection. Called 'improvement' at EOT visit day 14, but then 2 days later admitted to ICU with recurrent Streptococcus pneumoniae sepsis, bilateral otitis media, and worsening sinusitis. Begun on tobramycin + ticarcillin at that point. Day 25 EOS evaluation initially called 'failure' by investigator; months later, crossed out and called 'cure'. AE of 'Streptococcal septicemia' initially ascribed to study drug; investigator crossed out and put 'illness or caused by illness' as cause of event. Sponsor agrees with both EOS and EOT assessments, though made patient 'not assessable' for Clin Eval population at EOS due to the flu antimicrobials. Local lab MICs of blood isolate vs PCN were ; reference lab claims MIC was ; thus sponsor includes this subject as an evaluable at EOT penicillin-resistant Streptococcus pneumoniae 'favorable outcome'. See comments below.</i>
51680146	Avsar	AL	•	<i>Patient received 9 days of trovafloxacin; had drug-related dizziness and nausea starting day 4 which prompted discontinuation of drug before 10 days. Given clarithromycin on study day 12 to 22; despite this, EOT assessment at day 12 called 'improvement' by investigator and sponsor agrees. If the patient is improving, why is an additional 10 days of clarithromycin indicated? EOS eval done day 40, called 'not assessable' by sponsor (out of window visit) but ITT 'cure' by investigator; again sponsor agrees. Isolate = beta-lactamase + Moraxella catarrhalis.</i>
51710162	Ericsson	TX	✓	
51740006	Khan	NY	✓	
51740225	"—"		✓	<i>Patient received 6 days of trovafloxacin (2 IV, 4 PO) and developed rash on day 5 which led to premature discontinuation day 6. (Nonetheless investigator claimed study drug was NOT cause of this rash.) Initial sputum culture grew both Staph aureus and Haemophilus parainfluenzae; called clinical cure and microbiologic eradication at EOT (day 11) by both investigator and sponsor, even though sputum culture on day 11 again grew H. parainfluenzae.</i>
51740226	"—"		✓	
51760219	Levine	MI	✓	
51760220	"—"		✓	
53970424	Monie	UK	✓	<i>This 77 year old patient received 10 days of trovafloxacin (6 IV, 4 PO) for a right lower lobe pneumonia. Sputum grew no pathogen but initial blood culture grew Streptococcus pneumoniae (penicillin MIC 0.06). Atypical agents were not suspected; no erythromycin [i.e. placebo] was given. At EOT evaluation day 13, investigator thought there was some clinical improvement, though chest x-ray was reported to be unchanged. Despite this assessment of 'improvement', a bronchoscopy was done day 16, and a thoracentesis on day 21; neither culture was positive. The investigator considered the patient to be a failure at EOS (day 30), and the sponsor did not override this. Because no repeat culture demonstrated Streptococcus pneumoniae, the sponsor considers this an eradication of this organism but a failure to treat Legionella. The convalescent serologies returned with a Legionella antibody rise from the urinary antigen was negative. It is debatable whether this case actually was a true case of Legionella, rather than pneumococcal pneumonia with bacteremia in which subsequent cultures while on trovafloxacin therapy did not grow the organism.</i>

alatrofloxacin → trovafloxacin subjects (con't)

PID	Investigator	Location	OK?	Comments
55080510	Curran	France	✓	
55461027	Koffer	PA	✓	
56070185	Campbell	AZ	✓	<i>Patient (67 year old male) presents with Streptococcus pneumoniae bacteremia; vitals show patient afebrile, pulse 77, respiratory rate normal, peripheral . Although CRF pages regarding addition of erythromycin indicate that no erythromycin [placebo in this case] was given, handwritten note on page with atypical serologies indicates that investigator, when cognizant of baseline , added erythromycin to regimen.</i>
56271140	Martin	Spain	✓	
58350739	Cantoya	Spain	✓	
58351193	"_"		✓	
58351194	"_"		✓	
61151171	O'Neill	Ireland	✓	
61151172	"_"		✓	<i>Called clinically evaluable 'cure' at EOT visit (day 11), following 7 day course of trovafloxacin. On day 14, started on a seven day course of cefixime for 'infective exacerbation of COPD' and appropriately called 'not assessable' by the sponsor at EOS visit (day 32). This case points out the need to use EOS rather than EOT as the crucial endpoint, and the problems inherent with using the ITT analysis at EOS as the endpoint (since by the sponsor's ITT rules, this patient gets called a 'cure' despite the use of additional antimicrobials).</i>
62540916	Scicchitano	Australia	✓	
62540937	"_"			
63401166	Dhillon	UK	✓	

General Comments regarding CRF audit:

1. No radiology reports were provided for any of the CRFs for this study. A previous request to provide such reports for one of the other CAP studies (134) was made to the sponsor, and the appropriate documents were forthcoming. It is not necessary to repeat this exercise with this study as well.
2. The comments made above point out some questions raised by the interpretation of the clinical data provided to the sponsor in the CRFs. In general, the evaluability criteria and assignment of outcome categories specified in the Final Study Report appear to have been followed. The cases highlighted in the above comments do raise several points that are worthy of further discussion:
 - cases 50790235 and 53970424 raise the question of the validity of claiming a patient has a dual infection, when one of the putative agents is being diagnosed indirectly (i.e., by serology rather than by culture). How many patients in this study diagnosed with an atypical agent were also ascribed a bacterial pathogen (or pathogens) based on sputum or blood culture results? Of the 25 trovafloxacin-treated patients who were given an atypical diagnosis (as listed in Table 5.3a of the Final Study Report), 10 had one or more respiratory pathogens in the sputum and/or blood. Of these 10, 4 were considered Not Assessable at the EOS evaluation. Of the 27 ceftriaxone-treated subjects, only 5 had positive sputum and/or blood cultures; of these, one was Not Assessable. (See the overall Medical Officer conclusions for the CAP indication for a complete discussion of this issue.)
 - the issue of post-therapy use of additional antimicrobials for 'unrelated' infectious diagnoses (particularly 'exacerbation of COPD' or 'bronchitis') is once again raised by this study. Since such patients were called 'not assessable' at EOS evaluation by the sponsor, use of the Clin Eval at EOS subset will eliminate such patients from consideration. The larger issue is if and when such patients should be considered failures that are retained in this population. From a review of Table 2.4, Appendix 1 of Final Study Report, entitled "Listing of Concomitant Antibiotics Taken During Study", the explanations given for additions or changes to study drug regimen were as follows:

Reason stated in CRF	trovafloxacin	ceftriaxone/cefpodoxime
Inadequate response	15	24
Other respiratory diagnoses	12	8
Discontinued early due to side effects	12	4
Total N (all randomized patients)	218	225

It should be pointed out that the above determinations were made while the study was still blinded, both from the investigators and sponsors point of view. The above breakdown reveals that there were 4 more subjects in the trovafloxacin arm who were given additional or subsequent antimicrobials due to related 'other' respiratory infections. This difference is not considered to be of any consequence in the overall analysis. The last category, early discontinuation due to AEs, appears to be appreciably larger in the trovafloxacin arm. This has been described in other studies, both for this as well as other indications, and will be further discussed in the integrated summary of safety.

3. The comments regarding subject PID 51210141, the Trovan-treated patient with Streptococcus pneumoniae sepsis who was admitted to the ICU two days after being assessed as 'improvement', were related to the sponsor for clarification:

Please take a look at the patient profile and CRF for this subject. I need to follow the logic which categorized this subject as an EOS 'not assessable' by Clin Eval/'cure' by ITT at day 25, when he became bacteremic with Strep pneumo three days following completion of his oral trovan, leading to admission to the ICU. (This event happened 2 days after he had been categorized as an 'improvement'.)

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The following email response was provided by the sponsor:

This patient was discussed in the study report in the section "Subjects with Positive Blood Cultures at Baseline"- as follows:

"One subject (Subject 5121-0141) in the alatrofloxacin/trovafloxacin group had a follow-up culture that showed persistence of *S. pneumoniae* in the blood. A narrative for this subject is presented below:

Subject 5121-0141, a 25-year-old white male randomized to the alatrofloxacin/trovafloxacin treatment group, entered the study with a congenital immunodeficiency associated with recurrent bacterial infections including pneumonia, sinusitis, and bacteremia. This subject had an improvement in pneumonia by Day 10 and a complete resolution by Day 16 (per chest X-ray) and a negative blood culture on Day 3 for *S. pneumoniae*, indicating resolution of bacteremia. On Day 16, however, the subject had recurrent *S. pneumoniae* that was associated with sinusitis. This subject's MIC for *S. pneumoniae* was _____ at baseline and _____ on Day 16."

