MEDICAL OFFICER SUMMARY OF COMMUNITY ACQUIRED PNEUMONIA INDICATON:

Editorial Note: The applicant submitted 5 clinical studies in support of this indication: two uncontrolled studies; three randomized, double-blind, multicenter comparative studies. Each study was reviewed individually by the FDA, and the results of the individual study review follow this summary of safety and efficacy by the FDA. Narratives provided by the applicant summarize pertinent information regarding the individual studies and are quoted in the review. FDA comments are made under the heading of "Medical Officer Comments" and are located throughout the summary narrative provided by the applicant. Medical Officer Comments are italicized for purposes of separating the applicant's statements from the FDA comments. Finally, tables that were duplicated from the applicant's NDA report are referenced as to their location in the NDA by volume and page number.

Executive Summary

Bristol-Meyers Squibb has submitted NDA 21-061 and -062 (oral and intravenous formulation, respectively) to the FDA proposing seven indications. One of the indications, and the subject of this review is Community Acquired Pneumonia (CAP). The proposed dosage is 400 mg daily, orally for 7 to 14 days or iv switched to oral. The following is the indication as it appears in the proposed label:

> **"INDICATIONS AND USAGE**
> TEQUIN is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION.**)"
>
> "**Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (penicillin-susceptible and penicillin-resistant strains), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella pneumophila*."

The following table lists agents approved for Community Acquired Pneumonia and/or pneumonia due to atypical pathogens (eg. M. pneumoniae, C. pneumoniae, L. pneumophila).

Antibiotics Indicated for Community Acquired Pneumonia and/or Pneumonia due to Atypical Pathogens

Antibiotic	Community Acquired Pneumonia Indication	Atypical Pathogens
QUINOLONES:		
Sparfloxacin (Zagam)	Yes	*M. pneumoniae* *C. pneumoniae*
Trovafloxacin (Trovan)	Yes	*M. pneumoniae* *C. pneumoniae* *L. pneumophila*
Grepafloxacin (Raxar)	Yes	*M. pneumoniae*
Levofloxacin (Levaquin)	Yes	*M. pneumoniae* *C. pneumoniae* *L. pneumophila*
Ofloxacin	Yes	----------
MACROLIDES:		
Erythromycin		*M. pneumoniae* *L. pneumophila*
Dirithromycin (Dynavac)	Yes	*M. pneumoniae* *L. pneumophila*
Clarithromycin		*M. pneumoniae* *C. pneumoniae*
Azithromycin (IV only)		*M. pneumoniae* *C. pneumoniae* *L. pneumophila*
CEPHALOSPORINS:		
[redacted]	Yes	----------
Omnicef	Yes	----------

*note: as of this writing grepafloxacin was withdrawn from the market due to cardiac adverse events, and trovafloxacin has been limited to serious pneumonia requiring intravenous therapy in a hospital setting.

The NDA submission included data from 5 clincal studies; 3 controlled (Study 002, 037, 038), 2 open label (003,006). Gatifloxacin was given at a dose of 400 mg daily in each of the studies. Study 037 and 038 included an iv to oral switch, the other studies administered Gatifloxacin orally (Study 002, 003, 006).

Study Number	Study Design	Start-Completion Dates	Number of Subjects	Age (yrs)	Comparator
- 002	Randomized; double-blind, multi-center, Phase III	23Jun97-24Jun98	431	18-97	Clarithromycin 500 mg PO 7-14 days
- 037	Randomized, double-blind, multi-center, Phase III	16Nov97 - 26Jun98	283	18-92	Ceftriaxone 1-2g QD IV ± Erythromycin 0.5-1.0g QID IV with step down to Clarithromycin 500 mg PO BID 7-14 days
- 038	Randomized, double-blind, multi-center, Phase III	6Nov97-11Jun98	417	19-91	Levofloxacin 500 mg QD either PO or IV → PO 7-14 days
- 003	Open-label, Non-controlled, Phase II	18Feb97 - 30Apr98	150	18-92	NONE
- 006	Open-label, Non-controlled, Phase II	12Apr97 - 15Jan98	45	18-76	NONE

The applicant presented several analyses of clinical cure which included an All Treated Patient group, Eligible Patient group, and Evaluable Patient group. The All Treated and Eligible Patient groups represent an intent-to-treat analysis, while the Evaluable Patient group is the per protocol analysis. A Microbiologically Evaluable subgroup, comprised of patients with positive baseline-sputum cultures, was analyzed. This group included cases of community acquired pneumonia due to atypical pathogens diagnosed primarily by serology. The applicant chose the Evaluable Patient Group as their primary analysis group (per protocol analysis) while the FDA considered each of these analyses.

FDA review of the applicant's clinical trials for CAP was in general agreement with assignments and outcome evaluation. In addition the applicant's analyses were verified by the FDA review. Clinical Outcome rates are listed below for each of three clinical subgroups by study.

APPLICANT'S CLINICAL EFFICACY RESULTS BY SUBGROUP

Analysis Population	Gatifloxacin	Comparator	95% Confidence Interval
STUDY 002			
		Clarithromycin	
All Treated Patients (N=431)	82% (177/217)	85% (203/214)	-12.8%, 3.2%
Eligible Patients (N=412)	84% (173/207)	87% (178/205)	-11.7%, 4.4%
Evaluable Patients (N=381)	88% (169/191)	91% (172/190)	-10.1%, 5.1%
STUDY 037			
		Ceftriaxone	—
All Treated Patients (N=287)	73% (102/141)	70% (103/142)	-8.4%, 14.8%
Eligible Patients (N=276)	74% (100/136)	71% (99/140)	-8.5%, 15.0%
Evaluable Patients (N=212)	88% (92/104)	85% (92/108)	-7.6%, 15.3%
STUDY 038			
		Levofloxacin	
All Treated Patients (N=417)	83% (173/209)	88% (183/208)	-13.1%, 2.7%
Eligible Patients (N=400)	89% (168/203)	95% (175/197)	-14.5%, 1.7%
Evaluable Patients (N=350)	90% (154/172)	93% (166/178)	-11.5%, 3.6%
STUDY 003			
All Treated Patients	84% (126/150)	----------	77.1%, 89.5%
Clinically Eligible	84% (113/134)	----------	----------
Clinically Evaluable	89% (109/122)	----------	82.5%, 94.2%
STUDY 006			
All Treated Patients	62% (28/45)	----------	46.5%, 76.2%
Eligible Patients	68% (28/41)	----------	----------
Evaluable Patients	90% (27/30)	----------	73.5%, 97.9%

The clinical cure rates for gatifloxacin in the Evaluable Patient population ranged from 88% to 90% compared to the control group cure rates of 85% to 93%. The FDA performed several sensitivity analyses controlling for enrollment site, global failure rates (failures and relapses), severity of illness, and a conservative loss to follow-up analysis. In general the cure rates in the levofloxacin and clarithromycin treatment groups tended to be higher than those for gatifloxacin. The comparison of gatifloxacin to levofloxacin for the evaluable patient analysis demonstrated a 90% vs. 93% clinical cure rate, respectively. The lower bound of the confidence interval for this comparison (gatifloxacin - levofloxacin) was -11.5%. The applicant had assumed, for purposes of analysis, that the efficacy rates would be in the 80% range when defining the confidence interval for equivalence. In this case, the applicant stated that equivalence would be defined if lower limit of the confidence interval did not exceed -15%. Regarding this bound, where the efficacy rates were in the 90% range, the applicant made no comment. In the past the FDA had recommended the lower bound for the confidence interval of the

difference to be no greater than -10%; however, this recommendation is under reconsideration by the FDA. The overall conclusion regarding the comparison of gatifloxacin to levofloxacin shows that the clinical cure rates are lower than those of levofloxacin, and that a weak equivalence relationship was shown in this study. Gatifloxacin had a somewhat higher cure rate than ceftriaxone.

Overall, the lower limits of the confidence intervals did not exceed -15% in these analyses (where the outcomes were in the 80% range or lower), except for the very conservative loss to follow-up analysis. These analyses reported in the table above supported the overall assessment that gatifloxacin is efficacious for the treatment of community acquired pneumonia. Further, because of the activity to treat pneumonia, these studies are felt to be supportive of the acute exacerbation of chronic bronchitis indication.

Special population analyses did not reveal differences in outcome rates according to age and gender. FDA analysis verified this conclusion and is discussed in more detail in the integrated summary of efficacy. There were slight differences when analyses were done by race. (see integrated summary of efficacy).

Microbiological evaluation was based, for the most part, on clinical response in patients who had a positive baseline sputum culture. The applicant also reported the bacteriologic outcome on a subset of patients comparing baseline cultures to cultures taken at the Test of Cure (TOC) day.

Clinical Response Rate for Specific Pathogens in Microbiologically Evaluable Patients Treated with Gatifloxacin (Total N = 403 patients)

Pathogen	Cure Rate/Number of Patients (%)
Streptococcus pneumoniae	59/85 (81%)
(penicillin-susceptible)	40/46 (87%)
(penicillin resistant isloates)	2/2 (100%)
Haemophilus influenzae	59/62 (95%)
Haemophilus parainfluenzae	31/35 (89%)
Moraxella catarrhalis	26/28 (93%)
Klebsiella pneumoniae	3/3 (100%)
Staphylococcus aureus	33/35 (94%)

There were adequate numbers of patients treated with all of these pathogens except for *Klebsiella penumoniae* and penicillin-resistant *S. pneumoniae*. The cure rates in general were similar for the gatifloxacin treated group and the comparators in the individual treatment trials. The numbers of patients with documented bacteriologic eradication is a smaller subset of the patients presented above. Bacteriologic eradication in paired sputum cultures demonstrated similar success rates for gatifloxacin and comparators.

Atypical pneumonia is a cause of community acquired pneumonia and may be due to the following pathogens: *M. pneumoniae, C. pneumoniae, L. pneumophila.* Definitive

diagnosis based upon culture result is difficult due to the special culture requirements for these pathogens. Past regulatory experience has relied on serology for the diagnosis. In addition, these pathogens comprise a relatively small percentage of the causative agents responsible for community acquired pneumonia. Controversy still exists regarding the diagnostic criteria for *C. pneumonia* because of the nature of the serologic test kits, which may not be able to accurately diagnose acute disease. Diagnosis of L. pneumophila is relatively straightforward if selective BCYE agar is utilized, and Urinary Antigen testing has become more acceptable in the diagnosis of acute disease compared to serologic testing. PCR testing is still experimental; however, it may be highly sensitive depending on the laboratory performing the testing.

Given all of these problems with the diagnosis of these pathogens, the FDA undertook an additional analysis of the cases reported by the applicant. Criteria for serologic diagnosis recommended in the test kits were utilized, which differed somewhat from the applicant's criteria. In addition, cases where other typical pathogens were documented in sputum were rejected by the FDA because of the difficulty in attributing success or failure to either pathogen. The results of the FDA and sponsor analyses are displayed below.

Applicant's Clinical Cure Rates in Microbiologically Evaluable Patients (Studies 002,037,038)

Pathogens	Gatifloxacin	Comparator
M. pneumoniae	50/51 (98%)	48/49 (98%)
C. pneumoniae	32/32 (100%)	27/34 (79%)
L. pneumophila	18/19 (95%)	10/12 (83%)

(Combined rates from controlled trials)

The numbers of patients included in the FDA analysis is less that those included in the applicant's analysis because of the stricter criteria utilized.

