Table A1.
Outline of Study Procedures and Assessments

Procedures/Assessments	Visit 1	Visit 2	Visit 3	Visit 4
	Screening	On- R/x	EOT	Follow-Up
	Day 0	Day 2-4	2-4 Days Post-Therapy	21- 28 Days Post-Therapy
Written Dated Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Demographics	X			
Medical History/Physical Exam	X			
Vital Signs	X	X	X	X
Chest Radiograph	X[1]			X
Clinically Assess the signs/symptoms of CAP	X	X	X	X
Auscultatory Findings	X	X	X	X
Sample of Sputum/Respiratory Secretions	X		X	X
Blood Culture	X	X	X	
Blood Sample for Serology	X			X
Optional Blood for DNA Analysis	X			
Urine Sample for *Legionella* Antigen Test	X			
Pregnancy Test (urine and serum)	X			
Blood Sample (Hematology / Clinical Chemistry)	X	X	X	
ECG	X	X		
Prior/Concomitant Medications	X	X	X	X
Baseline Signs and Symptoms	X			
Adverse Experiences		X	X	X
Evaluation of Clinical/ Radiological Response			X	X
Assessment of Compliance			X	
Demographic Data	X			
Medical Procedures	X	X	X	X
ClinPhone®	X	X	X	X
Medical Resource Use				X

[1] A chest radiograph within the 48-hour period prior to randomization.

Reasons for Withdrawal

The applicant classified withdrawals as any patient who was randomized to study medication but did not complete the study (whether or not the patient received study medication). The investigator could withdraw the patient at any time or the patient could withdraw him/herself at anytime. The reasons for study withdrawal were classified as follows:

- *Adverse experience:* patient had any AE deemed sufficiently severe to warrant withdrawal. This was to be recorded in the CRF and all AEs followed-up until resolution.
- *Insufficient therapeutic effect:* in the opinion of the investigator, there had been a clinical failure of study medication and further antibacterial treatment was required for CAP.
- *Protocol deviation:* non-compliance with study medication; concomitant treatment with a prohibited medication.
- *Patient was lost to follow-up.*
- *Other:* e.g., pregnancy; patient withdrew consent or requested cessation of treatment.

The applicant attempted to obtain a follow-up safety assessment 21 – 28 days after the last dose of study medication for all patients withdrawn from study.

Evaluability Criteria

The applicant defined 27 categories of protocol violations. From these, the applicant developed a list of 15 criteria that were employed to classify a patient as clinically and bacteriologically non-evaluable.

MO Comment: *The list of 15 criteria were selected from the list of 23 protocol violations because they were considered protocol violations that would interfere with the assessment of efficacy. These determinations were made before any data analysis took place and prior to code break.*

- An inclusion criterion was marked 'No'.
- An exclusion criterion was marked 'Yes'.
- The patient had a complicating infection that might compromise treatment evaluation. *(Applied on an individual patient basis where the infection was judged to affect efficacy assessment).*
- The patient received other antimicrobial treatment outside the protocol-specified window. *(Applied for oral, IV, IM or other systemic antibacterial therapy only; not applied where antibacterial therapy was given for clinical failure or clinical recurrence; ≤24 hours of antibacterials for the present episode of CAP were permitted).*

- The patient received an investigational drug/vaccine or device within 30 days, or five half lives, prior to/during the study. *(Applied for unlicensed medications for which impact on efficacy could not be determined).*
- The patient received a protocol prohibited prior/concomitant medication (e.g. systemic steroids at a dose of >10 mg per day of prednisone or equivalent). *(Not applied for the following medications: prednisone or equivalent given for treatment failure; single intra-articular injection of steroid; sucralfate; probenecid).*
- The patient had a life threatening or serious underlying disease. *(Applied on an individual patient basis where the disease was judged to affect efficacy assessment).*
- The patient had active alcohol or drug abuse. *(Applied).*
- The patient suffered an adverse experience/baseline event that might compromise treatment evaluation. *(Applied on an individual patient basis where the adverse experience/baseline event was judged to affect efficacy assessment).*
- The patient did not demonstrate sufficient compliance with study medication (i.e. 80% - 120% overall) and/or did not receive 100% of prescribed medication for the first 72 hours). *(Applied).*
- The patient did not demonstrate compliance with the protocol specified visit schedule.
- The patient did not have a clinical diagnosis of community-acquired pneumonia. *(Applied).*
- The patient had a clinical outcome of unable to determine. *(Applied).*
- The patient had a disease that could compromise efficacy in this indication. *(Applied).*
- The treatment was extended to 14 days but the patient did not take medication from the second pack. *(Applied).*

Patients in the CPP population were excluded from the BPP population if they violated the following condition:

- The patient had an initial pathogen bacteriological outcome of unable to determine for one or more initial pathogens. *(Applied).*

MO Comment: *The evaluability criteria and their application, as reviewed in the random sample and additional subsets of patients, were acceptable.*

Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was clinical response at the follow-up visit (Visit 4). The applicant also performed an ITT analysis, a logistic regression, and a multiple imputation analysis on the ITT population to evaluate clinical response at follow-up. These additional secondary or supportive analyses were performed to evaluate whether the findings corroborated the findings for the primary efficacy endpoint.

Secondary Efficacy Endpoints
The applicant also performed the following secondary efficacy analyses:

- Clinical response at the EOT
- Bacteriological response at follow-up
- Clinical and radiologic response at follow-up
- Bacteriological response at the EOT
- Radiological response at follow-up
- Time to discharge from hospital

A description of the applicant's efficacy endpoints follows:

Clinical Response at EOT and at Follow-Up:

Clinical response was determined based upon the assigned clinical outcome categories for the respective time points. Clinical response was a dichotomous outcome (success or failure).

Table A2
Criteria for Evaluating Clinical Response and Clinical Outcome

Visit	Clinical Response	Clinical Outcome	Criteria
EOT (Visit 3)	**Clinical Success**	*Clinical Success*	Sufficient improvement or resolution of the signs and symptoms of CAP recorded at screening such that no additional antibacterial therapy was indicated for CAP.
	Clinical Failure	*Clinical Failure*	Insufficient improvement or deterioration of signs and symptoms of CAP recorded at screening such that additional antibacterial therapy was indicated for CAP.
	Clinical Failure	*Unable to Determine*	An assessment of clinical outcome could not be made, e.g., the patient was lost to follow-up or did not consent to clinical examination.
Follow-up (Visit 4)	**Clinical Success**	*F/U Clinical Success*	Sufficient improvement or resolution of signs and symptoms of CAP for patients who were clinical successes at the EOT visit, such that no additional antibacterial therapy was indicated for CAP.
	Clinical Failure	*Clinical Recurrence*	Reappearance or deterioration of signs and symptoms of CAP for patients who were clinical successes at the EOT, such that additional antibacterial therapy was indicated for CAP.
	Clinical Failure	*Unable to Determine*	An assessment of clinical outcome could not be made, e.g., the patient was lost to follow-up or did not consent to clinical examination.

Note: For those patients withdrawing prior to the EOT, evaluation of their clinical outcome was determined at the time of withdrawal.
A patient considered to be a Clinical Failure at any visit was automatically counted as failure at all subsequent visits.

Bacteriologic Response at EOT:

Bacteriologic response was determined based upon the bacteriologic outcomes categories at the EOT visit. The bacteriologic outcomes at the EOT were as follows:

- Bacteriological Eradication – Absence of the initial pathogen from cultures performed at the EOT

- Presumed Bacteriologic Eradication – The patient is a clinical success at EOT who has not been cultured or has been incompletely cultured to detect the initial pathogen at EOT and all available cultures are negative.
- Bacteriological Persistence – The initial pathogen was present at the EOT or the initial pathogen was still present in the on therapy blood culture
- Presumed Bacteriologic Persistence – The patient was a clinical failure and was not cultured or was incompletely cultured at EOT and all available cultures were negative
- Unable to Determine – An assessment of bacteriologic outcome could not be made

For pathogens identified by non-culture methods only, the microbiologic response was presumed based upon the patient's clinical response.

For a pathogen identified from more than one source, the bacteriology outcome (microbiological outcome) was assessed for each source of the pathogen and then the worst-case scenario was assigned as the microbiologic outcome for the particular pathogen (Worst Case: Bacteriologic Persistence – Presumed Bacteriological Persistence – Unable to Determine – Presumed Bacteriological Eradication – Bacteriological Eradication: Best Case).

The applicant defined superinfection as the identification of a new pathogen at EOT in a patient with at least one initial pathogen who is symptomatic and requires additional antibacterial therapy (i.e., a clinical failure).

The applicant defined colonization as the identification of a new pathogen at the EOT in a patient with at least one initial pathogen who is asymptomatic at the EOT and does not require additional antibacterial therapy (i.e., a clinical success).

Bacteriologic response at EOT was determined using the above classifications for bacteriologic outcomes at EOT, superinfection, and colonization. Bacteriologic response was classified as success or failure. The Bacteriologic response category of success and failure are defined as follows:

- Success – a bacteriologic outcome of either eradication or presumed eradication of all initial pathogens and the absence of superinfection.
- Failure – a bacteriologic outcome category of persistence or presumed persistence of one or more of the initial pathogens, a superinfection, or an assessment of unable to determine for one or more of the initial pathogens.

Bacteriologic response was determined both per patient and per pathogen.

Bacteriologic Response at Follow-Up:

Bacteriologic response was determined based upon the bacteriologic outcomes categories at follow-up. For patients scored as bacteriologic eradication or presumed bacteriologic eradication at the EOT, the bacteriologic outcomes at follow-up were as follows:

- Follow-Up Bacterial Eradication – Absence of the initial pathogen from cultures performed at the EOT
- Follow-Up Presumed Bacterial Eradication – The patient was a clinical success at follow-up and an evaluable follow-up culture was not obtained
- Bacteriological Recurrence – The initial pathogen was present in any follow-up culture
- Presumed Bacteriologic Recurrence – the patient was a clinical recurrence and an evaluable follow-up culture was not obtained
- Unable to Determine – an assessment of bacteriologic outcome could not be made

For pathogens identified by non-culture methods only, the bacteriologic response was presumed based upon the patient's clinical response.