This patient should not have been enrolled with an immunodeficiency. He had had frequent pneumococcal infections related to this immunodeficiency. The investigator was clear that the pneumonia had resolved but the patient had another pneumococcal infection related to a sinusitis (per the investigator typical of his immunodeficiency). For this reason (another infection not related to the original pneumonia) he was excluded from final assessment.

The manner in which this subject was assessed again points out the inadequacy of using the EOT timepoint as the primary efficacy endpoint. At least when using the EOS Clinically Evaluable subset, such patients are dropped from the analysis. In this particular case, since the patient is noted on page 2 of the CRF to have hypogammaglobulinemia as an underlying diagnosis, it would have been reasonable to say he should not have been enrolled and therefore was a protocol violation. The sponsor, however, chose to include this patient in the analysis. (The Patient Profile shows him to be an Clinically Evaluable EOT 'improvement' by sponsor evaluation; he is 'not assessable' at EOS.)

4. As far as duration of therapy is concerned, table 3.1 of the Final Study Report demonstrates that the median duration of therapy for the comparator arm was 10 days, vis 3 of ceftriaxone and 7 of cefpodoxime. Of note, no patient received longer than 12 days of cefpodoxime. Recall that cefpodoxime (as monotherapy) is labeled for a 14 day course of therapy in the treatment of CAP. It is likely that an initial regimen of ceftriaxone should allow for some shortening of that 14 day regimen, but on average in this study a three day course of ceftriaxone (at a 1.0 gram per day dose) was followed by a seven day course of cefpodoxime. Might this difference contribute to the overall outcome of the study, in which the trovafloxacin arm in the EOS Clinically Evaluable analysis showed a slightly increased (81% vs. 76%) clinical cure rate? Perhaps. However, this difference was not of statistical significance. This dosing issue does not raise any major concerns about the overall applicability of this study to the requested indication.

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D. Medical Officer conclusions regarding CAP study 154-111:

Despite some questions regarding the interpretation and analysis of several individual subjects reviewed above, the medical officer's audit of this study did not reveal any evidence of systematic bias that would call the sponsor's results into question. It does, however, further emphasize the importance of using the EOS Clinically Evaluable population as the relevant group for efficacy analyses. As such, the trovafloxacin/alatrofloxacin subjects had an 81% clinical cure rate, compared to a 76% cure rate for the ceftriaxone/cefepodoxime arm.

The organism-specific eradication rates for this study are provided in the following table:

Pathogen-specific eradication rates at EOS (bacteriologically evaluable subjects)
Study 154-111

Pathogen	#eradicated (eradicated + presumed eradicated)/total	
	Trovan	Ceftriaxone/cefepodoxime
<i>Streptococcus pneumoniae</i>	25/27 (93%)	19/20 (95%)
<i>Haemophilus influenzae</i>	13/15 (87%)	22/24 (92%)
<i>Moraxella catarrhalis</i>	3/3	3/3
<i>Pseudomonas aeruginosa</i>	2/2	0/2
<i>Staphylococcus aureus</i>	3/3	6/7
<i>Chlamydia pneumoniae</i> *	2/2	7/8
<i>Legionella pneumoniae</i> *	7/10	8/10
<i>Mycoplasma pneumoniae</i> *	9/10	4/6

* these numbers include subjects co-infected with routine bacterial pathogens; see overall CAP conclusion for further discussion.

Medical officer review of CAP study 154-112

1. Per applicant

The synopsis of the applicant's final study report for study 112 is presented below; this is taken from the electronic submission, pages 11-16 of the Final Report (found in 8.G.1.A.1 of the NDA, under the 'Clinical Studies Relevant to the Claim Structure' section).

PROTOCOL 154-112: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN (CP-99,219) WITH AMOXYCILLIN AND OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Principal Investigators:

Dr. Alain Wurtz	Dr. P. Williams	Dr. Gerhard Neugart
Dr. Michel Arnould	Dr. J. A. Chapman	Dr. Marlis Pettelkau
Dr. Jean-Francois Bertrand	Dr. D. M. Allin	Dr. Mauersberger
Dr. M. Krigel	Dr. N. H. Patel	Dr. med R. Glanz
Dr. Jean-Marie Letzelter	Dr. D.A.J. Dutchman	Drs. med O Brückner and B. Kemmerich
Dr. Hubert Margraff	Dr. A. G. Thomson	Dr. Jochen Schaller
Dr. Pascal Raucourt	Dr. T.F.M. Cooper	Gerhard Ras, MD
Dr. Marc Steinberger	Dr. J. G. Geater	Dr. Johan Geysler
Dr. M. Aoun	Dr. B. M. Higginson	Dr. J. H. Mynhardt, MD
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Dr. P. Veyssier	Dr. P. McGarry	Dr. Philippe Gris
Dr. G. Vienne	Dr. B. O'Doherty	Dr. Karine Laurent
Professor Patri	Dr. M. Canning	Dr. Daniel Rozen
Christoph Pison, MD	Dr. J. Casey	John Upchurch, MD
Dr. Daniel Piperno	Dr. B. Crowley	Marvin Bittner, MD
Dr. Bsaibes	Dr. B. Cuddihy	Lala Dunbar, MD
M. J. Callander, MD	Dr. D. Forde	Richard Honsinger, MD
Dr. Adams Strump	Dr. Hanson	Thomas Decker, MD
Dr. A. Burton	Dr. L. McEntee	David Schreck, MD
Dr. I. D. Caldwell	Dr. McGinnity	
Dr. B. Cross	Dr. T. McMahan	
Dr. H. A. Duncalf	Dr. Niall Walsh	
Dr. J. A. Hughes	Dr. Philip Wiehe	
Dr. S. Hutchison	Dr. M. B. McDonnell	
Dr. Kesson	Dr. P. McDonagh	
Dr. P. N. Kulkarni	Dr. P. Quinn	
Dr. T. G. Maxwell	Dr. E. Hartman	
Dr. J. P. Nagle	Dr. D. Dwyer	
Dr. R. F. Quigley	Dr. O. Muller and Dr. E. Klingelhofer	
Dr. R. N. Snook	Dr. Gerhard Orlovius	
Dr. D. Sutherland	Dr. Borrás	
Dr. Thomson	Dr. Luckau	

Study Publication: Not Applicable

Study Dates: 9 December 1994 - 12 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to amoxicillin, with optional erythromycin, for the treatment of subjects with community acquired pneumonia.

Study Design: Study 154-112 was a randomized, multicenter, double-blind, double-dummy trial of trovafloxacin administered orally for 7 to 10 days of total treatment versus amoxicillin administered orally for 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

	Evaluation Groups:			
	Trovafloxacin (200 mg/day)		Amoxicillin (500 mg TID)	
Entered Study ^a	151		152	
All Treated	150	(100%)	152	(100%)
Completed Treatment	136	(91%)	139	(91%)
Completed Study	140	(93%)	136	(89%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	148	(98%)	149	(98%)
Clinically Evaluable ^b	138	(91%)	141	(93%)
Bacteriologically Intent-to-Treat	60	(40%)	55	(36%)
Bacteriologically Evaluable	55	(36%)	52	(34%)
Assessed for Safety				
Adverse Events	150	(100%)	152	(100%)
Laboratory Tests	144	(96%)	148	(97%)

a Subjects who were randomized.
b Clinically evaluable at end of treatment.

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 were eligible to participate in this study.

Drug Administration: Study drug was in the form of tablets (trovafloxacin) and capsules (amoxicillin), which were packaged in blister cards and/or bottles, 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, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Confidence intervals (95%) for differences in clinical success (no signs or symptoms of a primary infection) rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

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Efficacy Results: Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment supported equivalence of the two treatment regimens for clinically evaluable (trovafloxacin: 93%, 128/137; amoxicillin: 91%, 128/140 [CI: -4.2, 8.2]) and intent-to-treat (trovafloxacin: 90%, 132/147; amoxicillin: 88%, 130/148 [CI: -5.2, 9.1]) subjects. Sponsor-defined pathogen eradication rates at the end of treatment for the most frequently isolated pathogens (*H. influenzae* and *S. pneumoniae*) were comparable between the two treatment groups for bacteriologically evaluable and intent-to-treat subjects. A trend towards higher pathogen eradication rates for *H. influenzae* was noted for subjects in the trovafloxacin group compared to subjects in the amoxicillin group at the end of treatment and end of study. Among bacteriologically intent-to-treat subjects, two in the trovafloxacin group had positive blood cultures for *S. pneumoniae* at baseline and at least one follow-up blood culture during the study. The post-baseline pathogen outcome for these pathogens was eradication. In addition, these subjects were clinically improved or cured at the end of treatment and end of study.