FDA Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin (Studies 002,037,038)

	M. pneumoniae	*C. pneumoniae*	*L. pneumophila*
Culture positive or PCR	14*	2	0
Definitive (4X rise in IgG or IgM)	1	4	5
Presumptive (single high titer)	16	14	14
Urinary Antigen	NA	NA	0
TOTAL	31	20	19

*culture proven

All of these patients were clinical cures except for one that was diagnosed with *M. pneumoniae*. In addition, M. pneumoniae was the only pathogen in which cultures were positive. When the "10% rule" is applied to the microbiologically evaluable patient population then 40 cases would be required (see appendix A. page viia). However, from an epidemiological point of view, these pathogens may cause from 2-5% of the community-acquired pneumonia encountered in the population at large. Taking this in to

consideration would allow for between 8-20 cases to be studied in order for these organisms to be included in the label. Based upon the FDA analysis each of these pathogens may be included. Finally, regulatory history shows that for C. pneumoniae and L. pneumophila, inclusion of these pathogens was based solely upon serologic criteria. The approval of Levofloxacin was based upon161 cases of C. pneumoniae and 10 cases of L.pneumophila, Azithromycin IV was based upon 21 cases of C. pneumoniae and 16 cases of L. pneumonphila, Grepafloxacin was not granted the indication for L. pneumophila due to fewer than 10 cases being studied.

APPEARS THIS WAY
ON ORIGINAL

Recommendation:

This medical officer recommends approval of gatifloxacin for the treatment of community acquired pneumonia based upon the review of the clinical study results reviewed in this NDA. This reviewer is in general agreement with the applicant's list of "typical" pathogens (see proposed label above) within this indication with the following exceptions: *S. pneumoniae* (penicillin-susceptible only), delete *Klebsiella pneumoniae*. There is insufficient evidence to support efficacy against penicillin-resistant *S. pneumonia*, or *K. pneumoniae*. For the atypical pathogens, based upon the strict analysis by the FDA and previous regulatory history, this reviewer would recommend that all there of these pathogens be included in the label for CAP. It should not be stated that there was Microbiologic Eradication of these atypical pathogens, even though the definition in the protocol states that this could be based on clinical cure as a presumptive eradication. This study supports the inclusion of these pathogens in the proposed label; however, it is highly recommended that a statement be made regarding the low numbers treated and the method of detecting the pathogen (serology).

APPEARS THIS WAY
ON ORIGINAL

8.1.1 STUDY #AI420002 : A Randomized, Double-blind, Multicenter, Comparative Phase III Study of Oral Gatifloxacin Versus Clarithromycin in The Treatment of Community-Acquired Pneumonia

8.1.1.1 STUDY DESIGN:

OBJECTIVES: To demonstrate efficacy of gatifloxacin in the treatment of community-acquired pneumonia and to compare the safety and efficacy of gatifloxacin at 400 mg PO daily for 7-14 days to a standard regimen of clarithromycin (500 mg PO BID daily for 7-14 days).

METHODOLOGY: Randomized, double-blind, multicenter, prospective, comparative study.

Medical Officer Comment: Note that a dynamic randomization method stratified by center was used in the conduct of this study. Further analysis of the impact of such a process on the efficacy outcome estimate and confidence intervals will be commented on in the Efficacy Section (for a full discussion of this procedure please refer to the statistical review).

STUDY PERIOD: 23 June 1997 to 24 June 1998
CLINICAL PHASE: III.
INVESTIGATORS: Multiple (59).

STUDY CENTERS: 29 centers in the U.S.; 14 centers in Canada; 4 centers in Argentina; 1 center in Australia; 5 centers in South Africa; 4 centers in Mexico; 1 center in Brazil; 1 center in Puerto Rico.

Medical Officer Comment: The majority of patients were enrolled from centers in North America (see below for details).

PUBLICATIONS: None.

PROTOCOL AMENDMENTS:
An amendment, dated October 6, 1997, applied only to investigators in Brazil and excluded from enrollment all women of childbearing potential. A second amendment, dated October 20, 1997, applied only to investigators in the United States and Canada. It clarified the definition of clinical response (i.e., cure, failure, relapse), modified/added exclusion criteria and added pre-treatment oropharyngeal culture and PCR for detection of atypical pathogens. An administrative letter (October 30, 1997)), which applied to all investigators in "other Countries," clarified the definition of clinical response (i.e., cure, failure, relapse) and modified/added exclusion criteria.

Medical Officer Comment: The amendments were a result of discussions held between the applicant and the FDA. While the applicant relied upon serology for the detection of atypical pathogens in the original protocol, FDA recommended culture be performed in order to document a portion of these infections microbiologically.

8.1.1.1.1 DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women, 18 years of age or older, with clinical, laboratory, and radiologic findings suggestive of community-acquired pneumonia likely due to typical (e.g., *S. pneumoniae* or *H. influenzae*) or to atypical (e.g., *M. pneumoniae, L. pneumophila*, and *C. pneumoniae*) pathogens. Clinical evidence of pneumonia must be demonstrated by a new infiltrate(s) on chest x-ray, and two or more of the following: fever (>38°C or 100.4°F); leukocytosis (>10,000 WBC/mm^3 or >15% bands); cough; purulent sputum (>25 PMN and <10 squamous epithelial cells per low power field); chest pain; auscultatory findings such as rales or egophony; chills; headache; malaise.

Medical Officer Comment: Clinical resolution was based on those signs and symptoms listed above. Additional symptoms were collected, however; those listed above were considered to constitute the clinical definition for community acquired pneumonia.

8.1.1.1.2 NUMBER OF PATIENTS: The target enrollment was 376 patients (188 patients in each treatment arm). An attempt to reach the target enrollment in North America alone resulted in a final accrual of 432 patients. Three hundred and sixty (360) were enrolled at 43 sites in North America, including 189 in Canada and 171 in the United States. Seventy two (72) patients were enrolled at 16 sites in "other countries", including 29 patients in Argentina, 29 in Mexico, 10 in South Africa, two in Puerto Rico, one in Australia and one in Brazil. More than half of the patients (53%) were enrolled at eight sites. Twenty-eight sites enrolled less than 4 patients. All but one received at least one dose of study therapy (i.e., All Treated Patients 431).

Medical Officer Comment: It is noteworthy that the difference between number of patients enrolled at a site and number of patients clinically evaluable at that site is small, ranging from 0-3 patients. One center appears to be responsible for the difference in numbers between enrolled patients and clinically evaluable. This suggests that clinical follow-up in this study was good.

Two hundred seventeen (99 female, 118 male) received gatifloxacin, 214 (115 female, 99 male) received clarithromycin.

Medical Officer Comment: The demographic distribution between treatment arms was well balanced for age, gender, race, and weight. Underlying pulmonary conditions were evenly distributed between treatment arms.

8.1.1.1.3 DISTRIBUTION OF PATIENTS:
Eligible Patients: 412 (207 gatifloxacin, 205 clarithromycin).
Clinically Evaluable Patients: 381 (191 gatifloxacin, 190 clarithromycin).
Microbiologically Evaluable Patients: 184 (90 gatifloxacin, 94 clarithromycin).

Definitions:
All Treated Patients: All patients who received at least one dose of study drug.

Clinically Eligible Patients: All treated patients with a diagnosis of community-acquired pneumonia at entry.

Clinically Evaluable Patients: All Eligible Patients who met the minimum dosing requirement of at least 5 days, (at least 3 days for treatment failures), had an end-of-treatment (in the case of failure) or post-treatment assessment (test of cure) in the interval Day +7 to Day +14, and did not receive a systemic antibacterial agent with documented activity against the causative pathogen between the time of the pre-treatment visit and the post-treatment assessment unless to treat a clinical failure.

Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had a bacterial pathogen susceptible to both study drugs isolated from a pre-treatment sputum and/or blood culture, or an atypical pathogen diagnosed by culture, PCR, and/or serology; a sputum Gram stain performed for patients still producing sputum at the Test of Cure Visit, and a sputum culture performed for patients still producing sputum at the Test of Cure Visit if the sample was of good quality (i.e., >25 PMN and <10 epithelial cells).

APPEARS THIS WAY
ON ORIGINAL

Distribution of Patients in Subgroups and Reasons for Exclusion, All Treated Patients Protocol AI420-002

	Number of Patients (%)					
Subgroup/Reason	**Gatifloxacin**		**Clarithromycin**		**Total**	
Treated	217	(100)	214	(100)	431	(100)
Clinically Eligible	207	(95)	205	(96)	412	(96)
Clinically Ineligible	10	(5)	9	(4)	19	(4)
Reason Ineligible						
No Evidence of Pneumonia on Pre-treatment X-ray	9	(90)	9	(100)	18	(95)
No Study Medication given[a]	1	(10)			1	(5)
Clinically Evaluable	191	(88)	190	(89)	381	(88)
Clinically Unevaluable	26	(12)	24	(11)	50	(12)
Reason Clinically Unevaluable						
Patient Clinically Ineligible	10	(38)	9	(38)	19	(38)
Inadequate dosing	9	(35)	6	(25)	15	(30)
No Test of Cure Visit	2	(8)	4	(17)	6	(12)
Other	3	(12)	3	(13)	6	(12)
Concomitant systemic antibiotic given	1	(4)	1	(4)	2	(4)
>1 dose of pre-treatment systemic antibiotic	1	(4)	1	(4)	2	(4)
Microbiologically Evaluable	90	(41)	94	(44)	184	(43)
Microbiologically Unevaluable	127	(59)	120	(56)	247	(57)
Reason Microbiologically Unevaluable						
No pathogen documented	111	(87)	102	(85)	213	(86)
Pathogen Resistant to Study Drug	11	(9)	7	(6)	18	(7)
Clinically Unevaluable	5	(4)	11	(9)	16	(6)

[a] One patient inappropriately classified as ineligible (Reference: Study report vol 2, p.70).

Medical Officer Comment: FDA review of reasons for Clinical Ineligibility via examination of the SAS transport data sets and CRF (case report forms) was generally in agreement with the applicant's table above. The patient who was randomized and never took drug was assigned to gatifloxacin. There was an additional patient in this group who was classified as not having taken any study drug, however, this was incorrect. This patient was given one dose and was lost to follow-up (89-00070) and is listed in the

ineligible population. If the patient was included, they would be considered to be a failure in the all treated analysis, and unable to determine in the clinically evaluable analysis. Two of the patients in the clarithromycin group were listed as not having a baseline CXR (44-00522, 44-00523) (Chest X-ray).

Review of the reasons for Clinical Unevaluability via SAS transport data sets and CRF was generally in agreement with the applicant's table above. Four patients in the clarithromycin arm and two patients in the gatifloxacin arm did not have a Test of Cure Visit. In the "other category" two patients on gatifloxacin and 3 patients on clarithromycin had CXRs beyond day +28 (ranging from day 29 to day 37) (patient # 35-00392, 48-00778, 07-00132, 37-00394, 86-00425). These patients had clinical evaluations which were noted as "cured" within the window, however, the patients were unable to get a CXR until later. As per protocol these patients would be unevaluable. However, all of them, did show clinical resolution and ultimate resolution on CXR (outside the protocol designated window). An analysis counting these patients as cured would not change the overall efficacy outcome results of the study. (see below for additional discussion - Section 8.1.1.1.5)

Review of the reasons for Microbiologically Unevaluable via SAS transport data sets and CRF was generally in agreement with the applicant's table above.

In general, the two treatment groups were balanced with regard to number of patients excluded from various analysis cohorts. Four percent of patients randomized were ineligible, 12 % were clinically unevaluable, and 43% were microbiologically unevaluable for analysis according to the protocol established criteria.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Gatifloxacin tablets, 400 mg PO, Lot numbers N97076, N97025; matching placebo tablets, Lot numbers N97092, N96162. Tablets were supplied in blister cards.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Clarithromycin tablets, 500 mg PO, Lot numbers N97072, N97185; matching placebo tablets, Lot number N97071. Tablets were supplied in blister cards.

8.1.1.1.4 **DURATION OF TREATMENT:** Gatifloxacin, QD x 7 to 14 days; clarithromycin, BID x 7 to 14 days.

EXTENT OF EXPOSURE: The total number of doses and total duration of exposure was comparable across treatment groups. More than 90 % of the patients in both groups received 7 to 14 days of therapy (see table below).