For a pathogen identified from more than one source, the microbiological outcome was assessed for each pathogen and then the worst-case scenario was assigned as the microbiologic outcome for the particular pathogen (Worst Case: Bacteriologic Persistence – Presumed Bacteriological Persistence – Unable to Determine – Presumed Bacteriological Eradication – Bacteriological Eradication: Best Case).

The applicant defined new infection as identifying a new pathogen in a symptomatic patient requiring additional antibacterial therapy for CAP (i.e., a clinical recurrence).

The applicant defined colonization as identifying a new pathogen at follow-up in an asymptomatic patient who did not require additional antibacterial therapy for CAP (i.e., a follow-up clinical success).

Bacteriologic response at follow-up was determined based upon the above classifications for bacteriologic outcomes at follow-up. Bacteriologic response at follow-up was classified as success or failure. The bacteriologic response at follow-up categories of success or failure are defined as follows:

Success – all initial pathogens were eradicated or presumed eradicated at the follow-up assessment, without any new infections.

Failure – recurrence or presumed recurrence of one or more of the initial pathogens at the follow-up assessment, a new infection, an assessment of unable to determine for one or more initial pathogens, or the EOT bacteriological response was failure.

Bacteriologic Response at Follow-Up was determined both per pathogen and per patient.

In addition to the above, the following criteria were applied to determine bacteriologic evaluability in subjects with atypical pathogens. These criteria were agreed to by the FDA.

Criteria for Bacteriological Evaluability

Criterion+		Definition
1.	Any pathogenic organism obtained from culture of sputum*, blood or other respiratory sample	Presence of one or more pathogens.
2.	*Legionella* from urine antigen	*Legionella pneumophila* was recorded as detected at visit 1.
3.	*Legionella* from serology	At least a four-fold rise in *Legionella pneumophila* antibody titre between visits 1 and 4. Note: the titre was recorded in the format 1:x at visit 1 and 1:y at visit 4; there was at least a four-fold rise in titre if $y/x \geq 4$.
4.	*Mycoplasma pneumoniae* from serology	*Mycoplasma pneumoniae* IgM was detected at visit 1 *and/or* visit 4 with an ISR ≥ 1.1 or *Mycoplasma pneumoniae* IgG was detected at visit 4 with an ISR ≥ 1.1 *and* there was a rise in *Mycoplasma pneumoniae* IgG ISR of ≥ 46% between visit 1 and visit 4.
5.	*Chlamydia pneumoniae or Chlamydia psittaci from serology***	At least a four-fold rise in *Chlamydia pneumoniae* or *Chlamydia psittaci* IgG or IgM titre between visit 1 and visit 4 or a single IgM titre of ≥ 1:10 at visit 1 *and/or* visit 4. Note: The titre was recorded in the form 1:x at visit 1 and 1:y at visit 4. There was a four-fold rise in titre if $y/x \geq 4$. In general, a titre recorded in the form 1:x is ≥ 1:y if $x \geq y$, (e.g., 1:32 is greater than 1:16).

*Note: an organism isolated from a sputum sample was only treated as a pathogen if it came from a sample with >25 WBCs per field and <10 squamous epithelial cells at 100x magnification at low power (x10 objective). This applied to sputum samples at all visits. All respiratory samples obtained by invasive methods were evaluable irrespective of Gram stain results.

***Chlamydia trachomatis* was not treated as a pathogen, irrespective of the observed titre, as it is not considered to be a respiratory pathogen.

Radiologic Response at EOT and at Follow-Up:

Radiologic response was determined based upon radiologic outcome. The applicant's category of radiologic outcome was determined by comparing the postero-anterior and lateral chest radiographs obtained at the EOT or at follow-up with the baseline chest radiograph.

- *Improved*: Improvement or resolution of radiological signs of CAP.
- *Unchanged*: No improvement in the baseline radiological signs of CAP.
- *Worse*: Worsening of the baseline radiological signs of CAP or the appearance of new radiological signs of CAP.
- *Unable to Determine*: A valid assessment of radiological outcome could not be made (e.g., the patient was lost to follow-up).

- *Presumed Improved*: A patient at follow-up whose radiological outcome was recorded as "unable to determine" was considered as presumed improved if the patient was a clinical success at follow-up and had an improved radiological outcome at the EOT
- *Presumed Failed*: A patient at follow-up whose clinical outcome was not clinical success was presumed failed.

The radiological response was then defined on the basis of the radiological outcome as follows:

- Success: the radiological outcome was "Improved" or "Presumed Improved"
- Failure: the radiological outcome was "Unchanged" or "Worse", "Unable to Determine", or "Presumed Failed.

Clinical and Radiologic Response at Follow-Up:

The applicant defined a composite category that was determined based upon both the clinical and radiologic outcomes as follows:

- *Success*: The clinical response was success at follow-up and the radiologic outcome was improved, unchanged, or presumed improved.
- *Failure*: the clinical response at follow-up was failure OR the radiologic outcome was worse, presumed failed or unable to determine.

Other Endpoints:

Therapeutic Response:

The combined clinical and bacteriologic response at the EOT and at the follow-up visit, defined as:

EOT: Success: Both the clinical and bacteriologic responses were "success"
Failure: The clinical and/or bacteriologic responses were "failure"

Follow-up: Success: Both the clinical and bacteriologic responses were "success"
Failure: The clinical and/or bacteriologic responses were "failure"

Time to Discharge from Hospital:

The number of days from the start of study medication to hospital discharge. Readmissions were not calculated.

Duration of Treatment: Calculated for patients who were successes at the EOT.

Time to Switch: For those patient s randomised to IV ceftriaxone, this was the number of days of IV R/x before switching to oral cefuroxime.

MO Comment: *The applicant's efficacy endpoints and the application of the endpoints, as determined by review of the random sample, were judged to be acceptable.*

Statistical Considerations:

The applicant's sample size calculation assumed an equivalent response rate of 85% at follow-up in the clinical per protocol population (the primary efficacy analysis) and chose a power of 90% to detect that the difference in success rates (gemifloxacin minus comparator group) was no less than –15%. They calculated that 380 evaluable patients would be required (190 per treatment arm). They estimated that 30% of randomised patients would be ineligible for the clinical per protocol population. Therefore, approximately 344 patients were to be recruited to provide 240 evaluable patients.

The applicant's primary efficacy analysis was based on an unstratified comparison of proportions between the treatment groups for the clinical per protocol population. Two-sided 95% confidence intervals (CI) were to be used to estimate the differences in the proportion of successes between treatment groups. A conclusion of non-inferior efficacy of gemifloxacin was to be made if the lower limit of the 95% CI for gemifloxacin minus trovafloxacin was $\geq$-15%.

The primary efficacy analysis was also evaluated by performing other analyses to corroborate the findings of the primary analysis. Clinical response at follow-up was also evaluated in the ITT population, using a logistic regression analysis, and using a multiple imputation analysis on the ITT population. The logistic regression analysis included categorical covariates for country, CAP severity, and treatment

The applicant defined the following four analysis populations.

CITT: All randomised patients including those randomised and not treated.

BITT: All randomised patients who had at least one pathogen identified from a sputum sample culture, blood sample culture, urine antigen, blood serology, or nasopharyngeal or throat swab at screening.

CPP: This population excluded patients who violated the protocol to an extent that could bias efficacy results. The CPP population was a subset of the CITT population.

BPP: This population excluded patients who violated the protocol to an extent that could bias efficacy results. The BPP population was a subset of the BITT population, i.e. all patients in this population had at least one pre-therapy pathogen identified at screening.

Medical Officer's Comment: *The F/u PP population was not always a subset of the EOT PP population. Rather patients were excluded from each population only from the time the protocol violation occurred.*

Evaluability Windows: Prior to evaluation and in order to increase sample size, the applicant increased the evaluability window of the TOC visit from post-treatment days 21 – 28 to days 19 – 41.

Medical Officer's Comments: *The change in the evaluability windows was deemed acceptable by the MO as the TOC in other applications has ranged from days 14 – 28 post-treatment.*

Study Results

Populations:

345 patients were randomized to receive study medication. Of these, 172 received gemifloxacin and 173 received comparator. There were 3 patients randomized to gemifloxacin and one patient randomized to comparator that did not receive study medication.

Table A3
Patient Disposition (All Randomized Patients) (Study 185)

	Treatment Group	
	Gemifloxacin 320 mg QD	Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid
Population	**n**	**n**
Randomised	172	173
Received Study Medication (ITT)*	169	172
Completed Study	140	145
Number Withdrawn	32	28
Clinical PP EOT	123	129
Clinical PP Follow-Up	116	121
Bacteriology ITT	88	82
Bacteriology PP EOT	67	65
Bacteriology PP Follow-Up	64	63

*These patients comprised the ITT population for efficacy and the safety population.
3 gemifloxacin and 1 comparator patient did not receive study medication.
Of the 3 gemifloxacin patients that withdrew prior to R/x, 1 withdrew consent, 1 had an SAE and one a protocol violation. The 1 untreated comparator arm patient withdrew consent.

There were 69 centers from 15 countries.

Demographic and Baseline Characteristics

There was an imbalance in the ratio of males to females in the comparator group (61% vs. 39%) as compared to the gemifloxacin group where both sexes were similarly represented (51% vs. 49%). Other baseline patient characteristics were quite similar in the two treatment groups.

Medical Officer's Comment: *The applicant did not collect information regarding current or previous smoking habits.*

The demographic and baseline characteristics for the CPP population were also tabulated (data not shown) and were similar to what was observed in the ITT population.