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.

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A Summary of the Sponsor's Assessment of Clinical Response				
(Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=138)	Amoxicillin 500 mg TID (N=141)	Trovafloxacin 200 mg (N=122)	Amoxicillin 500 mg TID (N=127)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	137 (100%)	140 (100%)	122 (100%)	127 (100%)
Success (Cure + Improvement)	128 (93%)	128 (91%)	107 (88%)	110 (87%)
Distribution of Clinical Response:				
Cure	71 (52%)	75 (54%)	98 (80%)	97 (76%)
Improvement	57 (42%)	53 (38%)	9 (7%)	13 (10%)
Failure	9 (7%)	12 (9%)	9 (7%)	12 (9%)
Relapse	Not Applicable	Not Applicable	6 (5%)	5 (4%)
(Clinically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=148)	Amoxicillin 500 mg TID (N=149)	Trovafloxacin 200 mg (N=148)	Amoxicillin 500 mg TID (N=149)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	147 (100%)	148 (100%)	148 (100%)	149 (100%)
Success (Cure + Improvement)	132 (90%)	130 (88%)	126 (85%)	126 (85%)
Distribution of Clinical Response:				
Cure	74 (50%)	75 (51%)	113 (76%)	112 (75%)
Improvement	58 (39%)	55 (37%)	13 (9%)	14 (9%)
Failure	15 (10%)	18 (12%)	16 (11%)	18 (12%)
Relapse	Not Applicable	Not Applicable	6 (4%)	5 (3%)
A Summary of the Sponsor's Assessment of Pathogen Outcome				
Sponsor-Defined Eradication Rates For the Most Frequently Isolated Baseline Pathogens ^a				
(Bacteriologically Evaluable Subjects)				
	End of Treatment		End of Study	
Pathogen	Trovafloxacin 200 mg (N=55)	Amoxicillin 500 mg TID (N=52)	Trovafloxacin 200 mg (N=53)	Amoxicillin 500 mg TID (N=44)
Number and Percentage (%) of Pathogens				
<i>H. influenzae</i>	21/21 (100%)	17/20 (85%)	19/20 (95%)	10/14 (71%)
<i>S. pneumoniae</i>	21/21 (100%)	17/19 (89%)	20/21 (95%)	15/18 (83%)
<i>M. catarrhalis</i>	5/5	3/3	4/4	3/3
<i>M. pneumoniae</i>	4/5	2/3	4/5	1/2
<i>C. pneumoniae</i>	1/1	4/4	1/1	2/2
Sponsor-Defined Eradication Rates For the Most Frequently Isolated Baseline Pathogens ^a				
(Bacteriologically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
Pathogen	Trovafloxacin 200 mg (N=60)	Amoxicillin 500 mg TID (N=55)	Trovafloxacin 200 mg (N=60)	Amoxicillin 500 mg TID (N=55)
Number and Percentage (%) of Pathogens				
<i>H. influenzae</i>	22/23 (96%)	18/21 (86%)	20/21 (95%)	11/16 (69%)
<i>S. pneumoniae</i>	22/22 (100%)	18/21 (86%)	21/22 (95%)	15/20 (75%)
<i>M. catarrhalis</i>	5/5	3/3	5/5	3/3
<i>C. pneumoniae</i>	1/1	4/4	1/1	4/4
<i>M. pneumoniae</i>	5/6	2/3	5/6	2/3
<p>^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (<i>C. pneumoniae</i> and <i>M. pneumoniae</i>); percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline. Ref.: Tables 5.1.1, 5.1.2, 5.4.1, and 5.4.2</p>				

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

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Trovafloxacin (200 mg)		Amoxicillin (500 mg TID)	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	52/150	(35%)	44/152	(29%)
Treatment-Related Adverse Events	24/150	(16%)	22/152	(14%)
Discontinuations From Treatment Due to Adverse Events ^a	9/150	(6%)	7/152	(5%)
Clinically Significant Laboratory Values	49/144	(34%)	44/148	(30%)

a Five (5) and two discontinuations in the trovafloxacin and amoxicillin treatment groups, respectively, were treatment-related.
Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, 7.1, and Appendix I, Table 3.1

Twelve (12) subjects in the trovafloxacin group and 11 subjects in the amoxicillin group had serious adverse events. One subject in the trovafloxacin group had serious adverse events (sweating, faintness, vomiting, loss of consciousness, and allergic conjunctivitis) that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or concomitant treatment. Five (5) subjects in the trovafloxacin group and seven subjects in the amoxicillin group died during this study. None of the deaths was considered to be related to study drug.

Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxicillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were statistically equivalent for the sponsor-defined clinical success rates at the end of treatment for both intent-to-treat and evaluable subjects. Sponsor-defined eradication rates were comparable between the two treatment groups at the end of treatment for baseline isolates of *S. pneumoniae* and *H. influenzae*. All five trovafloxacin subjects who had penicillin-resistant (MIC ≥ 0.1 $\mu\text{g/mL}$) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study. One subject in the amoxicillin group had penicillin-resistant *S. pneumoniae* isolated at baseline and was a clinical failure at the end of treatment and end of study. Of the subjects with a clinical response of failure or relapse, none in the trovafloxacin group and two in the amoxicillin group had an outcome of persistence confirmed by microbiology. The percentage of subjects discontinued from treatment due to adverse events was 6% in the trovafloxacin group and 5% in the amoxicillin group. The overall percentage of all and treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the amoxicillin group (35% and 16% versus 29% and 14%, respectively). The most commonly reported treatment-related adverse events were

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dizziness (3%) and nausea (3%) for subjects in the trovafloxacin group and diarrhea (5%) and nausea (3%) for subjects in the amoxicillin group.

2. Per medical officer.

This study was designed and conducted in a manner similar to that of study 134. The study design and execution is consistent with IDSA guidelines for the design and conduct of clinical trials seeking the Community-Acquired Pneumonia indication.

The comparator regimen, amoxicillin ± erythromycin, does not provide coverage for beta-lactamase positive strains of organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis*; thus it is not surprising to see the comparator arm of this study showing reduced efficacy against these organisms. General recommendations for therapy of this disease in the US would call for an antimicrobial agent (or combination of antimicrobial with a betalactamase inhibitor) that has activity against such strains. This issue will need to be taken into account if the sponsor desires to make a claim of superiority to this comparator regimen.

Although a total of 86 investigators were listed as contributing to this study, only 45 of them eventually contributed enrolled subjects. Overall, the distribution of enrolled patients by geographic location was as follows:

<u>Country</u>	<u># enrolling investigators</u>	<u># subjects enrolled</u>
USA	5	23
UK	13	95
Ireland	12	118
France	7	27
Germany	3	20
S. Africa	4	19
<u>Belgium</u>	<u>1</u>	<u>1</u>
TOTAL	45	303

It can thus be seen that this study has disproportionate representation from Ireland and the UK, from which two countries came 213 out of the 303 enrollees. This relative paucity of enrollees from southern Europe and South Africa is a major reason why there were not as many isolates of penicillin-resistant *Streptococcus pneumoniae* as might otherwise have been.

The following ten investigators were the leading contributors to this study:

<u>Investigator</u>	<u>ID#</u>	<u>location</u>	<u>N</u>	<u>#subinvestigators</u>	<u>subjects per investigator</u>
O'Doherty	5294	Ireland	37	1	18.5
Maxwell	5342	UK	26	0	26.0
Quinn	5809	Ireland	23	0	23.0
McGarry	5292	Ireland	13	0	13.0
Allin	5675	UK	13	0	13.0
Dutchman	5744	UK	13	0	13.0
Thompson	5745	UK	13	0	13.0
Honsicker	5556	NM, USA	12	2	4.0
Geyser	6313	S. Africa	12	0	12.0
Veyssier	5365	France	11	0	11.0

The number of enrollees per investigator in this study is much higher than was seen in study 134. This is because the European investigators are all (with a rare exception) listed as the sole investigator at that study site, as opposed to the American investigators in study 134 who often listed multiple (as many as 26) subinvestigators. This may be a reflection of practice patterns (solo practitioner vs. large group practice) in Europe as opposed to the USA, more than anything else.