Study Medication Usage, All Treated Patients
Protocol AI420-002

	Number of Patients (%) Gatifloxacin N = (217)[a]		Clarithromycin N = (214)		Total N = (431)	
Number of Doses						
1 - 5	10	(5)	8	(4)	18	(4)
6 - 13	8	(4)	10	(5)	18	(4)
14	10	(5)	16	(7)	26	(6)
15 - 19	16	(7)	7	(3)	23	(5)
20	56	(26)	64	(30)	120	(28)
21 - 27	19	(9)	19	(9)	38	(9)
28	96	(45)	90	(42)	186	(43)
Unknown	2		0		2	
Duration (Days)						
1	4	(2)	3	(1)	7	(2)
2	4	(2)	3	(1)	7	(2)
3 - 6	7	(3)	9	(4)	16	(4)
7	12	(6)	15	(7)	27	(6)
8 - 9	10	(5)	7	(3)	17	(4)
10	60	(28)	65	(30)	125	(29)
11 - 13	16	(7)	16	(7)	32	(7)
14	96	(45)	93	(43)	189	(44)
≥15	6	(3)	3	(1)	9	(2)
Unknown	2		0		2	

[a] Two patients were lost to follow-up and the exact duration of therapy is unknown.(reference vol 2, p 80)

Within each geographic area (North America vs Other Countries), there were no substantial differences between the two treatment groups in the number of doses and duration of dosing. Comparing the two geographic areas, however, a greater percentage of patients from "Other Countries" received 14 days of therapy (61% vs. 41%). Conversely, a greater percentage of patients from North America received seven to 10 days of therapy (43% vs. 24%).

Medical Officer Comment: Seventeen percent of patients enrolled in this study were from "Other Countries". Analysis by geographic area did not reveal any substantial difference in outcome between the two groups.

8.1.1.1.5 CRITERIA FOR EVALUATION:

Clinical and bacteriologic responses were determined from data at the Test of Cure Visit scheduled between Day +7 to Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit between Day +5 and Day +28 inclusive, was acceptable. Treatment failures could be assessed at any time during the treatment and follow-up periods, but patients had to receive a minimum of three days of therapy.

Study Procedures
Protocol A1420-002

Procedure	Pre-treatment (within 48 hrs prior to dosing)	During Treatment (Days 3 to 5)[a]	End of Treatment (Days +1 to +3)[b]	Post-treatment (Days +7 to +14)[a]	Post-study (Days +21 to +28)
Informed Consent	X	-	-	-	-
Inclusion/Exclusion	X	-	-	-	-
Medical History	X	-	-	-	-
Physical Exam[c]	X	X[d]	-	X	-
Vital Signs[e]	X	X	-	X	-
Clinical Signs and Symptoms	X	X	X[f]	X	X
Cultures/subcultures (blood)	X	X[g]	-	X[g]	X[g]
Sputum Evaluation[h]	X	X	-	X	-
Chest X-Ray	X	X[i]	-	X	-
Laboratory Tests	X	X[j]	-	X[j]	-
Serology Test	X[k]	-	-	X	X[l]
Oropharyngeal Swabs[m]	X	-	-	-	-
Pregnancy Test	X	-	-	X	-
Assess Adverse Events	-	X	X	X	X
Assess Study Medication Use	-	X	X	X	-

a Patients discontinuing study therapy prematurely will be evaluated at the time of termination.
b Telephone contact.
c Includes clinical chest exam.
d Chest exam only.
e Vital signs (blood pressure, pulse, respiratory rate, temperature).
f If not clinically improved, the patient was to be scheduled for an office visit for completion of procedures as outlined for the post-treatment visit.
g If clinically indicated, or if previous blood culture was positive.
h Macroscopic evaluation, Gram stain, culture/susceptibility testing if specimen obtained.

i If clinically indicated.

j Must be done. All abnormal laboratory test results should be repeated until they return to pre-treatment levels or are deemed clinically insignificant by the Investigator.

k Including *Legionella* urinary antigen (North America only).

l Serology testing at the Post-Study visit was mandatory at North American sites and mandatory in Other Countries only if post-treatment serologies were inconclusive.

m Two swabs, 1 for PCR (*M. pneumoniae, C. pneumoniae, Legionella sp.*) and *M. pneumoniae* culture, 1 for *C. pneumoniae* culture (North America only).

(Reference: vol 2, p 38)

Medical Officer Comment:

It is of interest to note that the applicant changed the test of cure window from +7 to +14 days to +5 to + 28 days. This was done in an analysis plan submission dated 6/19/98. The Database Lock/Unblinding Date was reported by the applicant to be 10/1/98. FDA and the applicant discussed this change, specifically the concern by FDA that the expanded window may complicate the analysis of relapse and failure. FDA noted that it would be important to indicate how many patients did not come back for follow-up at the later visit (+21-+28 days), in order to assess the relapse evaluation.

The majority of patients were evaluated for Test of Cure during the +7 to +14 day window. Only eleven were evaluated at a later time during the +21 to +28 day window. Nine of these were in the gatifloxacin group (19-00261, 23-00076, 55-00513, 60-00578, 78-00682, 81-00115, 89-341, 92-00477, 115-0005) , 8 of which were considered cures. Two were in the clarithromycin group (60-00577, 115-0006) both of which were considered a cure. These cases either had their CXR but not clinical visit in the first window, or had both CXR and clinical visit at the later follow-up date. FDA feels that it is appropriate to include these in the analysis of TOC. This is apparently why the window was widened.

The applicant supplied additional information regarding the number of patients, designated as cures, who returned for the +21-+28 follow-up visit.

" Of those who were clinically evaluable and were considered cures at the test of cure, 86% (294/341) did have a follow-up visit in this time frame and therefore were evaluable for RELAPSE. Only 47 did not have a +21-+28 day visit, however, this second visit was accomplished at day +14. Of these 47 subjects, eight had no late follow-up and 39 had follow-up visits after DAY +14 but outside of the +21 to +28 window. For 36 of these 39 subjects, this was a late follow-up visit [Day +15 to +20 (16), after day +28 (20)] after an earlier Test-of-Cure visit (+5 to +14 DAY). For three of these subjects this was considered the TOC."

When line listings, provided by the applicant, were reviewed there were 11 patients who had no follow-up (this included the three who used this later visit as the TOC). Seven were in the gatifloxacin group and 3 were in the clarithromycin group. If these were counted as Relapses this would make the overall number of relapses 5% (10/191) in the gatifloxacin group and 3% (3/190) in the clarithromycin group. These are small numbers; however, the rate is almost doubled in the gatifloxacin group. When an overall success/failure outcome is calculated, including failures and relapses, the comparative

outcomes between the groups remains unchanged (see section 8.1.1.2.1 for further discussion)

8.1.1.1.6 OUTCOME EVALUATION:

Clinical Evaluation:

Each patient was assigned a clinical response of Cured, Failure or Unable to Determine.

Medical Officer Comment: *FDA reviewed each of these assignments for outcome. The results of each review are listed in a Medical Officer Comment following the protocol definition for each outcome.*

CURED

- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required, and chest x-ray abnormalities were improved or had not progressed, OR
- All acute signs and symptoms of pneumonia were resolved or improved to a level such that no additional antimicrobial therapy was required, and no during or post-treatment chest x-ray was performed (These patients were not included in the evaluable subset).

Medical Officer Comment: *For all of the "cured" patients who were considered evaluable, signs and symptoms were reviewed via JMP data base for the Test of Cure Day. For the majority of patients that day was within 7-14 days after the end of therapy. The following distribution was seen in symptom response:*

FDA Evaluation of Cured by Clinical Status of Signs and Symptoms

Symptom Response Category	*Number of Symptoms*	*Number of Symptoms Related to CAP*	*Number of Cured Patients with CAP Symptoms*
Resolved	*2526*	*1443*	*348*
Improved	*383*	*324*	*161*
Same	*40*	*19*	*16*
Worse	*2*	*2*	*2*
Unknown	*19*	*9*	*8*
New	*26*	*6*	*4*

**note that the patient category is not mutually exclusive as the patients had two or more signs and symptoms evaluated.*

For the majority of symptoms recorded, the outcome evaluation was Resolved. Further review of the total symptom base revealed a subset of symptoms that defined CAP. The total number of patients with one or more CAP symptom reported to have resolved was 348 or 85% of the clinically eligible population. These symptoms were evenly divided between the treatment groups (gatifloxacin: 48%; clarithromycin: 52%).

As per the definition of cure, all signs and symptoms were to have resolved or improved to such a level that no further antibiotics were needed. As noted in the table, several

patients had CAP symptoms that remained the same, worsened, were of unknown, or were new. Because the TOC window was widened to include the follow-up visit at +21-28 days, review of these patients revealed now further worsening. In addition, other signs and symptoms in the same patient improved or resolved and the CXRs were improved or resolved. Of the2 patients who had symptoms recorded to have worsened, one patient had resolution of all symptoms except malaise (39-00931), and pneumonia on CXR was resolved. The other patient had chest pain at the +7-14 day visit that resolved at the +21-28 day visit. Hence, the FDA reviewer agrees with counting these as cures.

Regarding the issue of cure representing strictly the resolved signs and symptoms versus resolved and improved, the original study design allowed for evaluation of patients at the +7-14 day window and again at the +21-28 day window. This would allow any patient with improved symptoms the opportunity to further resolve or worsen, thus representing a relapse. When the applicant widened the window this made the definition of cure more difficult. As it turned out, most of the patients reported symptoms that resolved and most of the evaluation days were in the earlier window. Therefore, upon review of patients who had symptoms that improved as opposed to resolved, further investigation was undertaken, via CRF review, to ensure that these patients did not relapse at a later date. None of the patients listed with improved symptoms at TOC date went on to become relapses.

Finally, the assignment of cure that was used by the applicant was the one assigned by the applicant and not necessarily that checked off by the clinician at the time of final evaluation. There were only a small number of discrepancies between these assignments. FDA review of these changes was in agreement with the applicant's assignment. This was mostly due to additional data which was available at the time of the applicant's review. For example, there were 5 reassignments to failure by the applicant, 4 in the gatifloxacin group and 1 in the clarithromycin group.

Given the review of the definition of cure and the criteria used in this study, the FDA is satisfied with and accepts the applicant's assignment of cure.

FAILURE

One or more of the following:

- Signs and symptoms relevant to the original infection persisted or progressed after at least 3 days of therapy,
- New pulmonary or extrapulmonary clinical findings consistent with pneumonia developed,
- Radiographic abnormalities progressed,
- Additional antimicrobial therapy was needed for treatment of the pneumonia under study,
- Patient died and death was due to pneumonia.

Reason Clinical Response is Failure,
Clinically Evaluable Patients
Protocol AI420-002

Frequency/Reason	Number of Patients (%) Gatifloxacin N = (191)		Clarithromycin N = (190)		Total N = (381)	
Number of Failures	22	(12)	18	(9)	40	(10)
Persistence/Worsening/New Primary Signs/Symptoms	20	(91)	17	(94)	37	(93)
Worsening of Radiographic Abnormalities	2	(9)	1	(6)	3	(7)

(Reference; Vol.2, p. 96)

Medical Officer Comment: review of the CRFs of the above cases by the FDA is in agreement with the applicant's assignment of failure.

UNABLE TO DETERMINE

Extenuating circumstances which precluded classification as Cure or Failure; for example:

- A Test of Cure evaluation of clinical signs and symptoms was not obtained, or
- Another systemic antibiotic with documented (i.e., according to the package insert) activity against the causative pathogen was administered for an infection other than pneumonia between the pre-treatment and Test of Cure Visits.