Table A4
Demographic Characteristics (ITT Population)

	Treatment Group	
	Gemifloxacin 320 mg QD	Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid
Demographic Characteristic	**N=172**	**N=173**
Gender: n (%)		
Male	88 (51.2)	105 (60.7)
Female	84 (48.8)	68 (39.3)
Age (yr)		
Mean [SD]	59.6 (17.9)	58.4 (19)
Range	18-89	18-97
Race: n (%)		
White	148 (86)	149 (86.1)
Black	8 (4.7)	11 (6.4)
Oriental	9 (5.2)	8 (4.6)
Other*	7 (4.1)	5 (2.9)
Weight (kg)		
Mean [SD]	74.5 (19.3)	75.3 (18.4)
Range	37.7-150	38.2-159
Height (cm)		
Mean [SD]	168 (9.3)	169 (10.3)
Range	141 - 188	142 - 193

* Other included 5 Hispanics, one Lebanese, one Guamanian, one East Indian, one Asian/Thai, 2 Native Americans, and one Asian/Indian.

The clinical characteristics of patients with CAP at baseline by treatment group are listed in Table A. While there are some differences in the proportions of patients within each severity category for the characteristics analyzed, the populations overall appear comparable.

Table A5
Number (%) of Patients with Clinical Characteristics of CAP at Screening (CITT Population)

	Treatment Group			
	Gemifloxacin 320 mg QD N=172		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg BID N=173	
Characteristic	**n**	**(%)**	**n**	**(%)**
Sputum				
Purulent Sputum†	111	(64.5)	169	(68.8)
Change in Characteristics†	95	(55.2)	105	(60.7)
Cough				
New or Increased Cough	165	(95.9)	169	(97.7)
None	7	(4.1)	2	(1.2)
Mild	34	(19.8)	34	(19.7)
Moderate	99	(57.6)	98	(56.6)
Severe	32	(18.6)	39	(22.5)
Pleuritic Chest Pain				
None	95	(55.2)	87	(50.3)
Mild	33	(19.2)	25	(14.5)
Moderate	26	(15.1)	39	(22.5)
Severe	18	(10.5)	22	(12.7)
Dyspnea				
None	27	(15.7)	21	(12.1)
Mild	39	(22.7)	47	(27.2)
Moderate	78	(45.3)	82	(47.4)
Severe	28	(16.3)	23	(13.3)
Tachypnea				
None	40	(23.3)	39	(22.5)
Mild	59	(34.3)	67	(38.7)
Moderate	65	(37.8)	55	(31.8)
Severe	7	(4.1)	12	(6.9)
Unknown	1	(0.6)	0	
Hypoxemia†	69	(40.1)	62	(35.8)
None	89	(65.9)	192	(68.3)
Mild	33	(20.0)	46	(16.4)
Moderate	34	(9.7)	29	(10.3)
Severe	12	(4.1)	12	(4.3)
Unknown	4	(2.3)	3	(1.7)
Fever*	91	(52.9)	98	(56.6)
Abnormal WBC Count†**	112	(65.1)	108	(62.4)

* Fever was defined in the protocol as >38°C oral, >38.5°C tympanic, >39°C rectal measured in the clinic or by the patient in the previous 12 hours. However, for the purposes of analysis, the Applicant defined fever as Temp ≥38°C oral, ≥38.5°C tympanic, ≥39°C rectal measured in the clinic or by the patient in the previous 12 hours, in order to maintain consistency across gemifloxacin studies in CAP.

** An elevated total peripheral WBC count of >10,000 cells/mm^3, or >15% immature neutrophils regardless of total peripheral WBC count, or leukopenia with a total WBC count of <4,500 cells/mm^3.

† Patients with unknown severity of hypoxemia or who had unknown sputum purulence or characteristics or unknown abnormal WBC counts at each visit were not included in this table. However unknowns are included in the totals used to calculate the % for that sign/symptom.

The applicant also categorized patient severity by risk class prior to evaluation of the data using Fine criteria. 80% of the patients on each treatment arm were classified as non-severe low risk (classes I, II, III) or non-severe moderate risk and 20% as severe (classes IV and V).

Medical Officer's Comment: *Patients were retrospectively assigned to a risk class according to demographic, clinical and laboratory characteristics that stratified them by risk of mortality within 30 days. Patients in risk class I can usually be managed as outpatients, whereas those in classes IV and V are at high risk of death and usually require hospitalization. The use of the Fine criteria as a determinant of risk and severity of disease is accepted by the agency and has been utilized in the approvals of other antimicrobial agents (gatifloxacin).*

Table A6
Fine Criteria at Screening (CITT populations)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
Fine Criteria (Risk Class)	**n**	**(%)**	**n**	**(%)**
CITT Population	**N=172**		**N=173**	
I	43	(25)	52	(30.1)
II	55	(32)	46	(26.6)
III	38	(22.1)	40	(23.1)
IV	34	(19.8)	33	(19.1)
V	2	(1.2)	2	(1.2)

Withdrawals:

Of the 172 patients who were randomized to gemifloxacin, 32 were withdrawn from study. 28/173 patients who were randomized to comparator were withdrawn from study.

Table A7
Number (%) of Randomized Patients Who Completed the Study or Were Withdrawn (ITT Population)

	Treatment Group			
	Gemifloxacin 320 mg QD N=172		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid N=173	
	n	(%)	n	(%)
COMPLETED STUDY*	140	(81.4)	145	(83.8)
Reason for Withdrawal**				
Adverse Experience	14	(8.1)	15	(8.7)
Insufficient Therapeutic Effect	8	(4.7)	2	(1.2)
Protocol Deviation	2	(1.2)	1	(0.6)
Lost to Follow-Up	6	(3.5)	6	(3.5)
Other Reason***	2	(1.2)	4	(2.3)
TOTAL WITHDRAWN	32	(18.6)	28	(16.2)

* Patients were considered to have completed the study if they had taken study medication as directed during the 7 or 14-day treatment period and had attended all visits specified in the protocol.
** This table shows withdrawals occurring at any time during the study.
*** Other reasons for withdrawal as determined by the investigator included withdrawal of consent (one patient in each treatment group), inability to take oral medication (one patient in the comparator treatment group), and withdrawal because the patient did not have CAP

MO Comment: *The most frequent reason for withdrawal was an AE and the MO reviewed the patients that were withdrawn from the study for AE's. 8 gemifloxacin and 2 comparator-treated patients were failures at the EOT.*

Patients Excluded for Non-Evaluability

27% (93/345) patients were excluded from the CPP EOT population. 49 (28.5%) from the gemifloxacin arm and 44 (25.4%) from the comparator arm. 108/345 (31.3%) were excluded from the CPP population at follow-up, 56 (32.6%) from the gemifloxacin arm and 52 (30.1%) from the comparator arm.

The most common reason for exclusion from the clinical follow-up population was non-compliance in 25 subjects on each arm (14.5%), followed by a clinical outcome of unable to determine in 23 (13.4%) of gemifloxacin subjects and 22 (12.7%) of comparator subjects.

The primary reason for non-compliance was the use of alternative antimicrobials in 17% of the gemifloxacin compared to 10% of the comparator patients. As per the applicant this difference was due to the investigators not following the protocol.

175/345 (50.7%) of subjects were excluded from the BITT population because they did not have a pathogen isolated. 84 were from the gemifloxacin arm (48.8%) and 91 (52.6%) from the comparator arm. Thus of the remaining 170 patients who compromised

the BITT population, 88 (51.8%) were from the gemifloxacin group and 82 (48.2%), were from the comparator group.

21 gemifloxacin and 17 comparator patients were excluded from the BPP at the EOT and 24 and 19 respectively from the BPP at the follow-up TOC visit. The primary reason for exclusion was prohibited antibacterial treatment in 13 gemifloxacin and 6 comparator-treated patients.

MO Comment: *The protocol violations leading to exclusion form the PP populations were well balanced between the treatment arms.*

MO Comment: *The MO reviewed the patients that were discontinued for "insufficient therapeutic effect" to verify that they were scored correctly (i.e., when a patient represented and evaluable failure the patient was scored appropriately). The MO agreed with the scoring for these patients.*

Concomitant Macrolide Use: 67 (38.7%) of comparator-treated patients received macrolides. A review of the source tables revealed that 24/172 (14%) of the gemifloxacin treated subjects received macrolides (22 with one and 2 with two). All of these subjects were included in the ITT analysis. 4 of these subjects received macrolides prior to study treatment. It the ITT analysis, 10 subjects were successes and 14 were failures. 10 of the 24 subjects were included in the PP analysis. Included were the 4 clinical successes that received macrolides prior to study treatment. The remaining 6 were determined to be clinical failures.

Efficacy Results

The primary efficacy variable was clinical response at follow-up (19 – 41 days post-therapy) in the CPP population.

Clinical response at follow-up

The clinical success rate in the CPP Population for the gemifloxacin arm was 92.2% (107/116) compared to 93.4% (113/121) in the comparator arm. The 95% CI for the difference in clinical success rates (gemi-comparator) was within the lower bound of the protocol-specified delta of -15%. Clinical response at follow-up was also assessed for the CITT population, all randomized patients who took at least one dose of study medication. In the ITT analysis, patients with a clinical response of unable to determine were handled as failures. In that analysis the clinical success rate for gemifloxacin was 75.6% (130/172) compared to 78.6% (136/173) for the comparator arm. The 95% CI for the difference in success rates was within the lower bound of the protocol-specified delta of -15%. These results led to the conclusion that gemifloxacin was at least as good as the ceftriaxone/cefuroxime regimen.

In the ITT analysis at follow-up, the proportion of patients scored as failure because of an outcome of unable to determine, was 4.1% (7/172) for gemifloxacin compared with 4.6% (8/173) for the comparators. There was a larger number of patients coded a missing on the gemifloxacin arm (31, 18%) as compared to the comparator) 24, 13.9%), but a review revealed that missing indicated a clinical response of failure at the EOT that was carried over. Clinical recurrence rates were similar on both treatment arms (4 gemifloxacin (2.3%) vs. 5 comparators, 2.9%).