CRF and Patient Profile audit.

A random listing of 10% of the PIDs from study 112 was generated by the reviewing statistician. These 30 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.

Amoxicillin ± erythromycin patients

PID	Investigator	Location	OK?	Comments
52940036	O'Doherty	Ireland	✓	
52940246	"_"		✓	
52940269	"_"		✓	
53590275	Walsh	Ireland	✓	22 year old; no erythromycin given
53650329	Veyssier	France	•	no CRFs found in file
55560921	Honsicker	NM, USA	✓	Called clinical cure; received amoxicillin alone (without additional erythromycin). Had 4-fold rise in <i>Chlamydia pneumoniae</i> IgA and thus diagnosed as clinical and bacteriologic cure of <i>Chlamydia pneumoniae</i> but never received antimicrobial active against this infectious agent.
56750487	Allin	UK	✓	
56750604	"_"		✓	Radiologist report stamped "Drug trial"
57440102	Dutchman	UK	✓	
57740901	Decker	NH, USA	✓	
58130021	Higginson	UK	✓	Baseline CXR read as "probable minimal change? Infective left lung base" and in follow-up investigator writes "I suspect that initial appearance on balance did not represent active infection."
63130121	Geyser	South Africa	✓	Blood and sputum culture + for <i>Strep pneumoniae</i> ; penicillin MIC 0.06.
64030133	Fehrsen	South Africa	✓	Sponsor called patient unassessable at EOS because of single dose administration of metronidazole for trichomoniasis; patient clinically cured on amoxicillin alone, despite diagnosis of <i>Chlamydia pneumoniae</i> by 4-fold rise in serum IgG.

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Trovafloxacin patients

PID	Investigator	Location	OK?	Comments
52920563	McGarry	Ireland	✓	
52940034	O'Doherty	Ireland	✓	<i>called clinically and bacteriologically evaluable and cured by both sponsor and investigator; however, f/u CXR report states "Despite the clinical symptoms, the remainder of the lung fields remain clear."</i>
52940271	"—"		✓	
52940666	"—"		✓	<i>Baseline CXR read as "pleural shadowing in right cardiophrenic angle; possibly acute, possibly chronic." Patient experienced nausea/vomiting/headache on day 2 of therapy, called unrelated to study drug by investigator and ascribed to migraines despite no listing of migraines in subject's past medical history at entry.</i>
53420070	Maxwell	UK	✓	<i>Specific mention of "inclusion in drug trial" on baseline radiology report.</i>
53650354	Veyssier	France	•	<i>Called clinically evaluable cure by ITT at EOS by sponsor at day 34, despite having been given ofloxacin from days 30 to 36 for 'prostatitis', and clamoxyl (amoxicillin) from days 24 to 28 for 'urinary tract infection' (Appropriately called 'not assessable' by sponsor at EOS.) Recall that this NDA seeks prostatitis and UTI indications for trovafloxacin. When reviewing the CRFs for this investigator, all the CRFs for this study site were signed by a Dr. Cevallos rather than the listed investigator. There are no co-investigators listed in Appendix 2 of the study report for study 112, and a full-text search of the electronic submission failed to reveal an entry for a Dr. Cevallos. Thus it would appear that this Dr. Cevallos is not authorized to sign these documents as an investigator, and therefore the evaluability of all subjects enrolled at this site (N = 11) is questionable. As can be seen in Attachment 1, which is the complete CRF for one of these patients, there are multiple crossouts and other changes that make review of the CRF extremely difficult.</i>
55000933	Dunbar	LA, USA	✓	<i>Patient given 10 days of outpatient therapy for blood culture + Strep pneumoniae pneumonia but self-discontinued after 7 days. Only AE reported as left leg edema that was judged unrelated to study medication by investigator (despite fact that patient self-discontinued study medication at that point). Patient well at EOS day 32.</i>
55560907	Honsicker	NM, USA	✓	<i>Reading of baseline CXR: "Indistinctness of left hemidiaphragm could represent an early infiltrate."</i>
55560922	"—"		✓	<i>Baseline CXR read as "There is a chronic infiltrate in both the right middle and upper lobes" yet f/u film on day 29 called "completely resolved".</i>
55560928	"—"		•	<i>This subject was treated with 10 days of oral trovafloxacin, but was admitted to hospital for the first four days. (This is not a protocol violation per se, though the reason for admission was not clear from the CRFs.) Called clinically unevaluable by sponsor because patient received Keflex for four days immediately following trovafloxacin therapy for treatment of a superficial phlebitis of the left hand, secondary to intravenous therapy (?fluids) given during hospitalization. This is interesting given that the trovafloxacin NDA also seeks a Skin and Soft Tissue Infection indication. The CRFs also document that the patient's sputum Gram stain was of good quality, revealing 2+ GPC's, and the culture grew out Staph aureus. The microbiology results in the Patient Profile only show "normal/mixed flora" as the result. Overall, I agree with the sponsor's decision to call this subject unevaluable. However, the discrepancy between Patient Profile and CRF is disconcerting.</i>

Trovafloxacin patients (continued)

PID	Investigator	Location	OK?	Comments
56750486	Allin	UK	✓	<i>Baseline CXR: "A little increased shadowing suggestive of increased pulmonary edema... in keeping with superadded inflammatory changes" and is stamped "DRUG TRIAL". In keeping with this finding, the two f/u films both show no change, confirming that trovafloxacin has limited utility as an afterload reducing agent. Nonetheless this 89 year old man received 7 days of trovafloxacin, was called 'improved' (based on clinical symptoms, which the CRF states did improve), and thus qualifies as a 'clinical success'.</i>
56890081	Patel	UK	✓	
57440103	Dutchman	UK	✓	
58600421	Mauersberger	Germany	✓	
63430483	Wilson	UK	•	<i>Although this patient appeared to be accurately presented in the patient profile, compared to the CRFs, I found it disturbing that the patient had been on amoxicillin for 6 days, finishing a bit over 72 hours prior to study entry (thus meeting protocol entry criteria). Presumably this therapy had not produced an adequate response, yet the investigator felt comfortable entering him into a randomized study in which the subject presumably could have been continued on this inadequate therapy. It is furthermore disturbing to see that the subject's sputum grew out a beta lactamase positive Haemophilus influenzae (thus explaining the poor initial response to amoxicillin prior to study entry), yet the subject was continued on 'blinded' therapy which, fortunately for the patient, just so happened to be trovafloxacin. Such cases lead the medical officer to wonder about the integrity of the study blind, at the very least for this particular investigator and, inevitably, to some degree for the study as a whole.</i>
63430611	"—"		•	<i>Selected language from the baseline CXR report for this 72 year old study subject: "Main diagnosis is CHF... intercurrent infection cannot be excluded... follow-up film post-diuretics is recommended." The 'entry' CXR was taken four days prior to study entry. The sponsor called this patient an EOT improvement (in accord with the investigator) but an EOS 'not assessable' because the patient was given ciprofloxacin from day 26 to 33 for "other further chest infection". The sponsor did change the investigator's EOS evaluation of 'improvement' to 'failure' for the ITT analysis. If the sponsor considers this subject to be clinically evaluable (which is questionable, given the dubious nature of the baseline CXR), then the subject should be an evaluable EOS failure because of the need for additional antimicrobial (this same investigator [6343] as the previous subject quite brilliantly selecting ciprofloxacin in this instance, following an apparent failure of 'blinded' therapy with either a supposedly superior quinolone or amoxicillin). Interestingly, this investigator had a different patient (6343 0482) discounted by the sponsor for a protocol violation ("baseline CXR done > 48 hours prior to administration of study drug") but the sponsor did not exclude patient 0611 even though the same exclusionary criteria should apply.</i>
64610585	Pimm	UK	✓	<i>Appropriately called clinical failure at EOS. Baseline CXR report bears legend "ICON Study", indicating that radiologist was aware of patient's status as drug study participant.</i>

Comments:

