FDA Briefing Package

Anti-Infective Drugs Advisory Committee

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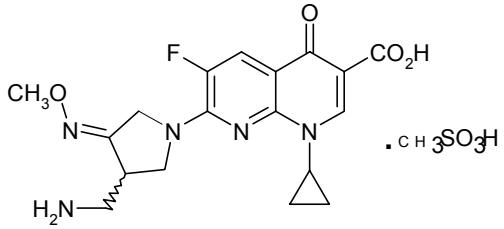

New Drug Application (NDA) 21-158

Factive (gemifloxacin mesylate)

Summary

This FDA briefing document contains a summary of the key data and issues within New Drug Application (NDA) 21-158 for Factive (gemifloxacin mesylate) tablets. The original NDA for this drug was submitted on December 15, 1999. In the original NDA submission the Applicant sought claims for the treatment of adults for three indications in the respiratory tract (community-acquired pneumonia (CAP), acute bacterial exacerbation of chronic bronchitis (ABECB), acute bacterial sinusitis (ABS)) and two indications in the urinary tract (uncomplicated urinary tract infection (uUTI) and complicated urinary tract infection (cUTI)). While the efficacy of gemifloxacin, in general, in 4 of the originally proposed five indications (CAP, ABS, ABECB, uUTI) was found to be non-inferior to the comparator regimens, during the course of the NDA review significant questions arose regarding the safety of gemifloxacin. These questions centered around the higher than expected rate of rash reported in patients receiving gemifloxacin and related questions regarding the mechanism of the observed rash, the potential for cross-sensitization, and the possibility that the frequent occurrence of rash may portend a risk for more serious infrequent cutaneous drug reactions. In addition, there were also unresolved questions regarding the hepatic safety profile of gemifloxacin.

To provide additional data to address the issues raised during the initial review of the NDA, especially rash and the potential for sensitization, the Applicant has performed an additional study (Study 344) to characterize the rash associated with gemifloxacin. The Applicant has also re-visited the proposed indications taking into consideration the higher rate of rash with gemifloxacin (especially in women and younger adults) and the increased frequency of rash as duration of treatment increases. The Applicant is currently requesting only the indications of CAP and ABECB in adults. In the re-submission of NDA 21-158 that is currently under review, in addition to the data on rash, the Applicant has also provided information on the microbiologic activity of gemifloxacin, additional clinical data from studies of CAP and ABECB. The additional CAP data and re-analyses of existing CAP data provide information on the severity of disease in patients from the CAP clinical studies and treatment of CAP due to resistant *S. pneumoniae*.

In the paragraphs that follow, the key issues are summarized. More complete details are available within the body of this document. References to the relevant sections of the document are provided within this summary. The reader is also referred to the table of contents within this document.

Microbologic Data

Gemifloxcain exhibits *in vitro* microbiologic activity against a number of gram-negative and gram-positive organisms. While gemifloxacin has lower MIC values for gram-positive organisms than many other flouroquinolones, the AUC and C_{max} values attained with the proposed dosing regimen of 320 mg po qd, is lower than for other fluoroquinolones, and largely offsets the MIC value advantage.

Community Acquired Pneumonia (CAP)

The clinical data in support of the proposed CAP indication were derived from a total of 6 studies. Four of the studies were controlled studies, three of which were double-blind randomized studies. There were also 2 additional uncontrolled studies (Table 1).

Table 1. Community Acquired Pneumonia: Controlled and Uncontrolled Studies of Gemifloxacin

Study	Treatment Regimen	Duration	N*	Geographic Region
Controlled studies				
011	gemifloxacin 320 mg po qd	7 days	168	Europe, S. Africa
	amoxicillin /clavulanate po 1g/125 mg tid	10 days	156	
012	gemifloxacin 320 mg po qd	7 or 14 days	319	U.S. Canada, Europe,
	cefuroxime 500 mg po bid /clarithromycin 500 mg po bid	7 or 14 days	322	S. Africa
049	gemifloxacin 320 mg po qd	7 or 14 days	290	U.S., Mexico, Spain
	trovafloxacin 200 mg po qd	7 or 14 days	281	
185	gemifloxacin 320 mg po qd	7-14 days	172	Australia, Europe, Philippines
	ceftriaxone 2g IV qd → cefuroxime 500 mg po bid**	1-7 days + 1-13 days (IV/oral= ≤14)	173	Guatemala, Lebanon, Singapore and North America
Uncontrolled studies				
061	gemifloxacin 320 mg po qd	7 days	216[§]	World-Wide (Except N. America)
287	gemifloxacin 320 mg po qd	7 days	188	Asia, U.S., Mexico Philippines

* N refers to the number of randomized patients (enrolled for uncontrolled studies)
[§] Study 061 was conducted in patients with CAP or ABECB. Only data from the 216 patients with CAP are included in this table and the discussion herein regarding CAP.

The patients enrolled in the CAP studies had a mean age of approximately 55 years of age. The racial distributions in the study populations were approximately 80% white with smaller percentages of Black, Oriental, and other race categories. The results from the controlled CAP studies support that gemifloxacin is non-inferior to its comparators (Table 2). Three of the four controlled CAP studies used a gemifloxacin regimen of "7 or 14 days" or "7 to 14 days." However, the Applicant is asking for a regimen for therapy of CAP of only 7 days duration (i.e., not 7 to 14 days). From the analyses of gemifloxacin associated rash, longer duration of therapy is associated with an increasing rate of rash.