Table A8
Clinical Response at Follow-Up (CPP and CITT Populations)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg BID	
CPP Population	**N=116**		**N=121**	
Success: n (%)	107	(92.2)	113	(93.4)
Failure: n (%)	8	(7.8)	8	(6.6)
Treatment Difference % (Gemi – Comparator)			- 1.15	
FDA 95% CI with CCF			(-8.5, 6.28)	
CITT Population	**N=172**		**N=173**	
Success: n (%)	130	(75.6)	136	(78.6)
Failure: n (%)*	42	(24.4)	37	(21.4)
Treatment Difference % (Gemi – Comparator)			- 3.03	
FDA 95% CI with CCF			(-12.47, 6.4)	

*Includes 31 patients in the gemifloxacin group and 24 patients in the comparator group with an outcome of unable to determine.

69 (39%) of the CITT comparator-treated subjects received a macrolide. 54 of these subjects (78.2%) were successes as compared to 83 (78.3%) of CITT comparator-treated subjects who did not take a macrolide.

Clinical Response at EOT

One of the applicant's secondary efficacy endpoints was clinical response at EOT (2 - 4 days post-therapy) in the CPP and CITT populations. The response rates corroborated the findings for the primary efficacy endpoint.

Table A9
Clinical Response at EOT (CPP EOT and CITT Populations)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
CPP EOT Population	**N=123**		**N=129**	
Success: n (%)	118	(95.9)	124	(96.1)
Failure: n (%)	5	(4.1)	5	(3.9)
Treatment Difference % (Gemi – Comparator)			- 0.19	
FDA 95% CI with CCF			(-5.81`, 5.43)	
CITT Population	**N=172**		**N=173**	
Success: n (%)	141	(82)	149	(86.1)
Failure: n (%)*	31	(18)	24	(13.9)
Treatment Difference % (Gemi – Comparator)			- 4.1	
FDA 95% CI with CCF			(- 12.45, 4.14)	

*Includes 16 patients in the gemifloxacin group and 14 patients in the comparator group with an outcome of unable to determine.

Bacteriological Response

For the secondary endpoint of per patient bacteriological response at EOT and at follow-up the applicant calculated the difference in treatment success rates (gemifloxacin – comparators) and their corresponding 95% confidence intervals. The overall results corroborated the findings of the primary efficacy endpoint although he comparator arm was numerically superior to the gemifloxacin arm in the BITT follow-up population and the lower bound of the 955 CI exceeding the prespecified – 15%. .

Table A10
Per Patient Bacteriological Response at EOT and at Follow-Up
(BPP and BITT Populations)

	Treatment Group			
	Gemifloxacin 320 mg QD		**Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg BID**	
BPP EOT Population	**N=67**		**N=65**	
Success: n (%)	65	(97)	60	(92.3)
Failure: n (%)	2	(3)	5	(7.7)
Treatment Difference % (Gemi – Comparator)			-1.4	
FDA 95% CI with CCF			(-4.46, 13.86)	
BITT EOT Population	**N=88**		**N=82**	
Success: n (%)	76	(86.4)	70	(85.4)
Failure: n (%)*	12	(13.4)	12	(14.6)
Treatment Difference % (Gemi – Comparator)			1.00	
FDA 95% CI with CCF			(- 10.67, 12.66)	
BPP Follow-up Population	**N=64**		**N=63**	
Success: n (%)	58	(90.6)	55	(87.3)
Failure: n (%)	6	(9.4)	8	(12.7)
Treatment Difference % (Gemi – Comparator)			3.32	
FDA 95% CI with CCF			(- 9.14, 15.79)	
BITT Follow-up Population	**N=88**		**N=82**	
Success: n (%)	67	(76.1)	65	(79.3)
Failure: n (%)*	21	(23.9)	17	(20.7)
Treatment Difference % (Gemi – Comparator)			- 3.13	
FDA 95% CI with CCF			(- 16.81, 10.55)	

Per pathogen bacteriological response at follow-up in the BPP population was also a secondary efficacy parameter. The Bacteriologic response rates for the category of "All Pathogens" were numerically superior in favor the gemifloxacin treatment arm.

Table A11
Bacteriological Response (Success) Rate at Follow-Up by Pre-Therapy Pathogen for Frequently Identified Pathogens in the BPPFU Population: CAP

	Bacteriology PP**			
	Gemifloxacin		Ceftriaxone/Cefuroxime	
Follow-Up	***n/N****	**%**	***n/N****	**%**
All Pathogens	80/87	92	80/89	89.9
Mycoplasma pneumoniae	19/19	100	14/15	93.3
Streptococcus pneumoniae	18/20	90	17/19	89.5
Chlamydia pneumoniae	12/13	92.3	14/15	93.3
Haemophilus influenzae	5/7	71.4	9/12	75.0

Note: Failures at EOT are carried forward to Follow-Up
* *n/N* = number of pathogens eradicated or presumed eradicated / number of pathogens.

The applicant also calculated bacteriological response rates at the EOT visit (results not shown). As would be expected, the rates at this earlier timepoint were consistent with what was observed at the follow-up visit except that the eradication/presumed eradication rates were generally, slightly higher.

PRSP: 3 subjects had PRSP and all 3 were bacteriologic successes at follow-up
The applicant tabulated the number of atypical pathogens identified at screening in the BITT and BPP populations.

Table A12
Number (%) of Atypical Pathogens Identified at the Screening Visit and the Method of Diagnosis (BITT and BPP Follow-Up Populations)

Pathogen Method of Diagnosis	Treatment Group Gemifloxacin 320 mg QD n (%)		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid n (%)	
BITT Population	**N=88**		**N=82**	
Mycoplasma pneumoniae				
Culture*	--	(10.8)	0	(9.8)
Serology	26	(29.5)	16	(19.5)
Total†	26	(43.3)	16	(43.1)
Chlamydia pneumoniae				
Culture*	-	(0.8)	-	(3.9)
Serology	19	(21.6)	18	(22)
Total†	19	(13.3)	18	(15.7)
Chlamydia psittaci				
Serology	0	--	1	(1.2)
Total†	0	--	1	(1.2)
Legionella pneumophila				
Culture*	0	--	0	--
Serology	1	(1.1)	0	--
Urine antigen	5	--	4	(4.9)
Total†	6	(5.7)	4	(6.9)
BPP Follow-Up Population	**N=64**		**N=75**	
Mycoplasma pneumoniae				
Culture*	-	--	-	--
Serology	19	(29.7)	15	(23.8)
Total†	19	(29.7)	15	(23.8)
Chlamydia pneumoniae				
Culture*	0	--	-	--
Serology	13	(20.3)	15	(23.8)
Total†	13	(20.3)	15	(23.8)
Chlamydia psittaci				
Serology	0	--	1	(1.6)
Total†	0	--	1	(1.6)
Legionella pneumophila				
Culture*	0	--	0	--
Serology	0	--	0	--
Urine antigen	3	(4.7)	1	(1.6)
Total†	3	(4.7)	1	(1.6)

*Culture included sputum and respiratory samples, nasopharyngeal swabs (only for *C. pneumoniae*) and throat swabs (only for *M. pneumoniae*).
† Total will not necessarily be the total of the methods used for each pathogen as the diagnosis may have been made by more than one method.

Medical Officer's Comment: The MO identified all subjects with a diagnosis of CAP due to *Legionella pneumophila* via review of line listing B12 (Pre-therapy Bacteriology for Pathogens). 6 cases were identified on the gemifloxacin arm and 4 on the comparator.

Of the gemifloxacin cases,

185.008.29558: *Legionella pneumophila* and *Haemophilus parainfluenzae* identified as pathogens. *Legionella pneumophila* identified by urinary antigen.

White female 62, with a PMH of MI, angina, and NIDDM, admitted with CP, a temperature to 37.4, bilateral infiltrates, a PO2 of 94%, dyspnea and no cough. The patient was categorized as a Fine class III. Sputum culture identified as normal flora as well as *Haemophilus influenzae*. Received 8 days of treatment and was determined to be a clinical success by the investigators at the EOT and follow-up visits with CxR improvement (Per Protocol at EOT and FU for both clinical and bacteriology).

185.015.30032: *Legionella pneumophila* identified as a sole pathogen via urinary antigen.

29 YO white female febrile with a PO2 of 90%, a new infiltrate on CxR, moderate dyspnea, and cough, categorized as Fine class II. Patient underwent a bronchoscopy that was culture negative. Received 8 days of treatment and declared a clinical success at the EOT and at follow-up. (Per Protocol at EOT and FU for both clinical and bacteriology).

185.068.29578: *Legionella pneumophila* identified as a sole pathogen via urinary antigen.

Elderly female with a history of aortic stenosis, fibrillation and hypertension, developed new infiltrate, cough, PO2 of 96% and fever. Received 7 days of gemifloxacin and was categorized as a clinical success. Urine antigen was positive but no other serologies were available. Patients had normal flora in a sputum sample. Patient was not assessed at the late visit. She was categorized as a Fine class II and was not evaluable at the late visit. (Unable to determine clinical and bacteriologic outcomes; Per Protocol at EOT, ITT at FU for both clinical and bacteriology)

185.070.30164: *Legionella pneumophila* identified as a sole pathogen via urinary antigen.

70 YO female, one previous episode of pneumonia, with consolidation on CxR, no sputum, no fever, mild hypoxemia and dyspnea. Received 7 days of treatment and was determined to be a clinical success. Screening and follow-up Mycoplasma IgG 1.37, IgM < 90. Initial Legionella Ab serology not obtained, repeat 1:128 (not diagnostic in absence of paired sera. Sole titer of 1:256 necessary for diagnosis) Urinary Ag was positive. Patient was considered evaluable at both EOT and FU (Per Protocol at EOT and FU for both clinical and bacteriology). Fine class II

185.204.29384: *Legionella pneumophila*, *Haemophilus parainfluenzae*, and *Mycoplasma pneumoniae* identified as pathogens. *Legionella pneumophila* identified by urinary antigen and Mycoplasma by serology.