Reason Clinical Response Is Unable to Determine,
Clinically Eligible Patients
Protocol AI420-002

Reason	Number of Patients Gatifloxacin N = (207)	Clarithromycin N = (205)	Total N = (412)
Number of Responses Unable to Determine	12	9	21
Adverse event	6	3	9
Inadequate Follow-up	2	4	6
Intercurrent illness	1	1	2
Other Systemic Antibiotic Given for an Infection Other Than Pneumonia	1	1	2
Patient request	1	0	1
Therapy ineffective	1	0	1

(Reference; Vol. 2,p.114)

Medical Officer Comment: *FDA review of SAS files and CRFs verified the above table. Patients with adverse events received generally less that 5 doses of medication and were withdrawn from the study. The number of patients ranked as unable to*

determine is similar between the two treatment groups. Calculation of the efficacy rates would include these patients in the denominator for the rate calculation in the Clinically Eligible analysis, and these patients would be excluded from the Clinically Evaluable analysis.

8.1.1.1.7 MICROBIOLOGICAL EVALUATION:

Each pre-treatment pathogen was assigned a bacteriologic response of Eradicated, Presumed Eradicated, Persisted, Presumed Persisted, or Unable to Determine according to definitions in the protocol. Typical bacterial pathogens such as *S. pneumoniae* were microbiologically evaluable for response only if susceptible to both study drugs. Atypical bacterial pathogens, regardless of diagnostic method, were microbiologically evaluable for response.

Medical Officer Comment: Microbiological Response was based upon clinical response of the patient who had a documented pretreatment pathogen. Thus, the response category of Cure is a clinical one, but when used in the expression Bacteriologic Eradication may connote the impression that the pathogen was demonstrated to be microbiologically eradicated. This leads to confusion when expressing the result for serologically diagnosed atypical pathogens, especially where the documentation of a single high titer made the diagnosis. Therefore, this reviewer recommends the results be discussed as a clinical response based upon a microbiologic diagnosis at entry.

The impact of this syntax will be discussed in the analysis section, and will include critique of the shorthand expression "Bacteriologic" eradication rate, where, especially for the atypical pathogens it is very misleading.

8.1.1.1.8 STATISTICAL METHODS:

Data Sets - There were four groups of interest:

- All Treated Patients: All patients who received at least one dose of study drug.
- Clinically Eligible Patients: All treated patients with a diagnosis of community-acquired pneumonia at entry.
- Clinically Evaluable Patients: All Eligible Patients who met the minimum dosing requirement of at least 5 days, (at least 3 days for treatment failures), had an end-of-treatment (in the case of failure) or post-treatment assessment (test of cure) in the interval Day +7 to Day +14, and did not receive a systemic antibacterial agent with documented activity against the causative pathogen between the time of the pre-treatment visit and the post-treatment assessment unless to treat a clinical failure.
- Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had a bacterial pathogen susceptible to both study drugs isolated from a pre-treatment sputum and/or blood culture, or an atypical pathogen diagnosed by culture, PCR, and/or serology; a sputum Gram stain performed for patients still producing sputum at the Test of Cure Visit, and a sputum culture performed for patients still producing sputum at the Test of Cure Visit if the sample was of good quality (i.e., >25 PMN and <10 epithelial cells).

Efficacy Analyses – The primary efficacy assessment was the clinical response taken at the Test of Cure Visit in the Clinically Evaluable group. Ninety-five percent confidence intervals for the difference between response rates were constructed using an exact method. Intervals were also constructed for the clinical response taken at the Test of Cure Visit in Clinically Eligible Patients and in All Treated Patients. Additional secondary efficacy analyses included clinical cure rate by prognostic factor and by severity of pneumonia for Clinically Evaluable Patients, as well as cure rate and eradication rate by pathogen for Microbiologically Evaluable Patients.

Based on an estimated 80% clinical cure rate for patients with community-acquired pneumonia treated with clarithromycin, 150 evaluable patients per arm would yield 90% power to claim the cure rate for gatifloxacin is at most 15% less than the rate for clarithromycin (α= 0.05, two-sided). Assuming an 80% "evaluable" rate, the necessary sample size was calculated to be 376 patients, 188 patients per treatment arm. By attempting to reach the target accrual in North America alone, however, the predicted sample size was exceeded due to additional patients enrolled from "Other Countries". With 360 patients enrolled in North America and 72 patients enrolled in "Other Countries", the final accrual for this study was 432 patients.

Medical Officer Comment: The All Treated and Eligible subsets would more closely represent the "intent-to-treat" population, while the Evaluable group represented the "per-protocol" analysis. The Microbiologically Evaluable subset represents a highly select group of patients who were evaluable and had a pathogen isolated from the sputum at study entry. All of these analyses will be considered by the FDA.

Safety Analyses – All patients who received at least one dose of study drug were evaluated for safety. Safety data were collected between the first day of study drug treatment and 30 days after the last day of such treatment. Variables included deaths, adverse clinical events, serious adverse clinical events, pregnancy and abnormal laboratory results. All safety data were summarized with descriptive statistics and tabulated.

8.1.1.2 EFFICACY RESULTS:

8.1.1.2.1 Clinical Efficacy:

Among Clinically Evaluable Patients (N=381), the cure rates for gatifloxacin and clarithromycin treated patients were 88% and 91%, respectively (95% C.I. –10.1%, 5.1%). Equivalence was also demonstrated in the Clinically Eligible (84% gatifloxacin, 87% clarithromycin; 95% C.I. -11.7%, 4.4%) and All Treated Patients (82% gatifloxacin, 86% clarithromycin; 95% C.I. –12.8%, 3.2%) populations. Clinical cure rates by relevant prognostic factors were comparable between treatment groups. In Clinically Evaluable Patients with severe pneumonia (N=97), the cure rates for gatifloxacin and clarithromycin-treated patients were 90% and 87%, respectively.

Applicant Clinical Efficacy Analysis

Subgroup	Gatifloxacin	Clarithromycin	Confidence Interval
All Treated Patients	82% (177/217)	85% (203/214)	-12.8%, 3.2%
Eligible Patients	84% (173/207)	87% (178/205)	-11.7%, 4.4%
Evaluable Patients (N=381)	88% (169/191)	91% (172/190)	-10.1%, 5.1%

Medical Officer Comment: In general, the FDA was able to verify the applicant's assessment as described above. However, the FDA performed additional sensitivity analyses. One of the most conservative analyses counted the losses to follow-up as failures in the gatifloxacin group and successes in the clarithromycin group. The 95% confidence intervals for the difference in success rates were somewhat wider with this analysis (-17.5%, -2.5%). The results of this study are not robust for this conservative analysis.

An analysis of more clinical interest is that of global failure, where patients who failed at the "test of-cure" visit or relapsed or had a new respiratory infection would be counted as failures. The 95% confidence interval for the difference in success rates for this analysis in the evaluable subset was -16%, 1.6%. In this study, gatifloxacin had both a slightly larger number of subjects without a follow-up after day +14 and a slightly larger number of subjects with a new respiratory infection than clarithromycin. (For more details please see the statistical review).

In conclusion, the applicant has demonstrated similar, although slightly lower clinical efficacy when compared to clarithromycin for the treatment of community acquired pneumonia.

8.1.1.2.2 MICROBIOLOGICAL EFFICACY:

Clinical Outcome for Microbiologically Documented Infections:
The distribution of pre-treatment pathogens between treatment arms in the Clinically Evaluable Population was comparable and similar to that among All Treated Patients. Approximately 50% of patients had a pre-treatment pathogen isolated. Of these 70% and 68% of patients had a single pathogen documented for gatifloxacin and clarithromycin, respectively.

Among Microbiologically Evaluable Patients (N=184), the cure rate was higher in the gatifloxacin arm (95%) than in the clarithromycin arm (90%) A clinical response of Cure was obtained in nearly all of the gatifloxacin Microbiologically Evaluable Patients from whom one of the principal respiratory pathogens was identified: 92% (12/13) *H. influenzae*, 90% (19/21) *S. pneumoniae*, 100% (3/3) *M. catarrhalis*, 100% (4/4) *S. aureus*. 83% (5/6), *H. parainfluenzae*, 100% (28/28) *M. pneumoniae*, 90% (9/10) *L. pneumophila* and 95% (19/20) *C. pneumoniae*. Cure rates were notably higher in gatifloxacin Microbiologically Evaluable Patients with *H. influenzae* (92% vs. 80%), *M. catarrhalis* (100% vs. 83%), *C. pneumoniae* (95% vs. 82%) and *L. pneumophila* (90% vs. 75%)

Clinical Cure Rate by Pathogen, Microbiologically Evaluable Patients Protocol AI420-002

Pathogen[a]/Subtype	Number Cured/Number Isolated or Documented (%) Gatifloxacin N = (90)		Clarithromycin N = (94)		Total N = (184)	
H. influenzae	12/13	(92)	12/15	(80)	24/28	(86)
Beta Lactamase +	2/2	(100)	3/4	(75)	5/6	(83)
Beta Lactamase -	10/11	(91)	9/11	(82)	19/22	(86)
S. pneumoniae	19/21	(90)	26/26	(100)	45/47	(96)
Penicillin Susceptible	13/15	(87)	21/21	(100)	34/36	(94)
Penicillin Intermediate	4/4	(100)	3/3	(100)	7/7	(100)
Penicillin Resistant	1/1	(100)			1/1	(100)
Penicillin Susceptibility Unknown	1/1	(100)	2/2	(100)	3/3	(100)
M. catarrhalis	3/3	(100)	5/6	(83)	8/9	(89)
Beta Lactamase +	2/2	(100)	4/5	(80)	6/7	(86)
Beta Lactamase -	1/1	(100)	1/1	(100)	2/2	(100)
S. aureus	4/4	(100)	9/10	(90)	13/14	(93)
Methicillin Susceptible	4/4	(100)	7/8	(88)	11/12	(92)
Methicillin Susceptibility Unknown			2/2	(100)	2/2	(100)
H. parainfluenzae	5/6	(83)	11/12	(92)	16/18	(89)
Beta Lactamase +	1/1	(100)	1/1	(100)	2/2	(100)
Beta Lactamase -	4/5	(80)	10/11	(91)	14/16	(88)
Other Gram-positive[b]	10/10	(100)	4/4	(100)	14/14	(100)
Other Gram-negative[c]	4/4	(100)			4/4	(100)
M. pneumoniae	28/28	(100)	31/32	(97)	59/60	(98)
L. pneumophila	9/10	(90)	3/4	(75)	12/14	(86)
C. pneumoniae	19/20	(95)	14/17	(82)	33/37	(89)
Total pathogens	113/119	(95)	114/127	(90)	227/246	(92)

a A patient may have more than one pathogen isolated pre-treatment.

b *S. milleri* 2, *S. pyogenes* 2, *S. viridans* 1, *S. canis* 1, Group C *Streptococcus* 1, S. *mitis* 1, *S. agalactiae* 1, *Enterococcus sp.* 1, *S. epidermidis* 1 (blood), Staphylococcus coagulase negative 1, *P. acnes* 1 (blood), *Propionibacterium sp.* 1 (blood).

c *P. putida* 2, *C. freundii* 1, *Neisseria sp.* 1.

(Reference: Vol 2, p. 107)

Medical Officer Comment:
FDA review of the data base provided by the applicant is in agreement. It should be noted that patients may have more than one pathogen documented at baseline and the above table applies clinical outcomes to each pathogen without deciding on which may be the putative agent causing the CAP (Community Acquired Pneumonia).

In addition, this outcome measure subsets the clinically evaluable patients into a group having a microbiologic diagnosis (culture or serology) at baseline, with CURE being defined clinically. Thus, the oddity of stating that the Atypical Pathogens were eradicated in a microbiologically evaluable patient. Further analyses should be applied to some of these pathogens (see discussion of atypical pathogens below).

There was only one S. pneumoniae penicillin resistant isolate documented in this study and it was considered a clinical cure in the gatifloxacin arm. Evaluation of the Penicillin-Resistant S. pneumoniae pathogen will be considered in the overall summary of CAP, where the opportunity to review additional isolates from the other studies will be viewed.