1. This study, unlike the other CAP studies in the electronic submission of the NDA, included all radiology reports of CXRs taken at entry and at follow-up. Review of these initial radiology reports was helpful for several reasons: it allowed for verification of the handwritten interpretation that the investigator (or study nurse) would enter onto the appropriate page of the CRF; it allowed the medical officer to see that

- a fair number of patients were enrolled with questionable or 'soft call' infiltrates; and it demonstrated which of the investigators were in situations in which the status of the patient as a drug study participant was plainly stamped on the radiology report. This latter issue was seen in a small minority of CRFs, but is nonetheless important because it may bias the radiologist towards calling something an infiltrate, thus allowing the subject to be entered into the study (and the investigator to get reimbursed for same). This type of bias, if real, would presumably distribute such patients evenly between the two treatment arms.
2. The great majority of audited charts showed patients receiving 10 days of therapy. In fact, Table 3.1 of the final study report for study 112 shows that of the 150 patients randomized to trovafloxacin, 94 received 10 or 11 days of therapy whereas 39 received 7 days of therapy.
 3. Study site 5365 is problematic, given that the name of the supposed investigator, Dr. Pierre Veyssier, appears nowhere on the CRFs. The printed name and signature on all CRFs for this study site are for a Dr. Cevallos. There is no listing for this person anywhere in the electronic submission, nor is there a CV for anyone other than Dr. Veyssier (a one-page CV) under center 5365. The results from this center should thus be disregarded. Eleven subjects were enrolled, of which 9 were considered clinically evaluable and one was clinically evaluable at end of study, with a baseline pathogen. There are seven sets of CRFs included in the CRF Casebook section of the NDA; thus, four of the enrolled subjects have no documentation whatsoever. Attachment 1 to this review demonstrates the condition of one of these CRFs. Also included (the last 2 pages of this attachment) is the "Baseline Chest X-Ray Interpretation" from an additional two subjects from this center. These two sheets, neither of which even identify the subject by name or PID number, are handwritten replicas of the Pfizer CRF page of the same title. Overall, this study site demonstrates poor data collection, multiple strikeouts/corrections/changes, and a total lack of any signature by the investigator of record.
 4. The total number of subjects contributed to the study by investigator 5365 was relatively small, and the total number of bacteriologically evaluable subjects at EOS was only one; therefore, removal of all these subjects from consideration will not fundamentally change the sponsor's conclusions from this study.
 5. There was only one CRO responsible for the monitoring of all the European and American study sites for study 112:
The findings listed above for study site 5365, along with the other Medical Officer comments from the CRF audit, appear to demonstrate a worrisome lack of attention to detail; if this is representative of the oversight provided by this CRO to the remaining investigator sites, then this study is fundamentally flawed and should not be considered supportive of the indication. The audit of the remaining CRFs did not appear to demonstrate the same degree of inept CRO oversight, although it did raise a question regarding the integrity of the study blind.
 6. As noted in the CRF audit, a patient with beta-lactamase positive H. flu who was previously treated with 6 days of amoxicillin was entered into the study, only to randomize to the trovafloxacin arm. This leads to the question: how many subjects in this study had a beta-lactamase positive isolate at baseline, and of these, how many randomized to trovafloxacin vs. amoxicillin? Table 18, Appendix 5 of the final study report for study 112 lists all microbiology isolates, including whether they were beta-lactamase positive or negative. A review of this table reveals the following:

Total number of baseline microbiology isolates characterized by beta-lactamase production, study 112

	<i>H. influenzae</i>		<i>M. catarrhalis</i>		<i>H. parainfluenzae</i>	
	β -lac +	β -lac -	β -lac +	β -lac -	β -lac +	β -lac -
trova	3	20	4	1	1	3
amox	3	21	2	1	0	5

Thus it can be seen that the beta-lactamase positive isolates in this study were fairly evenly distributed between the two treatment arms. This provides no evidence that the study blind was compromised.

7. Although the sponsor's summary and conclusions (page 5 of this review, highlighted) states that

All five trovafloxacin subjects who had penicillin-resistant (MIC ≥ 0.1 μ g/mL) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study. One subject in the amoxicillin group had penicillin-resistant *S. pneumoniae* isolated at baseline and was a clinical failure at the end of treatment and end of study.

a review of Table 18, Appendix 5 of the study report reveals that of the trovafloxacin subjects with 'resistant' pneumococcal isolates recorded, eight had MICs of 0.12 μ g/mL; of these, one isolate grew on follow-up sputum culture on day 32 (b)(4) and another of these isolates was cultured from a day 11 sputum specimen (b)(4). An additional four subjects had MICs of 0.25 μ g/mL recorded; of these, one (b)(4) was collected on day 4 of trovafloxacin therapy. It is unclear how the sponsor arrived at the assertion quoted above, but nonetheless there is a paucity of clinical and microbiological data in this study upon which to make any statement regarding the efficacy of trovafloxacin in the treatment of community-acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (which to the best of my knowledge means an MIC of > 1.0 μ g/mL).

Medical officer conclusions regarding study 112:

With the exception of one study site, study 112 appears to have been conducted in an adequate and well-controlled manner, and demonstrates the equivalence of trovafloxacin and amoxicillin in the treatment of community-acquired pneumonia. If the rate of beta lactamase producing strains had been equivalent to what is currently seen in the United States, the amoxicillin arm would probably have done substantially worse than the trovafloxacin arm; this was not the case.

No conclusions regarding activity of trovafloxacin against penicillin-resistant strains of *Streptococcus pneumoniae* can be reached from this study.

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Overall Medical Officer conclusions for Community Acquired Pneumonia indication

A. Clinical results

1. Oral studies (154-112, 154-134)

Both of these studies were well-designed double blind, double-dummy studies of large size and geographic distribution. Study 134 was predominantly domestic. It utilized a BID comparator that has an approved indication of pneumonia, including pneumonia caused by at least one 'atypical' agent (Mycoplasma pneumoniae). (NB: Clarithromycin is not labeled for pneumonia due to Legionella pneumophila or Chlamydia pneumoniae.) Study 112 was an international study, using a comparator that was somewhat less efficacious (amoxicillin ± erythromycin). It, too, was double-blind, double-dummy in design; however, given that amoxicillin is a TID drug, and erythromycin is a QID drug, the subjects in this study who were judged to require the addition of erythromycin (or placebo) to their regimen were taking a total of 16 tablets and/or capsules daily. This was presumably daunting to even the most motivated of study enrollees. (Such concerns over compliance would be shared equally between the two randomization arms.)

Combined clinical efficacy for these two studies at EOS in the Clinically Evaluable subset is presented in the following table:

Study	Clinical Outcome at End of Study (EOS) timepoint Clinically Evaluable subset		
	Cure	Improvement	Failure /Relapse
Study 112 amoxicillin ± erythromycin	112/149 (75%)	14/149 (9%)	23/149 (16%)
	trovafloxacin	113/148 (76%)	13/148 (9%)
Study 134 clarithromycin	113/144 (78%)	11/144 (8%)	20/144 (14%)
	trovafloxacin	108/135 (80%)	12/135 (9%)

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Thus it can be seen that the two oral comparative studies demonstrate clinical equivalence to two different approved comparative regimens. In reviewing these two studies, the medical officer was troubled to find that the radiologists' interpretation of the entry chest x-rays was not included in the original set of CRF data. Upon request, the sponsor was able to provide the appropriate entry radiology reports for all audited patients. (These reports were included in the CRFs for study 112 patients.) Otherwise, the medical officer's audit of these studies essentially confirmed the interpretations of patient outcomes provided in the Patient Profiles compiled by the sponsor. There were some questions regarding the clinical course and outcome of certain individual patients, but the overall conclusion was that the sponsor's Clinically Evaluable at EOS subset was valid.

2. IV → oral studies.

Studies 110 and 111 were the two large, phase 3, multicenter studies conducted to evaluate the efficacy of atrofloxacin and trovafloxacin, given sequentially, in the treatment of CAP. As with the above oral only studies, these two studies were designed as double blind, double-dummy trials using comparator regimens that had been previously discussed with and agreed to by DAIDP during end-of-phase-2 deliberations. Once again, one of these studies (study 110) used a regimen that has no labeled activity against Legionella pneumophila, whereas the other allowed the addition of optional erythromycin (or placebo) if the investigator suspected an atypical agent in the differential diagnosis. As with the oral only studies, one of these were predominantly domestic (study 110 included 53 South African patients and 9 Canadian patients out of a total of 396 randomized), whereas the other (study 111) was truly international (including France, Spain, UK, and Australia).