27 YO white male with a PMH of ETOH abuse, pancreatitis, and cholelithiasis, presented with fever, PO2 of 92%, new infiltrate on CxR, purulent sputum, moderate cough, and mild dyspnea. Patient was categorized as Fine class I. Sputum culture was positive for *Haemophilus influenzae* and the subject was treated for 10 days and determined to be a clinical success at the EOT but subsequently lost to follow-up. (Unable to determine clinical and bacteriologic outcomes; Per Protocol at EOT, ITT at FU for both clinical and bacteriology).

185.603.30179: *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* identified as pathogens via serology (Legionella urinary antigen negative). *Bacteroides fragilis* isolated from the blood.

Elderly female received only 2 days of gemifloxacin before switchover to ceftriaxone and metronidazole for an ongoing intrabdominal process. Patient had high fever, dyspnea, cough, hypoxemia and new infiltrates at study entry. Of note were baseline borderline positive serologies for all atypical pathogens with fourfold increases in titer for all 3 at 4 weeks in addition to positive blood cultures. Patient was categorized as a Fine class IV and because of non-compliance , other antibacterial treatment and unable to determine clinical and bacteriologic outcomes she was included in the ITT at EOT and FU for both clinical and bacteriology populations but was not considered evaluable.

Of the comparator cases:

185.027.29329: *Legionella pneumophila* identified as a sole pathogen via urinary antigen.

Male subject with a history of COPD, new infiltrate, afebrile, mild hypoxemia was treated for 8 days. Patient was a Fine class I and considered not evaluable because of non-compliance. He was included in the ITT at EOT and FU for both clinical and bacteriology as clinical success.

185.068.29580: *Legionella pneumophila* identified as a sole pathogen via urinary antigen.

40 YO male with a history of COPD, admitted with CP, new infiltrate and pleural effusion on CxR, no fever, mild to moderate cough and dyspnea, a PO2 of 85% with a saturation of 94%. Patient did not receive erythromycin for treatment but only comparator regimen for a total of 8 days and was determined to be a clinical success. Sputum samples were consistent with normal flora. Fine class I. ITT at EOT and FU for both clinical and bacteriology; Unable to determine clinical and bacteriologic outcomes

185.252.29625: *Legionella pneumophila* identified as a sole pathogen via urinary antigen.

89 YO white male enrolled in study on 2/22/00, received Augmentin (? Doses), H/o COPD, PUD, HTN, afebrile, received erythromycin with comparators, CxR with consolidation and urinary antigen positive, cough, purulent sputum, PO2 92%, sputum culture negative. Clinical success at EOT and follow-up. Received antibacterial treatment: ITT at EOT and FU for both clinical and bacteriology; Fine class III

185.304.29866: *Legionella pneumophila* identified as a sole pathogen via urinary antigen. Per Protocol at EOT and FU for both clinical and bacteriology; Fine class I

REQUEST:
An explanation as to why in the Appendices (B12), subjects 185 008 29558 and 185 204 29384 were identified as having H. parainfl. in sputum but as having H. influenzae in the CRFs. Also a similar explanation for any such cases whose CRFs I have not yet seen is requested.

RESPONSE:
Initial cultures were performed at a local lab. Isolates were sent to the Central lab for confirmation of identification and susceptibility testing. Microbiology data captured in the CRF are manually transcribed from the local lab report issued to the study site. Central lab data are uploaded directly into GSK's clinical database which is the source for all analysis and reporting. The apparent discrepancies between the CRF data and the clinical database (Listing B12) for these two patients are most likely due to a misidentification of the pathogen at the local lab or errors at the study site transcribing the local lab data into the CRF.

Since GSK does not reconcile local lab/CRF microbiology data with the Central lab data, we are unable to identify any other cases where this type of discrepancy may exist.

Radiological Response

The applicant also calculated radiological response rates for the CPP and CITT populations at follow-up. The results corroborate the results for the primary efficacy endpoint.

Table A13
Radiological Response at Follow-Up and EOT

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
CPP Follow-Up Population	**N=116**		**N=121**	
Success: n (%)	102	(87.9)	110	(90.0)
Failure: n (%)	14	(12.1)	11	(9.1)
Treatment Difference % (Gemi – Comparator)			- 2.98	
FDA 95% CI with CCF			(-11.66, 5.77)	
ITT Population at Follow-Up	**N=172**		**N=173**	
Success: n (%)	127	(73.8)	130	(75.1)
Failure: n (%)	45	(26.2)	43	(24.9)
Treatment Difference % (Gemi – Comparator)			- 1.3	
FDA 95% CI with CCF			(-11.09, 8.47)	

Combined clinical and radiological response at follow-up in the CITT and CPP populations was also evaluated. The results were similar to those above.

Table A14
Clinical and Radiological Response at Follow-Up and EOT

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
CPP Follow-Up Population	**N=116**		**N=121**	
Success: n (%)	106	(91.4)	111	(91.7)
Failure: n (%)	10	(8.6)	10	(8.3)
Treatment Difference % (Gemi – Comparator)			- 0.36	
FDA 95% CI with CCF			(-8.28, 7.57)	
CITT Population at Follow-Up	**N=172**		**N=173**	
Success: n (%)	129	(75)	134	(77.5)
Failure: n (%)	43	(25)	39	(22.5)
Treatment Difference % (Gemi – Comparator)			- 2.40	
FDA 95% CI with CCF			(-12.02, 7.10)	

The applicant also evaluated therapeutic efficacy (a response category that combines clinical and bacteriological response) in the BPP and BITT populations at both the follow-up and EOT visits.

Table A15
Therapeutic Response at Follow-Up (BPP and BITT Populations F/u)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg BID	
BPP Follow-Up Population	**N=64**		**N=63**	
Success: n (%)	58	(90.6)	55	(87.3)
Failure: n (%)	6	(9.4)	8	(12.7)
BITT Population	**N=88**		**N=82**	
Success: n (%)	67	(76.1)	65	(79.3)
Failure: n (%)	21	(23.9)	17	(20.7)

Table A16
Therapeutic Response at EOT (BPP EOT and ITT Populations)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
BPP EOT Population	**N=67**		**N=65**	
Success: n (%)	65	(97.0)	60	(92.3)
Failure: n (%)	2	(3.0)	5	(7.7)
BITT Population	**N=88**		**N=82**	
Success: n (%)	74	(84.1)	69	(84.1)
Failure: n (%)	14	(15.9)	13	(15.9)

The therapeutic response rates at follow-up and EOT were similar between gemifloxacin and comparators for both the BPP and BITT populations.

Evaluation of Microbiological Isolates in Treatment Failures

The applicant evaluated the available microbiological isolates (including their MIC to study drug) for patients who were either clinical or bacteriological failures at either the follow-up or EOT visits. There was no apparent association with the MIC of the organism at admission to study drug that explained clinical or bacteriological failure. In those infrequent instances where a microbiological isolate obtained after admission was available from a patient who failed, evaluation of the MIC data to study drug did not explain the patient's failure.

There were 5/123 gemifloxacin-treated CPP patients (4.1%) and 5/129 comparator-treated CPP patients (3.9%) who were clinical failures at the EOT. Of these, 2 gemifloxacin and 3 comparator patients had a pathogen isolated at screening. One, patient 185.202.29371 who received gemifloxacin, had *Pseudomonas aeruginosa* (2 isolates with MICs of 2 and 4 mcg/mL) and *Streptococcus pneumoniae* (MIC 0.03 mcg/mL) at screening. All isolates were presumed persistent at the EOT. The other gemifloxacin-treated patient, 185.005.29316 had *Haemophilus influenzae* at baseline and again an

outcome of presumed persistence was assigned. There were an additional 8 CITT subjects who were failures at the EOT and again all isolates were sensitive at baseline. The remaining 3 gemifloxacin CPP EOT patients who were failures were excluded from the BITT population due to lack of a pathogen. 2 of these subjects were Fine class IV and one was a Fine class I.

On the comparator arm, 3 of the 5 clinical failures had a pathogen isolated at screening. Patient 185.068.29613 had *Chlamydia Pneumoniae* positive serology and no sputum isolate. Patient 185.305.29900 had *Haemophilus influenzae* and *Streptococcus pneumoniae* isolated from the initial sputum. Again an outcome of presumed persistence was assigned in this class V patient and failure did not appear to be due to initial resistance. The final subject 185.355.29791 had *Mycoplasma pneumoniae* identified by screening serology and was also a presumed persistence.

There were 7 CITT patients who were classified as failures on the comparator arm.

At the follow-up visit there were 14 CITT patients on the gemifloxacin arm associated with clinical recurrence and 9 on the comparator arm. 2 of the 14 gemifloxacin subjects and 3 of the comparator subjects were included in the CPP populations. There was no trend in the type of isolates found in these subjects if any.

Response Rates in Bacteremic Patients:

21/88 (24%) of the BITT gemifloxacin patients and 16/82 (19.5%) of the comparator BITT patients were bacteremic at baseline. 15/88 (17%) of the gemifloxacin and 9/82 (11%) of the comparator patients were bacteremic with *Streptococcus pneumoniae. Streptococcus pneumoniae* was isolated from the blood of 12/64 (18.8%) gemifloxacin BPP follow-up patients and 5/63 (7.9%) of the comparator patients. 16/64 (25%) of the gemifloxacin BPP follow-up patients were bacteremic as compared to 9/63 (14.2%) comparator.

The applicant tabulated the clinical and bacteriological response rates by blood culture status.