Bacteriologic Responses in Microbiologically Documented Infections:
For Microbiologically Evaluable Patients, the bacteriologic eradication rate was also higher in the gatifloxacin arm (95%) than in the clarithromycin arm (89%). All isolates of *M. catarrhalis*, *S. aureus* and *M. pneumoniae* were eradicated. All but one of the *S. pneumoniae*, *H. parainfluenzae*, *L. pneumophila* and *C. pneumoniae* isolates were eradicated. All but two of the *H. influenzae* isolates were eradicated, which was superior to the eradication rate in clarithromycin-treated patients with pre-treatment *H. influenzae* (85% vs. 73%).

Medical Officer Comment:
It is of interest to note that the eradication rate which is quoted by the applicant above is comprised of patients with documented eradication (positive culture followed by a negative culture, in the case of culture proven cases) or presumed eradicated (microbiologically evaluable without a follow-up culture obtainable due to lack of productive cough). The majority of these responses "eradicated" were presumed eradication. The types of response were relatively similar between treatment arms. It is important to understand the use of the terms bacteriologic eradication rates, and that in this model it does not have the same stringency that it would in an animal model where confirmation of bacteriologic cure would have a much higher proportion of follow-up tissue culturing performed.

Bacteriologic Response Classification for Microbiologically Evaluable Isolates

	Gatifloxacin	Clarithromycin	
Eradicated	8	5	13
Presumed eradication	105	110	215
Persisted	1	3	4
Presumed Persisted	5	11	16
TOTAL	119	129	248

Based on SAS transport file analysis.

In addition, the atypical pneumonia that were documented were documented by serology for the most part. It is misleading to state that "All but one of the ..... L. pneumophila and C. pneumonia isolates were eradicated". Only M. pneumoniae were reported by culture, and only 14/65 All Treated Patients diagnosed with M. pneumonia had it

documented by culture. For further evaluation of the atypical pathogens please see below.

8.1.1.2.2.1 NEW INFECTIONS:

Forty-five (12%) of clinically evaluable patients experienced new infections, 26 in the gatifloxacin arm and 19 in the clarithromycin arm (see below).

New Infections, Clinically Evaluable Patients
Protocol AI420-002

	Number of Patients		
Infection Type/Diagnosis	Gatifloxacin N = (191)	Clarithromycin N = (190)	Total N = (381)
Number of Patients Reporting Any New Infection[a]	26	19	45
Upper respiratory infection	9	7	16
Vaginal candidiasis/vaginitis/vaginal infection	5	4	9
Sinusitis	5	2	7
Bronchitis	2	1	3
Pneumonia	2	1	3
Oral candidiasis	3	0	3
Bronchiectasis	2	0	2
Viral syndrome/common cold	1	1	2
Dental abscess	0	1	1
Otitis media	1	0	1
Urinary tract infection	0	1	1
Tonsillitis	0	1	1
Influenza A infection	0	1	1
Pharyngitis	1	0	1

[a] Patients may have more than one new infection.
(Reference: Vol.2 , p. 112)

Medical Officer Comment: Review of the patients with "New Respiratory" infections was undertaken utilizing the CRFs and e-submission (electronic-submission). Given the data submitted, the FDA agrees with the applicant that these appear to be new infections, and NOT relapses. However, if the new respiratory infections were counted as failures of therapy, being evenly distributed, there is no change in the overall comparative efficacy of these agents.

8.1.1.2.2.2 RELAPSES:

Three relapses occurred in the study, all in patients who had been treated with gatifloxacin. None were microbiologically confirmed.

Patient (039-927) with a history of recurrent pneumonia (2 episodes within the previous 12 months) presented with mild to moderate pneumonia. No pre-treatment pathogen was identified. A 14-day course of gatifloxacin was administered and on Day +10, signs and symptoms were resolved or improved and chest x-ray was improved. On Day +23, signs and symptoms remained improved compared to pre-treatment, but the chest x-ray showed a 50% residual infiltrate and the patient was treated with levofloxacin (Day +24 to +38).

Patient (074-700) with a history of recurrent pneumonia (1 episode in the previous 12 months) presented with severe pneumonia. Chest x-ray showed a patchy left basilar infiltrate and a left pleural effusion. No pre-treatment pathogen was identified. An 11-day course of gatifloxacin was administered and on Day +15, all signs and symptoms were resolved except for dyspnea which was stable. Chest x-ray was improved, with a persistent left pleural effusion. On Day +27, the patient was hospitalized for recurrent pneumonia and possible left pleural empyema. The patient was treated with antibiotics (unknown) and was discharged on Day +33.

Patient (092-256) with a history of COPD presented with severe pneumonia. Chest x-ray showed a left lower lobe infiltrate. S. agalactiae was isolated from pre-treatment sputum and L. pneumophila serology was positive. A 14-day course of gatifloxacin was administered and on Day +8, signs and symptoms were all resolved. The chest x-ray, however, showed "persistent opacities at the left base compatible with superinfected bronchiectasis". On Day +23, the patient presented with recurrent cough, sputum production, wheezing and rales. A chest x-ray showed worsening opacities at the left base suggesting superinfection bronchiectasis. A local sputum culture grew both S. aureus (gatifloxacin disk = 24mm) and P. aeruginosa (gatifloxacin disk = 0mm). He was ultimately hospitalized on Day +26 and treated with intravenous cloxacillin plus intravenous ceftazidime. A bronchoscopy revealed no evidence of malignancy and bronchoalveolar lavage cultures grew P. aeruginosa and S. maltophilia. He was discharged on Day +39 on oral ciprofloxacin for superinfection bronchiectasis and rehospitalized on Day +49 for the same condition.

Medical Officer Comment: Sensitivity analyses considering these patients as failures did not alter the conclusions regarding the efficacy of gatifloxacin in this study as described above.

8.1.1.2.2.3 RESISTANCE ISSUES:

All pre-treatment typical bacterial respiratory pathogens were susceptible to gatifloxacin: 35 were resistant to clarithromycin. In the Clinically Evaluable Population, 14 patients (8 in the gatifloxacin arm, 6 in the clarithromycin arm) had primary respiratory pathogens that were clarithromycin-resistant. All eight of the gatifloxacin patients were cured. Two clarithromycin patients failed: one was bacteremic with *S. pneumoniae* (which persisted in sputum culture) and the other had *K. oxytoca.* An additional two clarithromycin patients failed in the setting of clarithromycin resistance which developed during therapy (both had *Haemophilus sp.*). Only three clinically evaluable gatifloxacin-treated patients with primary typical respiratory pathogens failed; none of the isolates persisted at the Test of Cure Visit.

Medical Officer Comment: The above applicant's analysis was verified by FDA review of data provided.

8.1.1.2.2.4 ATYPICAL PNEUMONIA:

Atypical pathogens were identified in 56 gatifloxacin-treated patients and in 54 clarithromycin-treated patients (see below). Of these patients, more than two-thirds (74) had a single atypical pathogen identified and no typical pathogen identified. Three gatifloxacin patients had two atypical pathogens identified and no typical pathogen identified. The remaining 33 patients had both typical and atypical pathogens identified.

Atypical Pathogens
Protocol AI420-002

	Number of Patients (%)	
	Gatifloxacin	Clarithromycin
Number of patients with Atypical Pathogen	56	54
Single Atypical Pathogen Only	37	37
M. pneumoniae	18	25
C. pneumoniae	14	10
L. pneumophila	5	2
Two Atypical Pathogens Only	3	0
M. pneumoniae + *C. pneumoniae*	1	0
M. pneumoniae + *L. pneumophila*	2	0
Atypical and Typical Pathogens	16	17
M. pneumoniae + typical(s)	7	7
C. pneumoniae + typical(s)	4	5
L. pneumophila + typical(s)	3	1
C. pneumoniae + *M. pneumoniae* + typical(s)	2	2
C. pneumoniae + *L. pneumophila* + typical	0	1
M. pneumoniae + *L. pneumophila* + typical	0	1

(Reference, vol 2, p 81)

The diagnosis of infection with an atypical pathogen was made by serology alone in the vast majority of cases. Only 14 cultures were positive for atypical pathogens, all of which were M. pneumoniae.

In Microbiologically Evaluable Patients, the overall bacteriologic eradication rate was higher in the gatifloxacin arm (113/119 or 95%) than in the clarithromycin arm (113/127 or 89%). Among major respiratory pathogens, bacteriologic eradication rates were generally higher in the gatifloxacin arm. This was particularly evident in Microbiologically Evaluable Patients with *H. influenzae* (85% vs. 73%), *S. aureus* (100% vs. 90%), *C. pneumoniae* (95% vs. 76%) and *L. pneumophila* (90% vs. 75%).

Medical Officer Comment:
In an FDA analysis similar to that of the applicant, the overall rate of an atypical as a sole pathogen was somewhat lower than reported above (FDA rate 56%). If viewed by pathogen, somewhat less than half of those patients reported to have C. pneumoniae or L. Pneumophila infection had them as their sole pathogen. M. pneumonia was the sole pathogen reported in 63% of those reported to have M. pneumonia.

Microbiologically Evaluable Patients who met the Serologic Criteria for Atypical Pneumonia Pathogen (FDA)

	M.pneumoniae (N=60)	*C.pneumoniae (N=37)*	*L.pneumophila (N=14)*	*TOTAL*
Sole pathogen	*38 (63%)*	*18 (49%)*	*6 (43%)*	*62/111 (56%)*
Atypical + M. pneumoniae	*NA*	*5*	*3*	
Atypical+ C. pneumoniae	*5*	*NA*	*1*	
Atypical+ L. pneumophila	*3*	*1*	*NA*	
Atypical + typical path	*19 (32%)*	*18 (49%)*	*6 (43%)*	
Note: only Atyp+Atyp	*3*	*1*	*1*	

The FDA recommended that the applicant attempt to culture these pathogens as well as diagnose them by serologic methodologies. Only 14 M. pneumoniae were isolated by culture. It is unclear why the reference laboratory was unable to obtain L. pneumophila from sputum culture. Perhaps they did not utilize the selective media. (see appendix)

(Note: complete tables of each atypical pathogen are appended to this study review)

M. Pneumoniae Infections:
Review of M. pneumoniae pathogens reveals one-third of the patients had another "typical" pathogen isolated in culture. Serologic methodology which was used included [redacted] Criteria for diagnosis by the applicant per protocol was as follows:

Mycoplasma pneumoniae case definition (one or more of the following):

- A single IgM indirect fluorescent antibody (IFA) titer of ≥1:16 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A single IgG indirect fluorescent antibody (IFA) titer of ≥1:32 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive oropharyngeal PCR; and/or
- A positive oropharyngeal culture.

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits the applicant was using in these studies. Review of the test kit directions reveal the following discrepancies:

From the Zeus test kit directions for **IgM** provided by the applicant the interpretation/significance is as follows:

- "Fluorescence intensity of greater than +1 at the 1:16 screening dilution: Equivocal Results. Retest at a later date to evaluate the possibility of a seroconversion.
- Florescence intensity of greater than 1+ at 1:32 or higher: ACTIVE or CURRENT INFECTION with M. pneumoniae."

The applicant should have made a distinction between a single high titer which, according to the label should have been ≥ 1:32, and repeat titers with a four-fold rise beginning at 1:16. Many of the IgM titers were < 1:16. Only 4 isolates were diagnosed solely based upon the fact that the initial and repeat titers were only 1:16. These may be false positives.

From the Zeus test kit directions for **IgG** provided by the applicant the interpretation/significance is as follows:

- "Fluorescence intensity of greater than +1 at the 1:32 screening dilution but not more than 1:64: Equivocal Results. PRESENT OR PAST INFECTION with M. pneumoniae.
- Florescence intensity of greater than 1+ at 1:64 or higher: RECENT or PAST INFECTION with M. pneumoniae.

* It is recommended that in the event of borderline interpretations further testing be performed to evaluate the possibility of a later seroconversion."

The applicant should have used the criteria of greater than 1:32 rather than ≥ 1:32. Fourteen of the infections diagnosed as M. pneumonia were based solely upon a titer equal to 1:32. These may not be true infections. The only patient who was classified as a Clinical Failure was diagnosed to have M. pneumoniae based upon repeat IgG titers of 1:32. This patient also had S. aureus isolated from the sputum.