One would assume that the patients in these two studies were more severely ill than those in the oral only studies. The protocols did, after all, state that in order to be eligible for enrollment, subjects should be ill enough to be "... requiring hospitalization and initial intravenous therapy". However, these two protocols make no attempt to prospectively identify characteristics that easily differentiate between the patients enrolled in these IV to oral studies, as compared to those enrolled in the oral only studies.

The sponsor presents the following two tables in discussing the underlying severity of disease in the oral only vs. IV to oral patients:

Table 5: Summary of Baseline Characteristics and Co-Morbidity at Baseline (Clinical Intent-to-Treat Subjects - CAP, Oral)				
Baseline Characteristic	Trovafloxacin (N=361)		Comparator Agents (N=367)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	52.3		52.2	
Minimum	16		16	
Maximum	90		95	
16-44	144	(40%)	144	(39%)
45-64	104	(29%)	107	(29%)
65-74	60	(17%)	70	(19%)
≥75	53	(15%)	46	(13%)
Sex				
Male	198	(55%)	181	(49%)
Female	163	(45%)	186	(51%)
Smokers	118	(33%)	122	(33%)
Co-morbidity				
Number of Subjects With at Least One Co-morbidity	125	(35%)	120	(33%)
Chronic Obstructive Lung Disease	68	(19%)	75	(20%)
Asthma	35	(10%)	36	(10%)
Congestive Heart Failure	23	(6%)	24	(7%)
Diabetes Mellitus	29	(8%)	18	(5%)
Hepatic Disease	5	(1%)	6	(2%)
Impaired Renal Function	6	(2%)	3	(<1%)

Ref.: Tables H.4.6.1.2, H.4.6.3

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**Table 9: Summary of Baseline Characteristics, Co-Morbidity and Risk Factors at Baseline
(Clinical Intent-to-Treat Subjects - CAP, IV/PO)**

Baseline Characteristic	Alatrofloxacin/Trovafloxacin (N=408)		Comparator Agents (N=422)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	57.4		58.2	
Minimum	16		17	
Maximum	94		95	
16-44	120	(29%)	119	(28%)
45-64	111	(27%)	109	(26%)
65-74	87	(21%)	99	(23%)
≥75	90	(22%)	95	(23%)
Sex				
Male	240	(59%)	264	(63%)
Female	168	(41%)	158	(37%)
Smokers	150	(37%)	162	(38%)
Co-morbidity				
Number of Subjects With at Least One Co-morbidity	245	(60%)	243	(58%)
Chronic Obstructive Lung Disease	134	(33%)	153	(36%)
Congestive Heart Failure	69	(17%)	63	(15%)
Diabetes Mellitus	69	(17%)	55	(13%)
Asthma	63	(15%)	55	(13%)
Impaired Renal Function	33	(8%)	22	(5%)
Hepatic Disease	13	(3%)	15	(4%)
Risk Factors				
Pleuritic Chest Pain	251/405	(62%)	249/420	(59%)
Fever (>38°C)	227/404	(56%)	235/420	(56%)
Respiration Rate ≥24/min	183/395	(46%)	200/412	(49%)
Severe Cough	107/405	(26%)	106/420	(25%)
Severe Dyspnea	95/405	(23%)	98/420	(23%)
Hypothermia (<37°C)	67/403	(17%)	89/417	(21%)
Bacteremia ^a	41/389 ^b	(11%)	38/397 ^c	(10%)
Hypotension (Systolic ≤90mmHg)	17/405	(4%)	14/420	(3%)
Leukopenia (WBC <4000)	6/382	(2%)	7/395	(2%)
a Includes all subjects with any organism isolated from a baseline blood culture. b Includes 28 <i>S. pneumoniae</i> c Includes 18 <i>S. pneumoniae</i> Ref.: Tables H.4.7.1.2, H.4.7.3, H.4.7.3.1, and H.4.7.4				

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As can be seen from these two tables, the patients in the oral only studies generally had less 'co-morbidity' than those in the IV → oral studies (35% vs. 60%). There are no data collected however which speak to severity of illness in the oral studies, as there are presented above for the IV studies under the subheading 'Risk factors'. (What, precisely, these 'risk factors' put the patient at risk for is not defined in the text of the Integrated Summary of Efficacy.) These parameters should be compared with the American Thoracic Society definition of 'severe' community acquired pneumonia, which is defined as a new infiltrate in the presence of one or more of the following: admission respiratory rate of > 35/min; need for mechanical ventilation; chest radiograph indicating a 50% increase in the infiltrate over baseline, or bilateral multilobar involvement; need for vasopressors; severe lung injury; urine output < 20 cc/hr; or acute renal failure.

These data do not support wording that would indicate that trovafloxacin has been studied in 'severe' community-acquired pneumonia.

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The following table presents the clinical outcomes for the Clinically Evaluable subset at the EOS timepoint for both IV→ oral studies submitted:

Study	Clinical Outcome at End of Study (EOS) timepoint Clinically Evaluable subset		
	Cure	Improvement	Failure/Relapse
Study 110			
ciprofloxacin/ ampicillin	130/165 (79%)	15/165 (9%)	20/165 (12%)
alatrofloxacin/ trovafloxacin	106/140 (76%)	14/140 (10%)	20/140 (14%)
Study 111			
ceftriaxone/ cefprozime ± erythromycin	128/169 (76%)	10/169 (6%)	31/169 (18%)
alatrofloxacin/ trovafloxacin	128/159 (81%)	8/159 (5%)	23/159 (14%)

As can be seen, the overall cure rates are comparable between trovafloxacin and both comparator arms. The slightly higher rates for the comparator in study 110 and the trovafloxacin arm in study 111 are not of statistical significance.

In the Medical Officer's audit of CRFs from these two studies, several questions were raised concerning the interpretation of individual enrollees in both studies. None of the CRF audits revealed a pattern of outcome assignment that could be taken as evidence of bias. It is therefore concluded that these results are a valid reflection of the clinical efficacy of trovafloxacin in the setting of community acquired pneumonia.

B. Pathogen-specific results

1. 'Routine' respiratory pathogens

The combined results for the eradication rates for identified pathogens in the four studies collected above are presented in the following table. This table includes routine bacterial pathogens only; the discussion of atypical agents follows:

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**Eradication Rates for Identified Pathogens
Clinically and Bacteriologically Evaluable Subjects*
Community Acquired Pneumonia
(According to M-)
Study number, N**

Pathogen	Study number, N				Totals N = 241
	Study 110 N = 64	Study 111 N = 68	Study 112 N = 53	Study 134 N = 56	
<i>Streptococcus pneumoniae</i>	30/33	25/27	20/21	11/12	86/93 (92%)
<i>Haemophilus influenzae</i>	14/16	13/15	19/20	10/10	57/61 (93%)
<i>Moraxella catarrhalis</i>		3/3	4/4		7/7
<i>Klebsiella pneumoniae</i>	1/1				1/1
<i>Pseudomonas aeruginosa</i>		2/2			2/2
<i>Staphylococcus aureus</i>	3/3	3/3			6/6

* A subject could have more than one pathogen at baseline.

It is clear from this table that the sponsor has accumulated adequate numbers of *Streptococcus pneumoniae* and *Haemophilus influenzae* to warrant approval. It is also clear that the numbers of the remaining organisms are relatively scanty. These numbers are augmented somewhat if the results of the phase 2 study 154-102 are taken into consideration. This dose-ranging study did include a trovafloxacin arm that was dosed at the requested regimen (200 mg qd for 10 days), and was of a randomized, double-blinded design. The Final Study Report for this study includes the following numbers of pathogens in the clinically and bacteriologically evaluable subset of patients at EOS:

**Pathogens eradicated/pathogens isolated
Clinically and Bacteriologically Evaluable Patients at EOS
Study 102**

<i>Streptococcus pneumoniae</i>	2/2
<i>Haemophilus influenzae</i>	4/5
<i>Moraxella catarrhalis</i>	2/2
<i>Klebsiella pneumoniae</i>	6/6

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Even if these additional isolates are included in the tabulation, one is still left with a total of 9 *Moraxella catarrhalis*, 7 *Klebsiella pneumoniae*, 2 *Pseudomonas aeruginosa*, and 6 *Staphylococcus aureus* isolates.