Table A17
Clinical Response at Follow-Up by Bacteremic Status (CPP F/U)

	Treatment Group			
	Gemifloxacin 320 mg QD N= 116		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid N= 121	
Positive Blood Culture	**N= 17**		**N= 9**	
Success	17	100%	9	100%
Failure	0	0	0	-
Negative Blood Culture	**N= 99**		**N= 112**	
Success	90	90.9%	104	92.9%
Failure	9	9.1%	8	7.1%

Table A18
Bacteriological Response at F/U by Bacteremic Status (BPP F/U)

	Treatment Group			
	Gemifloxacin 320 mg QD N= 64		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid N= 63	
Positive Blood Culture	**N= 16**		**N= 9**	
Success	16	100%	8	88.9%
Failure	0	0	1	11.1%
Negative Blood Culture	**N= 48**		**N= 54**	
Success	42	87.5%	47	87%
Failure	6	12.5%	7	13%

Similar results were obtained for subjects (ITT and PP) with *Streptococcus pneumoniae.*

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Table A19
Clinical Response at Follow-Up for ITT and CPP subjects with *Streptococcus pneumoniae* (with and w/o bacteremia)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
	ITT			
	N= 27		**N= 25**	
Positive Blood Culture	**N= 16**		**N= 9**	
Success	14	87.5%	7	77.8%
Failure	2	12.5%	2	22.2%
Negative Blood Culture	**N= 11**		**N= 16**	
Success	8	72.7%	13	81.2%
Failure	3	27.3%	3	18.8%
	CPP			
	N= 21		**N= 19**	
Positive Blood Culture	**N= 13**		**N= 5**	
Success	13	100%	5	100%
Failure	0	0	0	0
Negative Blood Culture	**N= 8**		**N= 14**	
Success	6	75%	12	85.7%
Failure	2	25%	2	14.3%

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Table A20
Bacteriologic Response at Follow-Up for ITT and BPP subjects with *Streptococcus pneumoniae* (with and w/o bacteremia)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
	ITT			
	N= 26		**N= 25**	
Positive Blood Culture	**N= 15**		**N= 9**	
Success	13	86.7%	7	77.8%
Failure	2	13.3%	2	22.2%
Negative Blood Culture	**N= 11**		**N= 16**	
Success	8	72.7%	13	81.2%
Failure	3	27.3%	3	18.8%
	BPP			
	N= 20		**N= 19**	
Positive Blood Culture	**N= 12**		**N= 5**	
Success	12	100%	5	100%
Failure	0	0	0	0
Negative Blood Culture	**N= 8**		**N= 14**	
Success	6	75%	12	85.7%
Failure	2	25%	2	14.3%

Disease Severity at Baseline

Clinical response at follow-up was assessed for the PP ITT populations according to assignment to a risk group according to the retrospective application of the Fine criteria.

Medical Officer's Comment: *Clinical response rates were similar between treatment arms by risk category. On both arms, patients in classes I and II (low risk) had the highest success rates with a decrease in successful outcomes as mortality risk increased. Similar results were obtained for the PP and ITT populations. As approximately 20% of subjects were classified as having severe disease, it appears as if oral gemifloxacin treatment is an alternative to IV ceftriaxone followed by PO cefuroxime.*

Table A21
Clinical Response at Follow-Up by Severity of CAP (CPP Follow-Up Population)

	Treatment Group			
	Gemifloxacin 320 mg QD		Ceftriaxone 2 gm IV QD/ Cefuroxime 500 mg bid	
CAP Severity*	N/N	(%)	N/N	(%)
CPP	**N= 116**		**N=121**	
I	31/33	(93.9)	36/38	(94.7)
II	34/35	(97.1)	32/33	(97.0)
III	22/25	(88.0)	25/26	(96.2)
IV	19/22	(86.4)	20/23	(87.0)
V	1/1	(100.0)	0/1	0
CITT	**N= 172**		**N=173**	
I	36/43	(83.7)	45/52	(86.5)
II	41/55	(74.5)	38/46	(82.6)
III	27/38	(71.1)	30/40	(75.0)
IV	25/34	(73.5)	23/33	(69.7)
V	1/2	(50.0)	0/2	0

Response Rates by Age, Race, and Gender

Response rates stratified by age, race and gender are presented in the Integrated Summary of Efficacy within this review.

Summary of Efficacy Results for Study

Study 185 provides results from an open label controlled study evaluating the efficacy of gemifloxacin compared to ceftriaxone/cefuroxime with or without a macrolide in the treatment of patients with CAP. The study enrolled patients with clinical and radiographic evidence of CAP. The two treatment groups were comparable. This study included patients requiring parenteral antibiotic therapy or who had signs of disseminated infection. In addition, patients with a life-threatening or serious unstable underlying disease were also included.

The primary efficacy parameter for the study was clinical response (success or failure) at the follow-up visit (21 - 28 days post-therapy). The clinical success rates at follow-up were 92% for gemifloxacin-treated patients and 93% comparator-treated patients. The study demonstrated non-inferiority of gemifloxacin to comparators in the treatment of CAP within the Study 185 population where approximately 20% of subjects had severe disease as determined by Fine criteria. . The primary efficacy endpoint results were corroborated by the findings for the secondary efficacy endpoints.

TABLE A22

PATIENT DISPOSITION BY CENTER – ITT POPULATION (STUDY 185)

Center Location	Study Center	Treatment							
		Gemifloxacin				Comparators			
		R	C	EOT	F/U	R	C	EOT	F/U
		N=172	N=140	N=123	N=116	N=173	N=145	N=129	N=121
Germany	002	2	2	2	2	0	0	0	0
Germany	003	0	0	0	0	2	2	2	2
Germany	005	2	2	1	1	1	0	0	0
Germany	006	1	0	0	0	2	2	2	2
Austria	007	2	2	1	1	0	0	0	0
Germany	008	2	2	2	2	1	1	0	0
Germany	010	1	1	1	1	0	0	0	0
Germany	012	1	1	1	1	0	0	0	0
Germany	015	7	5	5	5	8	7	7	7
Germany	016	1	1	1	1	0	0	0	0
Germany	017	2	2	1	1	0	0	0	0
Germany	020	0	0	0	0	1	1	1	1
Germany	022	5	4	2	2	6	5	4	3
Austria	025	2	1	1	1	2	2	2	2
Germany	026	2	1	1	1	2	2	2	1
Germany	027	1	1	0	0	4	4	3	3
Italy	053	1	1	1	1	5	5	5	5
Italy	055	1	1	1	1	0	0	0	0
Italy	056	0	0	0	0	1	1	1	1
Italy	064	2	1	1	1	0	0	0	0
Italy	065	0	0	0	0	1	1	0	0
Italy	068	5	2	3	2	2	1	1	1
Italy	070	9	6	8	7	10	9	7	6
Belgium	104	1	1	1	1	2	1	2	1
Belgium	105	1	1	1	1	0	0	0	0
Hungary	153	2	2	2	2	3	1	3	1
Hungary	154	1	1	1	1	1	1	1	1
Poland	201	8	8	8	8	10	10	10	10
Poland	202	6	5	5	5	9	8	7	7
Poland	203	4	4	3	3	5	5	5	5
Poland	204	3	2	3	2	2	2	2	2
Poland	205	2	1	1	1	1	1	1	1
Poland	206	5	4	5	4	1	1	1	1
Poland	208	5	5	4	3	4	4	4	4
UK	252	2	2	0	0	2	1	1	0
UK	253	2	2	2	2	2	2	2	2
USA	302	1	1	1	1	0	0	0	0
USA	303	0	0	0	0	1	0	0	0
USA	304	3	2	2	2	5	5	5	5
USA	305	10	10	7	7	14	12	11	10
USA	309	6	5	2	2	7	5	4	4
USA	310	5	3	3	3	4	4	2	2
USA	311	4	4	3	3	0	0	0	0
USA	312	2	2	2	2	1	1	1	1
USA	313	1	1	1	1	1	0	0	0
USA	314	2	1	1	1	1	1	1	1
USA	315	1	1	0	0	0	0	0	0
Canada	351	2	1	1	1	2	1	1	1
Canada	352	0	0	0	0	1	0	0	0
Canada	353	1	1	1	1	2	2	2	2
Canada	355	4	4	4	4	6	5	6	6
Canada	356	4	4	2	2	2	2	1	1
Canada	357	4	1	1	1	5	3	3	3
Canada	358	3	3	3	3	2	0	0	0
Canada	359	0	0	0	0	1	1	0	0

Canada	362	4	4	2	2	4	3	1	1
Canada	363	3	2	2	2	1	0	1	1
Canada	364	1	1	1	1	1	1	0	0
Canada	365	0	0	0	0	1	1	1	1
Canada	366	1	1	1	1	0	0	0	0
Guatemala	441	3	2	2	1	3	3	3	3
Lebanon	521	2	2	2	2	3	3	1	1
Philippines	542	4	4	3	3	6	6	4	4
Singapore	561	2	0	0	0	2	1	1	1
Switzerland	601	1	1	1	1	3	2	1	1
Switzerland	602	2	2	2	2	1	1	1	1
Switzerland	603	4	3	3	3	1	1	1	1
Switzerland	612	1	0	0	0	1	0	0	0
Australia	671	0	0	0	0	1	1	1	1
R = randomized; C = completed; EOT = Valid for Clinical Per Protocol End of Therapy Population; F/U = Valid for Clinical Per Protocol Population									

Extent of Exposure:

152/172 (88%) gemifloxacin-treated subjects and 159/173 (92%) of the comparator-treated subjects received between 7 – 14 days of study drug.