PCR testing is experimental at this time. However, it had good correlation with the M. pneumoniae cultures. All 14 patients with culture positive M. pneumoniae had Positive PCR tests (14/20). Three of the culture negative/PCR positive had "brisk" serologic " responses, and 3 did not.

Overall, the number of infections attributable to M. pneumoniae may be somewhat less than the applicant states, given the above analysis. All of the patients, except one were clinically cured. Therefore, each study drug may be highly efficient in treating this pathogen. OR as the majority of cases of M. pneumonia resolve without treatment it may be difficult to attribute the exact clinical response rate in this circumstance.

Regarding the Bacteriologic response of M. pneumonia, only 14 patients had initial culture positive isolate. Follow-up information on these isolates was not provided by the applicant. Therefore, the only response could be presumed eradicated based upon clinical cure. Because the diagnosis for the majority was made on a serologic basis, it would be inaccurate to describe the pathogen as being eradicated. However, based upon the definition in the protocol one could designate them as being presumed eradicated.

C. pneumoniae:
Review of C. pneumoniae infections reveals that 49% of patients had another typical pathogen isolated in culture. Serologic methodology which was used included PCR, IgM and IgG by IFA. Criteria for diagnosis by the applicant per protocol were as follows:

Chlamydia pneumoniae case definition (one or more of the following):
- A single IgM indirect fluorescent antibody (IFA) titer of ≥1:10 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A single IgG indirect fluorescent antibody (IFA) titer of ≥1:512 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
- A positive oropharyngeal PCR; and/or
- A positive oropharyngeal culture.

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kits the applicant was using in these studies. Review of the test kit directions reveal the following discrepancies:

From the MRL Diagnositics' test kit insert for **IgM** provided by the applicant the interpretation/significance is a follows:
- "IgM endpoint titers of 1:20 and greater are considered presumptive evidence of infection.
- IgM endpoint titers less than 1:20 suggest that the patient does not have a current infection. This may be found in patients with either no history of Chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels."

The applicant should have utilized the level of ≥ 1:20 and not ≥ 1:10 according to the package insert. Utilizing a cut point of ≥ 1:20 would have removed two patients from this analysis, where the diagnosis was based solely on a titer of 1:10.

From the MRL Diagnostics' test kit insert for **IgG** provided by the applicant the interpretation/significance is as follows:
For C. pneumoniae:
- "IgG endpoint titers of ≥ 1:512 and greater are considered presumptive evidence of current infection.
- A single specimen endpoint titer ≥ 1:64 and < 1:512 should be considered evidence of infection at an undetermined time. A second specimen drawn 10 to 21 days after the original draw should be tested in parallel with the first. IF the second specimen exhibits a titer ≥ 1:512 or a four fold increase over that of the initial specimen, current (acute) infection is indicated. Unchanging titers ≥ 1:64 and < 1:512 suggest past infection.
- IgG endpoint titers less than 1:64 suggest that the patient does not have a current infection. This may be found in patients with either no history of Chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. "

The applicant applied the test kit criteria correctly for the IgG.

PCR testing is experimental at this time. In this group of pathogens there were no C. pneumoniae isolated by culture. Only two patients had positive PCR results for C. pneumoniae. Both had significant serologic documentation of the infection.

Overall the number of infections with C. pneumoniae was based solely upon serologic diagnosis. Only 4 patients were designated as clinical Failures (3 in the clarithromycin

group and 1 in the gatifloxacin group). Two patients in each group had typical pathogens isolated as well (one in each treatment group). Gatifloxacin appears to be equally efficacious in treating C. pneumoniae as clarithromycin.

Regarding Bacteriologic response for C. pneumoniae, no cultures were positive for this organism, hence the outcome is based upon the clinical outcome and would be classified as presumed eradicated. It would be inaccurate to describe a bacteriologic response for this pathogen as eradicated.

L. pneumophila:
Review of L. pneumophila infections reveals 43% of the patients had another" typical" pathogen isolated in culture. Serologic methodology which was used included PCR, Combined Titer, and Urinary Antigen Testing. None of the PCR tests were positive and none of the Urinary Antigen tests were positive. Criteria for diagnosis by the applicant per protocol was as follows:

" *Legionella pneumophila* case definition (one or more of the following):
1) A single **IgG/M/A indirect fluorescent antibody (IFA)** titer of ≥1:256 or a four-fold increase or decrease in titer from pre-treatment to post-treatment or final follow-up;
2) A positive urine antigen test;
3) A positive oropharyngeal PCR for *Legionella sp.*; and/or
4) A positive oropharyngeal culture."

These criteria were agreed to by the FDA upon the assumption that these were the recommended criteria of the approved test kit that the applicant was using in these studies. Review of the test kit insert for the combined titer reveals the following:

"A four-fold rise in titer ≥ 1:128 from the acute to the convalescent phase provides evidence of a recent infection with L. pneumophila. A standing or single titer ≥ 256 provides presumptive evidence of infection at an undetermined time. Single titers of less than 256 are not considered evidence of infection."

The criteria the applicant used to evaluate L. pneumophila infection is in agreement with the recommendations in the package insert regarding combined titers.

All of the patients, except one, designated as having L. pneumophila infections met the serologic criteria for presumed infection. One patient had rising titers. Only two patients were designated as to have failed clinically (one in each treatment arm). Both had other typical pathogens isolated from sputum.

Overall, the cure rate was similar between treatment groups. Regarding the Bacteriologic response of L. pneumophila, it can only be based upon serologic diagnosis as none of the cases had a culture proven infection. Thus, according to the protocol the patients could be designated as presumptive eradication. It would be inaccurate to describe the pathogen as being eradicated without culture documentation.

Summary of Efficacy in Atypical Pneumonia Patients:
The overall analysis by the applicant may over represent the number of cases due to atypical pathogens. While serology may be applied to identify potential cases, additional scrutiny is necessary given the uncertainty of the interpretation of test results. The FDA analysis is represented in the table below. Of the cases reported by the applicant, those listed in the table below may represent the cases most likely to have had community acquired pneumonia due to the atypical pathogens listed. The body of evidence required for these pathogens should err on the side of conservatism, especially in the case of L. pneumophila. Legionnaires' Disease has a high mortality rate, and in order to support the inclusion of this pathogen in the proposed label it is important to include well documented cases.

Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin According to Diagnostic Criteria

	M. pneumoniae	*C. pneumoniae*	*L. pneumophila*
Culture positive (PCR)	*8*	*0*	*0*
Definitive (4X rise in IgG or IgM)	*1*	*2*	*1*
Presumptive (single high titer)	*7*	*9*	*11*
Urinary Antigen	*NA*	*NA*	*0*
TOTAL	*16*	*11*	*12*

** note: test kit recommendations for single high titer are used in this analysis, in addition these categories are mutually exclusive (eg. If case is culture positive it is not counted in the serologic category) Also, patients may carry the diagnosis of more than one atypical. Cases may not have another "typical" pathogen isolated in the baseline sputum unless atypical culture was positive or case had definitive serology.*

FDA analysis reveals that cases of atypical pneumonia on the gatifloxacin treatment arm included 16 cases of M. pneumoniae, 11 cases of C. pneumoniae, and 12 cases of L. pneumophila pneumonia, which were documented according to strict criteria. All of these cases were considered clinical cures. As is noted in the table above, most of these infections were diagnosed upon the basis of a single high titer.

It is difficult to evaluate the true efficacy of gatifloxacin with regard to atypical pneumonia cases that were only documented by serology. M. pneumoniae has a clinical course that is somewhat different that C. pneumoniae and L. pneumophila. It may take a month or two for the symptoms to resolve even with treatment. A prospective study of each individual disease entity would be most informative with regard to efficacy. Culture is still the gold standard.

Given the data presented by the applicant and the problems inherent in diagnosis by serology, it appears that gatifloxacin is active against these pathogens.

8.1.1.3 SAFETY RESULTS:

8.1.1.3.1 Overall and Related Adverse Clinical Events:

Overall, three hundred twenty-three (75%) patients experienced one or more adverse clinical events. All adverse clinical events (77% gatifloxacin, 73% clarithromycin) and drug-related adverse clinical events (41% clarithromycin, 37% gatifloxacin) were comparable between the two treatment groups. Of note, drug-related gastrointestinal adverse events, such as taste perversion (11% vs. 7%), diarrhea (13% vs. 7%) and abdominal pain (5% vs. 1%), were more common in the clarithromycin group. The incidence of drug-related dizziness (4% gatifloxacin, 3% clarithromycin) and headache (3% in both groups) was comparable. For further information please see applicants tables below.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Adverse Clinical Events of All Causes by Relationship to Study Medication, All Treated Patients
Protocol A1420-002

	Number of Patients (%) Gatifloxacin N = (217)								Clarithromycin N = (214)							
Adverse Clinical Event	Related		Unknown Relationship		Not Related		Total		Related		Unknown Relationship		Not Related		Total	
Any Adverse Clinical Event	81	(37)	1	(<1)	84	(39)	166	(76)	88	(41)			69	(32)	157	(73)
Abnormal breath sounds	2	(<1)			38	(18)	40	(18)	3	(1)			37	(17)	40	(19)
Headache	7	(3)	1	(<1)	20	(9)	28	(13)	6	(3)			14	(7)	20	(9)
Increased sputum	1	(<1)			27	(12)	28	(13)	3	(1)			15	(7)	18	(8)
Nausea	19	(9)			8	(4)	27	(12)	17	(8)			6	(3)	23	(11)
Cough					24	(11)	24	(11)	1	(<1)			23	(11)	24	(11)
Diarrhea	14	(6)			6	(3)	20	(9)	27	(13)	1	(<1)	5	(2)	33	(15)
Pharyngitis	4	(2)	2	(<1)	13	(6)	19	(9)	2	(<1)			15	(7)	17	(8)
Pain, chest	2	(<1)	1	(<1)	15	(7)	18	(8)					20	(9)	20	(9)
Taste perversion	14	(6)			3	(1)	17	(8)	24	(11)			4	(2)	28	(13)
Dyspnea					16	(7)	16	(7)	1	(<1)			15	(7)	16	(7)
Vomiting	7	(3)	1	(<1)	6	(3)	14	(6)	7	(3)			2	(<1)	9	(4)
Rhinitis	1	(<1)			12	(6)	13	(6)					13	(6)	13	(6)
Pain	1	(<1)	1	(<1)	9	(4)	11	(5)	4	(2)			5	(2)	9	(4)
Dizziness	9	(4)			2	(<1)	11	(5)	6	(3)			3	(1)	9	(4)
Malaise					10	(5)	10	(5)	1	(<1)			12	(6)	13	(6)

Indication: Community Acquired Pneumonia (Study 002)
Revision Date: 22-Nov-99

Adverse Clinical Event	Number of Patients (%) Gatifloxacin N = (217) Related		Unknown Relationship		Not Related		Total		Clarithromycin N = (214) Related		Unknown Relationship	Not Related		Total	
Asthenia	2	(<1)			7	(3)	9	(4)	1	(<1)		7	(3)	8	(4)
Pain, back					8	(4)	8	(4)	2	(<1)		7	(3)	9	(4)
Pain, abdomen	3	(1)			5	(2)	8	(4)	10	(5)		5	(2)	15	(7)
Insomnia	2	(<1)	2	(<1)	4	(2)	8	(4)	5	(2)		3	(1)	8	(4)
Asthma	1	(<1)	2	(<1)	4	(2)	7	(3)				2	(<1)	2	(<1)
Hyperventilation					7	(3)	7	(3)				8	(4)	8	(4)
Vaginitis	4	(2)	1	(<1)	2	(<1)	7	(3)	4	(2)		1	(<1)	5	(2)
Flu syndrome					6	(3)	6	(3)				5	(2)	5	(2)
Infection	2	(<1)			4	(2)	6	(3)				4		4	(2)
Pneumonia					6	(3)	6	(3)	1	(<1)		2	(<1)	3	(1)
Rash	3	(1)	2	(<1)	1	(<1)	6	(3)	1	(<1)		2	(<1)	3	(1)
Constipation	1	(<1)			4	(2)	5	(2)	4	(2)		4	(2)	8	(4)
Dyspepsia	1	(<1)			4	(2)	5	(2)	1	(<1)		3	(1)	4	(2)
Sweating	1	(<1)			2	(<1)	3	(1)	1	(<1)		6	(3)	7	(3)

a All adverse clinical events occurring in >2% of the total number of treated patients.
(Reference: Vol 2, p. 118-120)