The Divisional Points to Consider document addresses the issue of organism-specific labeling as follows:

- the requested organism must be generally considered to be pathogenic in that indication;

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- the requested organism must represent at least 10% of the evaluable cases OR 10 total (whichever is higher); and
- the eradication rate must be clinically acceptable

When considering other organisms for labeling when they do not meet the '10% rule', the following additional caveats are to be taken into consideration:

- the *in vitro* activity of the drug against the organism is at least similar to that of other pathogens more substantially evaluated in clinical trials;
- the mechanism of resistance is similar to that of other pathogens more substantially evaluated in clinical trials;
- no scientific data exist suggesting differences in the management of infections due to these pathogens more substantially

It is also reasonable to consider related indications that have been studied in separate trials; for example, if there were sufficient evaluable numbers of *Klebsiella pneumoniae* from the nosocomial pneumonia studies (and an acceptable rate of clinical response/bacteriologic eradication), then it might be reasonable to grant this organism in the CAP indication despite the fact that there were only 7 evaluable patients with this organism among the five clinical studies submitted. This, however, is not the case (see the Nosocomial Pneumonia review by Dr. Alivasatos). Since CAP patients with pneumonia due to *Klebsiella pneumoniae* are at risk of developing severe disease, it would seem imprudent to label trovafloxacin for the treatment of this organism with such a relative paucity of accumulated experience in either the CAP or the Nosocomial Pneumonia indications

In the course of discussing the numbers of individual pathogens that were accrued from these studies, the sponsor's numbers were found to be discrepant with those cited above. As the above numbers were taken from the sponsor's own summary tables, it was unclear initially how such discrepancies came about. Following discussion with the sponsor, it was ascertained that the summary tables for each study, which appear in the Final Study Report for each individual CAP study, did not include all evaluable subjects by pathogen. In some (but not all) of these summary tables, those organisms with less than three evaluable isolates at EOS were not included. These small numbers were, however, tallied in the sponsor's table (see Attachment 1 to this portion of the NDA review, entitled "TABLE {CAP.X.2a}: Sponsor Assessment of Clinical Response by Baseline Pathogen") which was presented as a facsimile document during the course of teleconference discussions over the approvability of the CAP indication. A summary of that table will be presented below for the pathogens requested in the product labeling:

Organism	Initial MOC assessment	Revised for sponsor table CAP.X.2a
<i>Chlamydia pneumoniae</i>	9/12 (75%)	12/15 (80%)
<i>Haemophilus influenzae</i>	61/66 (92%)	61/67 (91%)
<i>Klebsiella pneumoniae</i>	7/7 (100%)	9/11 (82%)
<i>Legionella pneumophila</i>	8/11 (73%)	10/13 (77%)
<i>Moraxella catarrhalis</i>	9/9	16/16 (100%)
<i>Mycoplasma pneumoniae</i>	36/40 (90%)	37/40 (93%)
<i>Pseudomonas aeruginosa</i>	2/2	6/9
<i>Staphylococcus aureus</i>	6/6	14/14 (100%)
<i>Streptococcus pneumoniae</i>	88/95 (93%)	88/98 (90%)
Total N evaluable	258	283

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This slight augmentation in numbers brings a few of the requested organisms above the '10' mark, but also serves to increase the denominator and therefore the number required if using the '10% rule' as described in the Points To Consider document.

For the 'typical' (i.e., not 'atypical') pathogens under consideration, the revised numbers presented above do not make any substantive changes. An organism-by-organism discussion follows:

Streptococcus pneumoniae: numbers and outcome are adequate to approve labeling

Haemophilus influenzae: numbers and outcome are adequate to approve labeling.

Moraxella catarrhalis: numbers are borderline (> 10 but < 10% of evaluables) but MIC₉₀ is low (less than *Streptococcus pneumoniae*, against which trovafloxacin is clearly efficacious) and efficacy also demonstrated in other respiratory indications (AECB particularly). Furthermore, disease due to this organism is clinically similar to H. influenzae, for which the sponsor has presented sufficient information. Overall, the medical officer considers this organism appropriate to include in the product labeling for CAP.

Pseudomonas aeruginosa: does not appear to be approvable, since the number (9) remains inadequate.

Klebsiella pneumoniae: again, does not appear to be approvable. Although the revised numbers (11) bring the total isolates above 10, this is still considerably below the 28 that is necessary to meet the '10% rule'. Furthermore, this organism is not approvable in the nosocomial pneumonia indication because the number of evaluable patients was low in this indication as well (see review by Dr. Alivisatos). As an agent of community-acquired lobar pneumonia, this organism is predominantly seen in debilitated, elderly patients with coexisting medical conditions (particularly alcoholism, diabetes, and COPD) which serve to impair normal host respiratory tract defenses. Because of the necrotizing quality of the infection and the debilitated baseline condition of the patients who are predisposed to this disease, mortality is high. (A recent study by Jong et al [*Chest* 107(1): 214-17, Jan '95] of 28 alcoholic patients seen with *Klebsiella pneumoniae* CAP over a three-year period found an overall mortality rate of 64%.) CAP caused by *Klebsiella pneumoniae* is sufficiently severe to warrant the absolute requirement that it be studied in adequate numbers (i.e., 10% or 28 in this situation), in the opinion of the reviewing medical officer.

Staphylococcus aureus: the revised numbers bring the total from 6 to 14 patients, of whom 100% were reported to have a successful outcome (actually 12 cures out of 14). Again, these numbers fall in between the absolute '10' and the number mandated by the 'rule of 10%' (i.e., 28). The MIC₉₀ for this organism is less than that for *S. pneumoniae*, but one dilution greater than that of *Klebsiella pneumoniae*. If this organism appeared to be approvable for a related respiratory indication, this would be of interest; in the nosocomial pneumonia indication, however, the eradication rate was 12/19, or 63%. *S. aureus* was not granted for the sinusitis indication because the sponsor was unable to demonstrate in adequate numbers that this organism was the sole pathogen (rather than a possible colonizer) in this infection. A similar such reevaluation is underway for the AECB indication, in order to determine how many cases of *S. aureus* were accrued in which no co-pathogens were present. Regardless of the outcome of the AECB reanalysis, it is the opinion of this medical officer that the efficacy of trovafloxacin in this situation is not directly applicable to the pneumonia indication. CAP caused by *S. aureus* is adequately severe to warrant the absolute requirement that it be studied in adequate numbers (i.e., 10% or 28 in this situation) such that efficacy has been undisputably demonstrated rather than partially inferred from other respiratory indications. There were a total of 8 trovafloxacin-treated CAP patients who had *S. aureus* isolated as the sole respiratory pathogen; of these, 6 were cured and 2 were improved.

Requested labeling regarding penicillin-resistant *Streptococcus pneumoniae*:

Another issue to be considered in this discussion is the fact that the sponsor has requested wording in the label that reads "... *Streptococcus pneumoniae*, including penicillin-resistant strains...". Despite the robust numbers of *Streptococcus pneumoniae* isolates in the five combined studies submitted in support of this indication, there were not adequate numbers of such resistant isolates studied to warrant such labeling. In Table H.4.5.5 of the NDA, entitled

"Sponsor Defined Clinical Response and Pathogen Outcome of *Streptococcus pneumoniae* by Susceptibility to Penicillin for all Pneumonia Studies (Community Acquired and Nosocomial), End of Treatment Visit, Clinically Intent-to-Treat Subjects"

the sponsor tallies a total of four such patient isolates. Keep in mind that this is the most permissive, all-encompassing analysis possible: the clinically ITT subgroup at the EOT timepoint. Even casting this wide net (and allowing inclusion of all pneumonia studies), a total of 4 such isolates is inadequate to warrant such labeling. It should be noted that the statements made by the sponsor in some of the final study reports for the CAP indication, such as this one from study 112: "All five trovafloxacin subjects who had penicillin-resistant (MIC ≥ 0.1 $\mu\text{g/mL}$) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study" are defining 'resistant' strains as those with MICs that are considered 'intermediate' not 'resistant'. Some authors would define penicillin resistance in *S. pneumoniae* as an MIC of > 2.0 $\mu\text{g/mL}$; others use the breakpoint of > 1.0 $\mu\text{g/mL}$.