Table A23
Duration of Exposure to Study Medication

Duration of Exposure	Gemifloxacin 320 mg QD N = 172		Comparators N = 173	
	n	(%)	n	(%)
1 day*	1	(0.6)	2	(1.2)
2 days	4	(2.3)	1	(0.6)
3 days	4	(2.3)	4	(2.3)
4 days	3	(1.7)	3	(1.7)
5 days	3	(1.7)	0	(0)
6 days	1	(0.6)	1	(0.6)
7 days	25	(14.5)	11	(6.4)
8 days	7	4.1)	11	(6.4)
9 days	8	(4.7)	21	(12.1)
10 days	31	(18)	42	(24.3)
11 days	13	(7.6)	21	(6.4)
12 days	14	(8.1)	13	(7.5)
13 days	3	(1.7)	9	(5.2)
14 days	50	(29.1)	31	(17.9)
>14 days	1	(0.6)	2	(1.2)

Medical Officer's Comment: *A good portion of the patients in the database received 7 days or less of gemifloxacin 320 mg (24%) and 50% received 10 days or less of gemifloxacin 320 mg as compared to 12.7% and 55% of the comparator treated patients. Mean duration of treatment was 10 days for each group; maximum duration was 17 days for the gemifloxacin-treated patients and 15 for the comparator-treated.*

Adverse Events:

69.8% (118/169) of patients in the gemifloxacin 320 mg QD group and 62.2% (107/172) of patients in the all comparators group reported at least one AE during the interval on-therapy plus 30 days post-therapy.

Most frequent AEs were from the GI tract on both treatment arms, followed by AEs from the metabolic/nutritional, and respiratory systems. The body systems in which the reporting rate of AEs in the gemifloxacin 320 mg QD group exceeded the rate in the all comparators group by at least 2% were the CNS and skin and appendages body systems. The body as a whole, platelet and clotting, and liver and biliary systems were the systems in which the rate of adverse experiences in the all comparators group exceeded the rate in the gemifloxacin 320 mg QD group by at least 2%.

Table A 24
Adverse Experiences by Body System

	Treatment Group			
	Gemifloxacin 320 mg QD N=169		Comparators N=172	
Body System	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	118	(69.8)	107	(62.2)
Gastrointestinal	40	(23.7)	40	(23.3)
Metabolic and Nutritional	34	(20.1)	38	(22.1)
Respiratory	30	(17.8)	27	(15.7)
Central and Peripheral Nervous	15	(8.9)	6	(3.5)
Skin and Appendages	15	(8.9)	9	(5.2)
Body As A Whole	9	(5.3)	18	(10.5)
Resistance Mechanism	12	(7.1)	13	(7.6)
Musculoskeletal	8	(4.7)	5	(2.9)
Psychiatric	20	(11.8)	22	(12.8)
Urinary	6	(3.6)	5	(2.9)
Liver and Biliary	11	(6.5)	20	(11.6)
General Cardiovascular	9	(5.3)	10	(5.8)
Female Reproductive	0	0	1	(0.6)
White Cell and Reticuloendothelial	7	(4.1)	6	(3.5)
Platelet, Bleeding and Clotting	5	(3.0)	9	(5.2)
Autonomic Nervous	2	(1.2)	1	(0.6)
Vision	3	(1.8)	3	(1.7)
Heart Rate and Rhythm	4	(2.4)	5	(2.9)
Vascular Extracardiac	1	(0.6)	3	(1.7)
Neoplasm	2	(1.2)	5	(2.9)
Red Blood Cell	8	(4.7)	8	(4.7)
Male Reproductive	1	(0.6)	1	(0.6)
Myocardial, Endocardial, Pericardial, Valve	6	(3.6)	2	(1.2)
Application Site	0	0	3	(1.7)

The most frequently occurring (≥ 1%) AEs are presented below. Diarrhea and hypokalemia were the most common AEs by preferred term in both the gemifloxacin 320 mg QD group and the comparator groups. Other AEs reported in more than 5% of patients included hyperglycemia, insomnia, constipation, and rash on the gemifloxacin arm as compared to insomnia and increased SGPT on the comparator arm. .

There were 5.3% (9/169) patients with an AE of rash in the gemifloxacin 320 mg QD group compared to 4.8% in the original NDA gemifloxacin group, and 5/172 (2.9%) in the comparator group of the study under review.

Table A25
Most Frequently Occurring (≥2%) AEs (All Causality)

	Treatment Group			
	Gemifloxacin 320 mg QD N=169		All Comparators N=172	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	118	(69.8)	107	(62.2)
Headache	8	(4.7)	5	(2.9)
Diarrhea	17	(10.1)	18	(10.5)
Insomnia	12	(7.1)	12	(7.0)
Anemia	8	(4.7)	7	(4.1)
Nausea	7	(4.1)	5	(2.9)
Rash	9	(5.3)	5	(2.9)
Erythematous Rash	3	(1.8)	1	(0.6)
Abdominal Pain	5	(3.0)	5	(2.9)
Hepatic Enzymes Increased	5	(3.0)	3	(1.7)
Leucocytosis	5	(3.0)	4	(2.3)
Thrombocythemia	5	(3.0)	7	(4.1)
Vomiting	5	(3.0)	6	(3.5)
Dyspnea	4	(2.4)	3	(1.7)
Hypotension	4	(2.4)	3	(1.7)
Dizziness	6	(3.6)	1	(0.6)
Pneumonia	6	(3.6)	7	(4.1)
Back Pain	3	(1.8)	4	(2.3)
Pleural Effusion	4	(2.4)	3	(1.7)
Hypokalemia	13	(7.7)	13	(7.6)
Hyperglycemia	12	(7.1)	7	(4.1)
BUN Increased	3	(1.8)	2	(1.2)
HSV	3	(1.8)	1	(0.6)
Pruritus	3	(1.8)	1	(0.6)
Respiratory Tract Disorder	3	(1.8)	2	(1.2)
Constipation	11	(6.5)	6	(3.5)
SGPT Increased	3	(1.8)	10	(5.8)
Pharyngitis	4	(2.4)	1	(0.6)

Medical Officer's Comment: *The higher rate of CNS AEs on the gemifloxacin arm, appeared to be due to the higher number of patients with dizziness on that arm as compared to the comparator arm.*

Medical Officer's Comment: *The preferred terms rash, rash erythematous, rash maculo-papular and rash pustular were combined and presented as 'rash' when used in the applicant's adverse experience tables. This did not include terms such as dermatitis or urticaria. The combined incidences of these events was 11/169 (6.5%) for the gemifloxacin arm and 6/172 (3.5%) for the comparator arm. Intensity was mild to moderate in all cases except on the gemifloxacin arm. 1 patient was withdrawn from each arm due to this AE. There were no cases of Stevens Johnson syndrome or photosensitivity. A review of these cases by the MO showed that the majority of patients with skin and appendage disorders were included in the applicant's combined presentation of "rash". The majority of patients presented with a fine "ampicillin-type" rash as described previously.*

Adverse events historically associated with the quinolone class were reviewed (<1% of patients). Hepatic enzymes increased and abnormal hepatic function AEs were reported in 3% (5/169) of the gemifloxacin 320 mg QD patients, respectively, compared to 3 (1.7%) of the comparators. However, further review of the terms SGPT and SGOT increased revealed 3 (1.8%) and 2 (1.2%) gemifloxacin patients versus 10 (5.8%) and 8 (4.7%) of comparator patients respectively.

In the gemifloxacin 320 mg QD group, the overall incidence of musculoskeletal body system effects was found to be very low (3.7%). Preferred AE terms arthritis and myositis were reported in 2 (1.2%) and 1 (0.6%) of gemifloxacin treated patients and none of the comparator treated. There were no cases of tendonitis.

The severity of adverse experiences in clinical trials with the gemifloxacin 320 mg dose versus comparators is shown below

Table A26
Severity of Adverse Experiences

	Treatment Group			
	Gemifloxacin 320 mg QD N=169		Comparators N=172	
Severity	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	118	(69.8)	107	(62.2)
Mild	85	(50.3)	76	(44.2)
Moderate	64	(37.9)	64	(37.2)
Severe	21	(12.4)	24	(14)

Medical Officer's Comment: *The majority of AEs with gemifloxacin appeared to be of mild to moderate severity. Severe AEs included 1 event each of fever, cardiac failure, headache, stupor, bloody diarrhea, GI reflux, GI haemorrhage, intestinal obstruction, hepatic function abnormal, aortic stenosis, neoplasm, somnolence, sepsis, dyspnea, pleurisy, respiratory disorder, respiratory insufficiency, rash, ocular haemorrhage, leucocytosis, and lymphopenia. There were 3 severe events of pneumonia, 2 each of bloody diarrhea, pleural effusion, MI, anemia, and hepatic enzymes increased. The most frequent events on the comparator arm were dyspnea in 3 subjects, and pneumonia, cardiac failure, pulmonary carcinoma, and confusion occurring in 2 each.*

Drug-Associated Adverse Experiences

Investigators considered at least one AE to be of suspected or probable relationship to study medication for 16.6% (28/169) of patients in the gemifloxacin 320 mg QD group and 21.5% (37/172) of patients in the comparator group reported during the interval on-therapy plus 30 days post-therapy.

The most frequent AEs of suspected or probable relationship to study medication in the gemifloxacin 320 mg QD group were rash (3 %; 5/169), diarrhea (4%; 7/169) increased hepatic enzymes (3; 5/169). The most frequent AEs of suspected or probable relationship to study medication in the comparator group were diarrhea (6.4%; 11/172), hepatic enzymes increased (1.7%; 3/172), SGPT increased (4.7%; 8/169), and SGOT increased (3.5%; 6/172).

Table A27
Most Frequently Occurring (≥1%) AEs of Suspected/Probable Relationship to Study Medication

	Treatment Group			
	Gemifloxacin 320 mg QD N=169		Comparators N=172	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE of suspected/probable relationship to study med	28	(16.6)	37	(21.5)
Rash	5	(3)	2	(1.2)
Diarrhea	7	(4.1)	11	(6.4)
Hepatic Enzymes Increased	5	(3)	3	(1.7)
Nausea	1	(0.6)	2	(1.2)
SGPT Increased	1	(0.6)	8	(4.7)
Vomiting	1	(0.6)	3	(1.7)
Thrombocythemia	1	(0.6)	3	(1.7)
Moniliasis	0	0	4	(2.3)
Genital Moniliasis	2	(1.2)	2	(1.2)
Pruritus	2	(1.2)	0	0
SGOT Increased	0	0	6	(3.5)

Deaths and Serious Adverse Events:

3/169 (1.8%) gemifloxacin and 6(3.6%) comparator treated patients died during the study. Causes of death in the gemifloxacin patients were CA, aortic stenosis, and NP. On the comparator arm the causes were cardiac in 4 and respiratory in 2. None of these events or deaths appeared related to treatment.