Drug-Related Adverse Clinical Events by Severity of Event, All Treated Patients
Protocol A1420-002

Adverse Clinical Event[a]	Number of Patients (%) Gatifloxacin N = (217)								Clarithromycin N = (214)							
	Mild		Moderate		Severe		Very Severe	Total	Mild		Moderate		Severe		Very Severe	Total
Any Related Adverse Clinical Event	45	(21)	28	(13)	8	(4)		81 (37)	49	(23)	30	(14)	8	(4)	1 (<1)	88 (41)
Nausea	9	(4)	10	(5)				19 (9)	11	(5)	5	(2)	1	(<1)		17 (8)
Diarrhea	10	(5)	4	(2)				14 (6)	17	(8)	8	(4)	2	(<1)		27 (13)
Taste perversion	9	(4)	2	(<1)	3	(1)		14 (6)	20	(9)	4	(2)				24 (11)
Dizziness	7	(3)	1	(<1)	1	(<1)		9 (4)	6	(3)						6 (3)
Headache	3	(1)	4	(2)				7 (3)	3	(1)	2	(<1)			1 (<1)	6 (3)
Vomiting	4	(2)	3	(1)				7 (3)	3	(1)	3	(1)	1	(<1)		7 (3)
Pain, abdomen	2	(<1)	1	(<1)				3 (1)	3	(1)	6	(3)	1	(<1)		10 (5)

[a] All adverse clinical events occurring in >2% of the total number of treated patients.
(Reference: vol. 2, p. 122)

Medical Officer Comment:
FDA review of the safety data provided by the applicant in the SAS transport files and CRFs is in agreement with the applicant's analysis. It is of interest to note less commonly occurring events of interest such as dizziness and insomnia. Both are seen in similar rates between the two treatment groups. The within the Nervous System events of interest were events of dizziness, tremor, shaking or seizure. Review of dizziness did not reveal abnormal glucose as the underlying reason. The one patient listed as having severe dizziness was reported to be having an anxiety attack. Regarding seizures, there was only one patient in the gatifloxacin arm reported with a seizure who had a preexisting diagnosis of Down's Syndrome and was on neuroleptics for anxiety. One elderly woman on the gatifloxacin arm had tremors pre-existing and was discontinued because of anxiety and shakiness. Review of the Gastrointestinal System focused on liver abnormalities and pancreatitis. Only 4 patients were reported to have liver adverse events, two in each treatment group. Three had a history of alcohol abuse, and one patient in the gatifloxacin group, graded severe hepatitis, was discovered to have cancer metastases in the liver. No adverse events of pancreatitis were reported. Review of the Cardiovascular System did not reveal any overall differences between treatment groups. There were reports of arrythmias in each treatment group (5 patients in gatifloxacin group, 5 patients in the clarithromycin group). One patient in the clarithromycin group died with AV block. None of the patients in the gatifloxacin group were reported to have ongoing cardiac events. No evidence of tendon ruptures was reported among these study patients.

8.1.1.3.2 Discontinuation due to Adverse Clinical Event:
Fourteen patients in the gatifloxacin arm and eleven patients in the clarithromycin arm discontinued study therapy because of an adverse event or laboratory abnormality. Ten of the gatifloxacin discontinuations and five of the clarithromycin discontinuations were felt to be related to study drug. Gastrointestinal symptoms such as nausea, vomiting and diarrhea were among the most frequent reasons for discontinuation (six gatifloxacin-treated patients and four clarithromycin-treated patients).

Medical Officer Comment:
FDA review of the safety data provided by the applicant in the SAS transport files and CRFs is in agreement with the applicant's analysis. Of interest are the less frequent reasons for discontinuation. An 83 year old male in the gatifloxacin group discontinued study medication due to aggressive behavior, agitation, confusion and hypoglycemia. The patient was also receiving diabeta 5 gm daily and may not have been eating, the investigator reported this as not related to study drug. A 47 year old male in the clarithromycin arm was discontinued due to anxiety and audio hallucinations.

8.1.1.3.3 Serious Adverse Events and Deaths:
Twenty-three patients experienced serious adverse events (SAE) on study, only four of which were felt by the Investigator to be study-drug related (3 gatifloxacin, 1 clarithromycin). Pneumonia and carcinoma, each occurring in seven patients, were the most frequently noted.

One death occurred within 30 days of end of treatment and 3 deaths occurred beyond this point; all four were in clarithromycin-treated patients though none were pneumonia- or drug-related.

Medical Officer Comment:
FDA review of the safety data provided by the applicant in the SAS transport files and CRFs is in agreement with the applicant's analysis.

8.1.1.3.4 Laboratory Abnormalities:
In patients with normal pre-treatment laboratory values, decreased bicarbonate, decreased hemoglobin and elevated transaminases (i.e., ALT, AST) were the during- or post-treatment abnormalities most frequently noted in both groups. Nine patients (6 clarithromycin, 3 gatifloxacin) developed a Grade 3 abnormality and only one patient, treated with clarithromycin, developed a Grade 4 abnormality. In patients with abnormal pre-treatment laboratory values, the majority worsened only to Grade 2. Six patients in each arm worsened to Grade 3 and one patient, treated with clarithromycin, worsened to Grade 4

Abnormal Laboratory Test Values During or Post-Treatment in Patients with Normal Pre-treatment Values, All Treated Patients
Protocol A1420-002

	Number of Patients (%) Gatifloxacin N = (217)							Clarithromycin N = (214)						
Laboratory Test	N[a]	Grade 1		Grade 2		Grade 3	Grade 4	N[a]	Grade 1		Grade 2		Grade 3	Grade 4
Hemoglobin	151	25	(17)					159	26	(16)				
WBC	190	11	(6)	1	(<1)			185	9	(5)	2	(1)		
Neutrophils	190	13	(7)	6	(3)			186	11	(6)	4	(2)	1 (<1)	
Platelets	173	6	(3)					176	3	(2)				
Alkaline Phosphatase	165	8	(5)					166	8	(5)				
AST	168	14	(8)	1	(<1)	1	(<1)	168	21	(13)	1	(<1)		
ALT	173	18	(10)	2	(1)			173	23	(13)			1 (<1)	
Total Bilirubin	177			9	(5)			173			7	(4)	1 (<1)	
BUN/Urea	186	8	(4)					185	7	(4)				
Creatinine	190	4	(2)					192	3	(2)				
Glucose decrease (fasting)	12							8	1	(13)				
Amylase	190	5	(3)	1	(<1)	1	(<1)	188	4	(2)			1 (<1)	
Hyponatremia	168	5	(3)					165	5	(3)				
Hypernatremia	168	16	(10)					165	6	(4)			1 (<1)	
Hypokalemia	186	1	(<1)	1	(<1)			187	8	(4)				
Hyperkalemia	186	2	(1)	1	(<1)			187			1	(<1)		

Indication: Community Acquired Pneumonia (Study 002)
Revision Date: 22-Nov-99

	Number of Patients (%) Gatifloxacin N = (217)								Clarithromycin N = (214)							
Laboratory Test	N[a]	Grade 1		Grade 2		Grade 3		Grade 4	N[a]	Grade 1		Grade 2		Grade 3		Grade 4	
Hypochloremia	187								185	2	(1)	4	(2)				
Hyperchloremia	187	3	(2)			1	(<1)		185	5	(3)	1	(<1)			1	(<1)
Decreased Bicarbonate	123	29	(24)	1	(<1)				118	22	(19)	3	(3)	1	(<1)		
Increased Bicarbonate	123	9	(7)	1	(<1)				118	5	(4)	2	(2)				

[a] For each test, number of patients with a normal pre-treatment value who had at least one during or post-treatment value determined.
(Reference: Vol. 2, p. 133-134)

Worsened Laboratory Test Values During or Post-treatment in Patients with Abnormal Pre-treatment Values, All Treated Patients: Protocol A1420-002

	Number of Patients (%) Gatifloxacin N = (217)						Clarithromycin N = (214)					
Laboratory Test	N[a]	Worsened to Grade 2		Worsened to Grade 3		Worsened to Grade 4	N[a]	Worsened to Grade 2		Worsened to Grade 3		Worsened to Grade 4
Hemoglobin	44	2	(5)				30	1	(3)			
WBC	5	1	(20)				4					
Neutrophils	3	1	(33)				2					
Platelets	21			1	(5)		12	1	(8)			
Alkaline Phosphatase	30	1	(3)				29	2	(7)			
AST	29	1	(3)				28			1	(4)	
ALT	26	1	(4)				22	1	(5)	1	(5)	
Total Bilirubin	18			4	(22)		21			1	(5)	
Creatinine	10						7	1	(14)			
Glucose Increase (fasting)	5	1	(20)	1	(20)		8	1	(13)			
Hyponatremia	31						34	1	(3)			
Hypernatremia	31						34					
Hypochloremia	11						11	1	(9)			
Decreased bicarbonate	46	2	(4)				55	4	(7)	2	(4)	
Increased bicarbonate	46						55	1	(2)	1	(2)	1 (2)

[a] For each test, number of patients with an abnormal pre-treatment value who had at least one during or post-treatment value determined.
(Reference: Vol. 2, p. 136-137)

Indication: Community Acquired Pneumonia (Study 002)
Revision Date: 22-Nov-99

Medical Officer Comment:
As stated above, the patients with abnormal liver function tests had underlying histories of alcohol abuse and other complicating factors. Of the patients with normal baseline liver functions 11 in the gatifloxacin treatment group had a rise in the total bilirubin (1.1-1.6 x ULN) compared to 9 patients in the clarithromycin treatment group (1.1-1.8 x ULN). Only two of these patients had corresponding increases in the AST/ALT in the gatifloxacin group vs. 2 patients in the clarithromycin group. Considering AST/ALT at 2 times the upper limit of normal, only 2 patients in the gatifloxacin group compared to 6 patients in the clarithromycin group fit this category. None of those patients had a concomitant abnormality in total bilirubin. Most of these elevations were mild, and the one extreme value was from a patient with liver metastasis. The liver function abnormalities resolved without further problems. These abnormalities appear to be similar for both treatment groups. Clarithromycin has a large post-marketing experience and has not been found to be an hepatotoxin.

Hypoglycemia was looked for within the applicant's data base. The applicant only reported fasting glucose values. Of the study patients only 92 patients had fasting glucose values reported while on study medication (47 in the gatifloxacin group, 45 in the clarithromycin group). Only 4 of these patients were reported to be hypoglycemic (1 in the gatifloxacin group, 3 in the clarithromycin group). None of these patients had a history of diabetes mellitus nor were any on insulin or oral hypoglycemic agents. The values recorded were 61-68. None of these patients were hospitalized and none had their study medications discontinued. There were equal numbers of patients reported to have elevated amylases in both treatment groups. None of these patients had their medications discontinued because of these abnormal values, nor were any diagnosed as having pancreatitis.