As detailed in the microbiologist's review of this NDA, the MIC₉₀ for trovafloxacin appears to be the same *in vitro* against both penicillin-resistant *S. pneumoniae* and penicillin-susceptible *S. pneumoniae*. Thus it may well be that this drug will eventually prove to be clinically efficacious in the management of such infections; at present, however, the data are not adequate in this NDA to support such a labeling claim.

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2. Atypical pathogens

The sponsor has also requested the three major bacterial agents of 'atypical' community-acquired pneumonia: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* (formerly TWAR agent), and *Legionella pneumophila*. Because of the difficulty in reliably culturing these agents from clinical specimens, it has become acceptable to utilize indirect methods of diagnosis to document these infections.

A number of more direct and specific methodologies are currently coming into use to detect the presence of these organisms. These techniques include PCR, radiolabeled nucleic acid probes, and antigen detection methods. With the exception of the urinary antigen detection test for *Legionella*, the sponsor chose to utilize only indirect (antibody-based) methods for diagnosis of these agents.

The following discussion is excerpted from a reference text entitled "Use and Interpretation of Tests in Medical Microbiology", by Dr. James B. Peter (Santa Monica: Specialty Laboratories, Inc., 1990). Because the sponsor has not included any test-specific information in the NDA to determine the exact methodology utilized in the study determinations, this discussion will only be considered as background information:

1. *Chlamydia pneumoniae*: "The best evidence of an acute *C. pneumoniae* infection is a fourfold or greater rise in antibody titers between acute and convalescent samples, and the presence of *C. pneumoniae*-specific IgM by microimmunofluorescence (micro-IF) $\geq 1:16$. A single *C. pneumoniae*-specific IgG titer of $\geq 1:512$ or a single *C. pneumoniae*-specific IgM titer of $\geq 1:16$ is suggestive of acute infection. An IgG titer of $\geq 1:16$ and $< 1:512$ is evidence of past infection."
2. *Mycoplasma pneumoniae*: "EIA is preferred to CF because fourfold rises in CF titers are seen in only about 50% of patients, and because false-positives by CF can be seen in pancreatitis, bacterial meningitis, and other acute inflammatory diseases... Detection by EIA of *M. pneumoniae*-reactive IgM antibodies or demonstration of a significant increase of specific IgG antibodies is strong evidence for recent infection in the appropriate clinical setting. Fourfold increases in titer or fourfold increases AND titers $\geq 1:32$ with CF employing lipid antigen yield sensitivities of 53% and 90%, respectively, in culture-positive *M. pneumoniae* pneumonia."
3. *Legionella pneumophila*: "Direct detection of *L. pneumophila* in respiratory specimens by DFA (sensitivity ~70%, specificity ~97%) or DNA probe (sensitivity ~70%, specificity ~99%) is useful for rapid diagnosis but lacks sensitivity when low numbers of organisms are present. *L. pneumophila* soluble antigen in urine by EIA (sensitivity >70%, specificity ~99%) and RIA (sensitivity 93%, specificity 100%) can be detected within one day of onset of symptoms. The only reliable serological evidence of recent *L. pneumophila* infection is a fourfold rise in titer to a level $\geq 1:128$ between acute and convalescent specimens by IFA or EIA. A single result of $\geq 1:256$ is presumptive evidence of infection."

Given this discussion, several questions arise regarding the sponsor's methodology and interpretation of the tests utilized to diagnose these infections in the CAP studies:

- ◆ Is a fourfold rise of any magnitude sufficient, or does the antibody titer need to rise above a certain level in some of the assays?
- ◆ Is a rise of any antibody class (IgM, IgG, or IgA) acceptable, or are some more sensitive or specific than others?
- ◆ Is it of concern that such tests, which are usually used on individual patients when clinical suspicion warrants, have essentially been employed as screening tests in this patient population? Does such a use of these tests heighten concerns over false positive results?
- ◆ What are we to make of patients who are identified by standard culture techniques with one or more definite respiratory pathogen, in either the sputum or the blood, but who also are found

retrospectively to have a rise in antibody titer that is suggestive of an atypical infection as well? Is the clinical suspicion of the investigator at the time of enrollment worth considering?

The sponsor was queried as to the specific type of assay utilized for each of these diagnostic procedures. The following email responses were transmitted during the course of this review:

Serologies were not done at the sites. All serologies (and legionella urinary antigen) for Legionella and Mycoplasma were done on paired serum samples (baseline and day 30) using their standard assays. Chlamydia titers (also paired)

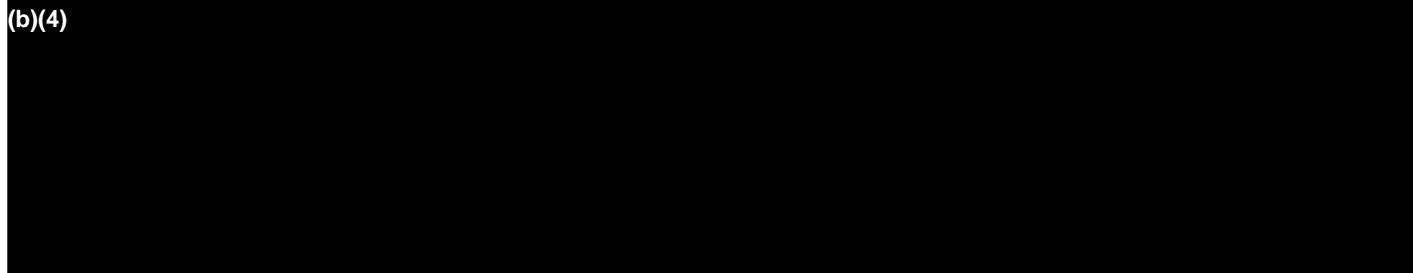
"specialty" assays

Chlamydia pneumoniae titers were done

Legionella titers

Mycoplasma titers were also

(b)(4)



1. Chlamydia pneumoniae

Intended use: "Since either the presence of antibodies to IgM or the detection of a fourfold IgG titer increase is highly diagnostic and indicative of acute or recent infection, it is recommended that both IgG and IgM determinations be performed on all patients suspected of Cp infection."

Prepared slides have wells labeled 'yolk sac', 'C.psittaci', 'C.trachomatis', and 'C.pneumoniae'. These other antigen spots "are provided as an aid to interpretation of the specificity of the C.pneumoniae serological reaction." In other words, this kit is not intended to diagnose C.psittaci infection. In fact, those patients who are claimed to have 'dual infections' probably have a nonspecific antibody and probably should be discounted.

Interpretation: a fourfold rise in antibody titer is highly diagnostic and indicative of active current or recent acute infection.

Limitations: "It is essential that all results from chlamydial serologies must be correlated with clinical history and other data available to the physician."

COMMENTS: The C.psittaci interpretations probably indicate nonspecificity and should be excluded. There is absolutely no mention of IgA; thus, these should be disregarded.

2. Mycoplasma pneumoniae IgG and IgM

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for the presence of circulating IgG and IgM antibodies to M.pneumoniae.
"A fourfold increase in antibody titer is considered diagnostic for a current infection if tested simultaneously" (run as paired sera).

Interpretation: (IgG) Fluorescence at 1:64 but not more than 1:128 = equivocal results.
Fluorescence at 1:128 or higher = active or past infection with M.pneumoniae

(IgM) Fluorescence at 1:8 but not more than 1:16 = equivocal results
Fluorescence at 1:16 or higher = active or recent infection with M.pneumoniae

Performance characteristics: utilizing the following criteria:

Negative: IgG of $\leq 1:32$ and IgM $\leq 1:4$
Borderline: IgG of $\geq 1:128$ and/or IgM of $\geq 1:8$
Positive: IgG of $\geq 1:128$ and/or IgM of $\geq 1:16$

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3. Legionella

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Assay: Detection and quantitation of antibodies to L. pneumophila serogroups 1-6. Polyvalent antiserum detects presence of IgG, IgM, or IgA in test serum that may bind to slide-fixed Legionella organisms.

Interpretation: "Serological evidence of a recent infection with LDB is indicated by a four-fold rise in titer between acute and convalescent sera. The rise in titer must be to $\geq 1:128$ to be considered as evidence of recent infection. A standing or single titer of $\geq 1:256$ is considered presumptive evidence of LDB infection at an undetermined time. Current data indicate that titers of 32 and 64 in the absence of detectable disease are common.

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