Serious Adverse Experiences

Of the 169 patients in the gemifloxacin 320 mg QD group, 25 patients (14.4%) reported serious AEs during the interval on-therapy to 30 days post-therapy. In the comparator group, 24 of 172 patients (14%) reported serious AEs during this interval.

Medical Officer's Comment: *As expected, greater numbers of serious AEs were reported in this study of an indication of greater disease severity, CAP, as compared to the 3.8% reported in the original NDA database. However, the number of SAEs reported on the gemifloxacin arm was consistent with the number reported in previously reviewed CAP studies such as study 011 where 24/167 (14.4%) of gemifloxacin-treated patients reported an SAE.*

The numbers of patients with SAEs regardless of relationship to study drug are listed in the Table below.

Table A28
Serious Adverse Experiences (≥1%) Regardless of Relationship to Study Drug

	Treatment Group			
	Gemifloxacin 320 mg QD N=169		Comparator N=172	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one SAE	25	14.8	24	14
Pneumonia	5	(3.0)	4	(2.3)
Pulmonary Carcinoma	1	(0.6)	2	(1.2)
COPD	2	(1.2)	0	0
Myocardial Infarction	2	(1.2)	2	(1.2)
Pleural Effusion	2	(1.2)	0	0
Respiratory Disorder	2	(1.2)	1	(0.6)
Cardiac Failure	0	0	2	(1.2)
Dyspnea	0	0	3	(1.7)
Acute Renal Failure	0	0	2	(1.2)
Hepatic Enzymes Increased and Hepatic Function Abnormal	4	(2.4%)	0	0

Medical Officer's Comment: *The type and number of SAEs reported from subjects on both treatment arms were similar with most events from the respiratory tract. A further breakdown of SAEs to those occurring on or post treatment, revealed that 12/169 (7.1%) of gemifloxacin patients and 13/172 (7.6%) of comparator patients had SAEs during treatment. Of these, 4 events of hepatic enzymes increased or hepatic function abnormal (2.4%) were reported from gemifloxacin-treated patients as compared to 1 episode of cholecystitis on the comparator arm and no episodes of serious hepatic enzyme abnormalities. Other SAEs that occurred during treatment on the gemifloxacin arm included 1 each of bloody diarrhea, cardiac failure, HTN, intestinal obstruction, angina, endocarditis, sepsis, pneumonia, pleural effusion, and ocular hemorrhage. There were also 2 reports of respiratory disorder.*

5 subjects on the gemifloxacin arm and none of the subjects on the comparator arm had SAEs attributable to treatment. The SAEs included an episode of bloody diarrhea (185.01529311) and 4 episodes of increased hepatic enzymes to 3 – 4 x NL (185.07029584, 185.20230261, 185.31029883, 185.357.29796). The LFT abnormalities occurred between days 5 – 7 of treatment and resolved in all subjects within the study period. In no case was there evidence of a concurrently increased bilirubin.

Adverse Experiences Associated with Treatment Discontinuation

Table A29
Patients in Either Treatment Group Withdrawn Due to AEs
On Therapy Plus 30 Days Post Therapy

	Treatment Group			
	Gemifloxacin 320 mg QD N = 169		All Comparators N = 172	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE leading to withdrawal	14	(8.3)	15	(8.7)
Hepatic enzymes increased or abnormal	3	(1.8)	0	0
Pneumonia	1	(0.6)	2	(1.2)
Abscess	0	0	2	(1.2)
Dyspnea	0	0	2	(1.2)
Fever	0	0	1	(0.6)
Cardiac Failure	0	0	1	(0.6)
Diarrhea	1	(0.6)	0	0
Abdominal pain	0	0	1	(0.6)
Flatulence	1	(0.6)	0	0
Intestinal Obstruction	1	(0.6)	0	0
Nausea	1	(0.6)	0	0
Vomiting	1	(0.6)	0	0
Arrhythmia	0	0	1	(0.6)
Cardiac Arrest	0	0	1	(0.6)
Aortic Stenosis	1	(0.6)	0	0
Myocardial Infarction	1	(0.6)	1	(0.6)
Pulmonary Carcinoma	0	0	1	(0.6)
Somnolence	1	(0.6)	1	(0.6)
Hypoxia	0	0	1	(0.6)
Pleural Effusion	0	0	1	(0.6)
Pleurisy	1	(0.6)	0	0
Respiratory disorder	0	0	1	(0.6)
Respiratory Insufficiency	1	(0.6)	0	0
Rash	1	(0.6)	1	(0.6)
Bullous Eruption	0	0	1	(0.6)
ARF	0	0	1	(0.6)
Leucocytosis	1	(0.6)	0	0

Medical Officer's Comment: *The most common reason for withdrawal on the gemifloxacin arm was elevation of hepatic enzymes. In all cases the elevations were determined to be serious by the investigators although the elevations were < 5 x NL and resolved in all cases. Pneumonia, abscess, and dyspnea were the most common reasons for withdrawal of the comparator arm.*

7 gemifloxacin and 2 comparator patients had AEs that led to withdrawal. On the gemifloxacin arm, in addition diarrhea (1) and 3 cases of increased LFTS, 1 patient

discontinued due to somnolence and stupor, one had an episode of nausea, vomiting, and flatulence, and 1 (185.36329797) discontinued because of a rash. On the comparator arm one patient discontinued due to rash and one due to an episode of abdominal pain.

Pregnancy: None

Electrocardiographic data:

Paired EKGs were obtained in 74/149 (44%) of the gemifloxacin and 66/172 (38%) of the comparator patients. The on-therapy EKGs were obtained at Cmax.

No patients from either treatment arm sustained a change of ≥ 60 msec from baseline QTc to on therapy. One gemifloxacin subjects had an increase of 55 msec from a baseline of 450 msec. This was the only subject with a measurement outside the upper range for QTc, this subjects was male. In addition, there were 2 subjects with baseline QTc intervals > 500 msec.

Laboratory:

43 gemifloxacin and 42 comparator patients had lab values that had changed from screening by more than a pre-specified amount AND were outside the pre-specified extended normal range at the on-therapy and EOT visits (F2F3 flagged). On the gemifloxacin arm, 24 patients at the on-therapy visit and 32 at the EOT visit had values of potential clinical concern as compared to 19 and 31 comparator patient s respectively.

Hematology

6 (22.1%) of the gemifloxacin and 33 (19.5%) of the comparator patients were associated with F3-flagged (outside an applicant defined extended normal range) high WBCs at screening. As would be expected with the treatment of the underlying pneumonia, the proportion of patients who had F3-flagged neutrophils and WBCs decreased considerably across visits for patients in each respective treatment group. The F2F3 flagged hematology values at the end of therapy visits are presented in Table 68.

Table A30
Number(%) of Patients with Hematology Values Outside the F2F3 Range at the EOT Visit (Gemifloxacin 320 mg vs. Comparator)

Functional Group/Variable	F2F3 Range	Gemifloxacin 320 mg QD N = 169		Ceftriaxone 2 GM IV QD Cefuroxime 500 mg BID N = 172	
Hematology		**n/N***	**(%)**	**n/N***	**(%)**
Hemoglobin	Low	3/160	(1.9)	5/155	(3.2)
Hematocrit	Low	2/157	(1.3)	1/155	(0.6)
RBCs	Low	1/157	(0.6)	1/155	(0.6)
Neutrophils	Low	2/149	(1.3)	2/139	(1.4)
Platelets	High	14/157	(8.9)	15/153	(9.8)

*n/N = number of patients with flag/number of patients evaluated for the particular parameter

Medical Officer's Comment: *The numbers of patients with abnormalities in hematologic parameters is not unexpected as part of the syndrome of CAP. There seemed to be a trend toward higher platelet values as the end-of-therapy in both groups. This was similar to values found in the review of CAP study 011. This finding does not appear to be clinically significant.*

Clinical Chemistries

The incidence of F2F3 flagged liver function parameters relatively unchanged between the on-therapy and EOT visits with a higher incidence of increased ALT on the gemifloxacin arm.

The numbers of patients with abnormalities in BUN and creatinine were small and similar in both gemifloxacin and comparator treated patients at the on-therapy and end-of-therapy time points.

Table A31
Number (%) of Patients with Clinical Chemistry Values Outside the F2F3 Range at the On-Therapy Visit

Functional Group/ Variable	F2F3 Range	Gemifloxacin 320 mg QD N = 169		Ceftriaxone 2 GM IV QD Cefuroxime 500 mg BID N = 172	
Clinical Chemistry		**n/N***	**(%)**	**n/N***	**(%)**
ALT	High	7/152	(4.6)	4/161	(2.5)
AST	High	3/152	(2.0)	5/161	(3.1)
ALK-P	High	1/151	(0.7)	2/160	(1.3)
BUN	High	6/153	(3.9)	3/160	(1.9)
Creatinine	High	2/148	(1.4)	2/159	(1.3)
Calcium	Low	1/152	(0.7)	1/157	(0.6)
Total Protein	Low	1/152	(0.7)	1/158	(0.6)
Total Bilirubin	High	2/152	(1.3)	0/159	(0.0)
Albumin	Low	2/152	(1.3)	1/158	(0.6)
Sodium	Low	0/152	(0.0)	1/162	(0.6)

*n/N = number of patients with flag/number of patients evaluated for the particular parameter