8.1.1.3.5 Medical Officer Safety Summary:
The most frequent adverse events were related to the gastrointestinal system, excluding those which may be related to pneumonia. The rates were similar when gatifloxacin was compared to clarithromycin in this study. Numerically, nausea and diarrhea were reported less frequently in the gatifloxacin treatment group as compared to the clarithromycin treatment group. There was a similar discontinuation rate for adverse events between the gatifloxacin and clarithromycin groups. Of the 4 deaths which occurred in this study (3 at > 30 days after study treatment), all of them were in the clarithromycin treatment group. Laboratory abnormalities were similar between treatment groups. For the most part liver function abnormalities were few and of mild severity. Only two patients in each treatment group, who enrolled with normal liver function tests, had abnormal post treatment values which included the combination of AST/ALT and Total Bilirubin. These were mild and did not cause any clinical symptoms.

There were no drug class related events reported in this study including phototoxicity, tendon rupture, seizures, hypoglycemia, HUS or torsades de point.

Gatifloxacin appears to be equally well tolerated in comparison to clarithromycin in the treatment of Community Acquired Pneumonia patients.

8.1.1.4 OVERALL CONCLUSIONS:

APPLICANT'S CONCLUSIONS: The results of this study demonstrate that gatifloxacin, given at a dose of 400 mg PO once daily for seven to 14 days, is comparable to a regimen of clarithromycin 500 mg PO twice daily for seven to 14 days, when given for the empiric treatment of community-acquired pneumonia due to typical and atypical bacterial respiratory pathogens. Gatifloxacin offers several advantages, including once daily dosing, more favorable safety profile and more reliable activity against resistant bacterial respiratory pathogens. (DATE OF REPORT: 10-Dec-1998).

MEDICAL OFFICER SUMMARY OF EFFICACY AND SAFETY OF STUDY 002:

This double-blind, randomized, controlled study demonstrated the efficacy of gatifloxacin, given at a dose of 400 mg PO once daily for 7 to 14 days was comparable to the regimen of clarithromycin 500 mg PO twice daily for 7 to 14 days. The cure rates were somewhat lower for the gatifloxacin group in comparison to the clarithromycin treated group (88% vs 91%, respectively in the clinically evaluable patients [C.I. -10.1%, 5.1%]). The difference between the two treatment groups was slightly larger when the "all treated" or "eligible" populations were evaluated; however, the lower limit of the confidence intervals was above -15%. The patients in this study were treated as outpatients, thus, having potentially milder forms of pneumonia.

Applicant Clinical Efficacy Analysis

Subgroup	Gatifloxacin	Clarithromycin	Confidence Interval
All Treated Patients	82% (177/217)	85% (203/214)	-12.8%, 3.2%
Eligible Patients	84% (173/207)	87% (178/205)	-11.7%, 4.4%
Evaluable Patients (N=381)	88% (169/191)	91% (172/190)	-10.1%, 5.1%

With regard to microbiologically documented infections, as would be expected in a pneumonia study, slightly more than half of the patients enrolled did not have a baseline pathogen identified in the sputum. Adequate numbers of *S. pneumoniae and H. influenzae* were successfully treated in this study, supporting the proposed label. *M. catarrhalis, S. aureus*, and *H. parainfluenzae* were not represented in adequate numbers, and will have to be considered in total, across all of the CAP studies.

APPEARS THIS WAY

FDA Breakdown of Atypical Pneumonia Cases Treated with Gatifloxacin According to Diagnostic Criteria

	M. pneumoniae	C. pneumoniae	L. pneumophila
Culture positive (PCR)	8	0	0
Definitive (4X rise in IgG or IgM)	1	2	1
Presumptive (single high titer)	7	9	11
Urinary Antigen	NA	NA	0
TOTAL	16	11	12

* note; test kit recommendations for single high titer are used in this analysis, in addition these categories are mutually exclusive (eg. If case is culture positive it is not counted in the serologic category) Also, patients may carry the diagnosis of more than one atypical. Cases may not have another "typical" pathogen isolated in the baseline sputum unless atypical culture was positive or case had definitive serology.

Atypical pneumonia was diagnosed by serology for the most part. According to the applicant, *M. pneumoniae* was isolated in culture from 14 patients, all of these patients had a successful clinical outcome. There were 10 patients diagnosed with *L. pneumophila*, primarily by single high titer, treated with gatifloxacin, all of which were considered clinical successes. *C. pneumoniae* was diagnosed by serology, again many of these patients were diagnosed based on single high titer. However, 19 of 20 patients were considered clinical cures. FDA analysis of diagnostic criteria excluded cases where other typical pathogens were also documented in the baseline sputum. While it is important to document clinical activity to all potential pathogens involved in community acquired pneumonia, the diagnosis of atypical pneumonia remains problematic. It should not be stated that there was Microbiologic Eradication of these atypical pathogens, even though the definition in the protocol states that this could be based on clinical cure as a presumptive eradication. This study supports the inclusion of these pathogens in the proposed label; however, it is highly recommended that a statement be made regarding the low numbers treated and the method of detecting the pathogen (serology).

The safety profile of gatifloxacin was similar to that of clarithromycin at 500 mg bid. It appeared that gatifloxacin was tolerated slightly better than clarithromycin regarding the gastrointestinal side effects. Liver function abnormalities did occur in both treatment groups at a low level, and to a mild degree. No significant clinical effects were a result of these changes. In addition, these changes may be, in part, due to the underlying pneumonia. No quinolone class adverse events were reported in this study: seizures, phototoxicity, tendon rupture, hypoglycemia, HUS or torsades de pointe.

APPENDIX A

Atypical Pathogen Serologic Data

* indicates culture positive cases of *M. pneumoniae*

Where serologic results are unchanged from the pre- value, only one value is listed.
Where a pre- or post- test was not performed it is listed as ND.

APPEARS THIS WAY
ON ORIGINAL

5 ***pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.***

8.1.2 STUDY # AI420-037: A Randomized, Double-Blind, Multicenter, Comparative Phase III Study Of Gatifloxacin Versus Ceftriaxone In The Treatment Of Community-Acquired Pneumonia Requiring Hospitalization.

8.1.2.1 STUDY DESIGN:

OBJECTIVES: To demonstrate the safety and efficacy of gatifloxacin (400 mg IV daily +/- step-down to 400 mg po daily) in the treatment of community-acquired pneumonia requiring hospitalization; and to compare the safety and efficacy of gatifloxacin 400 mg IV daily (+/- step-down to gatifloxacin 400 mg po daily) to a standard regimen of ceftriaxone 1 or 2 gm IV daily with or without erythromycin 0.5 or 1 gm IV every 6 hours (+/- step-down to clarithromycin 500 mg po twice daily) administered for a period of 7 to 14 days in the treatment of adults with community-acquired pneumonia requiring hospitalization. Step-down to oral therapy was permitted at the discretion of the clinician at the end of 2 days of IV(intravenous) treatment.

METHODOLOGY: Randomized, double-blind, multicenter, prospective, comparative study.

Medical Officer Comment: Note that a dynamic randomization method stratified by center was used in the conduct of this study. Please refer to Statistical Review for full discussion of this issue.

CLINICAL PHASE: III.
STUDY PERIOD: 16-November-1997 to June 26, 1998.
INVESTIGATORS: Multiple (45).
STUDY CENTERS: 44 centers in the U.S. and 1 center in Canada.
PUBLICATIONS: None.

PROTOCOL AMENDMENTS:
There was one amendment to the protocol, which applied to all investigators. It clarified the inclusion/exclusion criteria; clarified the dosing of IV erythromycin; revised the pre-treatment studies to include additional tests for the detection of atypical pathogens; changed the nature of the post-study assessment; clarified the definition of Clinical Failure: corrected the concentration of gatifloxacin intravenous solution; clarified procedures to be done at the investigative site vs. the central lab; corrected the infusion time of ceftriaxone; clarified the statistical analyses to be performed; and clarified when pharmacokinetic samples were to be collected and the shipping address.

Medical Officer Comment: These amendments were a result of discussions held between the applicant and the FDA. While the applicant relied upon serology for the detection of atypical pathogens in the original protocol, FDA recommended culture be performed in order to document a portion of these infections microbiologically.

8.1.2.1.1 DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women, 18 years of age or older, newly hospitalized (<24 hours) with clinical, laboratory, and radiologic findings suggestive of community-acquired pneumonia likely due to typical (e.g., *S. pneumoniae* or *H. influenzae*) or atypical (e.g., *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*) pathogens.

Clinical evidence of pneumonia was to be demonstrated by a new infiltrate(s) on chest x-ray, and two or more of the following: fever (>38° C or 100.4°F taken orally, >38.5°C or 101.2°F taken tympanically, or >39°C or 102.2°F taken rectally); leukocytosis (>10,000 WBC/mm^3 or >15% bands); cough; chest pain; purulent sputum (>25 PMN and <10 squamous epithelial cells per low power field); transtracheal aspirate, bronchial brushings, or biopsy material with Gram stain revealing neutrophils, and a predominant pathogen suspected by smear; direct lung aspirate with identification of a predominant pathogen on Gram stain; auscultatory findings such as rales or egophony.

Medical Officer Comment: Clinical resolution was based on those signs and symptoms listed above. Additional symptoms were collected, however; those listed above were considered to constitute the clinical endpoint definition for CAP.

8.1.2.1.2 NUMBER OF PATIENTS: A minimum enrollment of 376 patients, with target enrollment of 188 patients in each treatment arm. The accrual was stopped early because it was felt that the objectives of the study had been met. Total enrollment: 287 patients: all but four received at least one dose of study therapy (i.e., All Treated Patients 283).

One hundred forty-one patients (79 female, 62 male) received gatifloxacin and 142 (65 female, 77 male) received ceftriaxone.

Demographics: The median age was 66 years in the study, slightly more females were enrolled into the gatifloxacin group (56% vs 46%), and there were more Blacks in the ceftriaxone group (21% vs 12%). Otherwise the groups were well balanced.

Prognostic Factors, All Treated Patients
Protocol AI420-037

	Number of Patients (%)					
Prognostic Factor	Gatifloxacin N = 141		Ceftriaxone N = 142		Total N = 283	
Severity						
Mild to Moderate	41	(29)	36	(25)	77	(27)
Severe	100	(71)	106	(75)	206	(73)

(Reference: Vol. 4, p. 86)

Medical Officer Comment: The slight differences in gender would not be expected to influence the overall outcome. Slightly more than half of all patients were enrolled at

eight sites, with two sites enrolling 13% and 6% of the patients. The remaining sites enrolled nine or fewer patients. It is of interest to note that two of the eight sites with the highest enrollment had significant numbers of patients that were not clinically evaluable, and 3 sites in the lower enrolling group had a similar disparity. However, when the statistical analysis controls for center, there is no influence on the clinical outcome rates.

It should also be noted that approximately 75% of patients enrolled were considered to have severe pneumonia in this study.

8.1.2.1.3 DISTRIBUTION OF PATIENTS:
Eligible Patients: 276 (136 gatifloxacin, 140 ceftriaxone).
Clinically Evaluable Patients: 212 (104 gatifloxacin, 108 ceftriaxone).
Microbiologically Evaluable Patients: 104 (50 gatifloxacin, 54 ceftriaxone).

Definitions:
All Treated Patients: All patients who received at least one dose of study drug.

Clinically Eligible Patients: All treated patients with a diagnosis of community-acquired pneumonia at entry.

Clinically Evaluable Patients: All Eligible Patients who met the minimum dosing requirement of at least 5 days, (at least 3 days for treatment failures), had an end-of-treatment (in the case of failure) or post-treatment (Test-of-Cure) assessment with a chest x-ray in the interval Day +7 to Day +14, and did not receive a systemic antibacterial agent with documented activity against the causative pathogen between the time of the pre-treatment visit and the post-treatment assessment unless to treat a clinical failure.

Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had a bacterial pathogen susceptible to both study drugs isolated from a pre-treatment sputum and/or blood culture, or an atypical pathogen diagnosed by culture, PCR, and/or serology; a sputum Gram stain performed for patients still producing sputum at the Test of Cure Visit, and a sputum culture performed for patients still producing sputum at the Test of Cure Visit if the sample was of good quality (i.e., >25 PMN and <10 epithelial cells/lpf).