Table 2. Summary of Clinical Response at Follow-Up in the Clinical Per Protocol Population: CAP Controlled and Uncontrolled Studies 011, 012, 049, 185, 061 and 287

	Success Rate		Treatment Difference
	Gemifloxacin % (n/N)	Comparator* % (n/N)	% (95% CI)**
Controlled Studies			
Study 011	88.7% (102/115)	87.6% (99/113)	1.1 (-7.3, 9.5)
Study 012	87.6% (220/251)	92.6% (238/257)	-5.0 (-10.1, 0.2)
Study 049	94.0% (202/215)	89.9% (186/207)	4.1 (-1.1, 9.3)
Study 185	92.2% (107/116)	93.4% (113/121)	-1.15 (-7.73, 5.43)
Uncontrolled Studies			
Study 061	91.7% (154/168)	-	(86.1, 95.2)
Study 287	89.8% (132/147)	-	(84.9, 94.7)

Analyses were conducted by both the Applicant and the Agency to evaluate treatment outcomes in patients by duration of therapy. The results of the Agency's analysis presents clinical response in the CAP studies for patients where the only protocol specified duration of therapy was 7 days of therapy and then separately for the patients who were in the 7-day planned duration of treatment group or the 14-day planned duration treatment group from studies that include the option for "7 or 14 days" or "7 to 14 days." (note: "14-days" in Table 3 includes all patients who were to receive a planned duration of therapy of more than 7 days.) In the CAP studies that include durations of therapy of "7 or 14 days" or "7 to 14 days," patients were not randomized to 7 or 14 days.

Table 3. FDA Analysis of Clinical Response at Follow up by Duration of Therapy – Clinical Per Protocol Population

7-day CAP studies*	**Treatment Group**	
	Gemifloxacin n/N (%)	**Comparators n/N (%)**
Controlled (011)	102/115 (88.7)	99/113 (87.6)
Uncontrolled (061, 287)	286/315 (90.8)	
Combined (Controlled and Uncontrolled)	388/430 (90.2)	
"7 -14" day CAP studies**		
7 days	329/363 (90.6)	319/348 (91.7)
14 days†	200/219 (91.3)	218/237 (92.0)
All patients	529/582 (90.9)	537/585 (91.8)

* includes Studies 011, 061, and 287

** includes Studies 012, 049, and 185 – all were controlled studies

† note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

The duration of treatment was for 7 days with an option to extend to 14 days in Studies 012 and 049. Study medication could be extended to 14 days if the patient had a severe infection, if the pneumonia was confirmed or suspected to be due to an atypical pathogen (including *Legionella pneumophil*a), or at the investigators' discretion in Studies 012 and 049. All patients received 7 days of treatment with gemifloxacin in Study 011. In the CAP studies where treatment beyond 7 days was an option under the protocol, 35% to 40% patient received a duration of treatment beyond 7 days.

The Applicant also provides data on evaluating outcomes of CAP in relation to severity of CAP based upon baseline characteristics using the Fine score. (In most instances, the scoring was applied retrospectively using the available data.) The Applicant seeks a claim for community acquired pneumonia for gemifloxacin tablets 320 mg po qd for 7 days with no limitation on the severity of disease for CAP (i.e., not just an indication for mild and moderate CAP). The majority of the patients that investigators enrolled in the CAP studies were Fine category I – III. Approximately 10% of patients enrolled in the CAP studies were categorized as Fine class IV. There were 4 total Fine Class V patients in the ITT population from all of the CAP studies. Analysis of the mortality rates for patients by Fine category in the patients in Fine Class IV were less than what has been reported by Fine et. al.[1] (Table 4).

Table 4. Fine Score Risk Class Specific Mortality Rates - CAP studies/ITT – All Patients

Fine Class (score)*	Data from NDA 21-158 Factive (gemifloxacin)						Data from Fine et. al.[1]			
	Comparative Studies				Non-Comparative Studies		MedisGroups Validation Cohort		Pneumonia PORT Validation Cohort All Patients	
	gemifloxacin		comparators		gemifloxacin					
	Number of patients	n (%) who died	Number of patients	n (%) who died	Number of patients	n (%) who died	Number of patients	(%) who died	Number of patients	(%) who died
	n	n (%)	n	n (%)	n	n (%)	n	(%)	n	(%)
I	347	1 (0.3%)	369	3 (0.8%)	154	0	3,034	(0.1)	772	(0.1)
II (≤70)	330	2 (0.6%)	287	2 (0.7%)	166	3 (1.8%)	5,778	(0.6)	477	(0.6)
III (71-90)	164	4 (2.4%)	181	3 (1.7%)	63	2 (3.2%)	6,790	(2.8)	326	(0.9)
IV (91-130)	104	5 (4.8%)	90	4 (4.4%)	21	0	13,104	(8.2)	486	(9.3)
V (>130)	4	0	5	1 (20.0%)	0	0	9,333	(29.2)	226	(27.0)
Total	949	12 (1.3%)	932	13 (1.4%)	404	5 (1.2%)	38,039	(10.6)	2287	(5.2)

While a variety of explanations for the lower observed mortality rates in the class IV patients in the NDA 21-158 data are possible, it is conceivable that patients that investigators were willing to consider for enrollment in a CAP study that included an oral agent and the inclusion/exclusion criteria for the studies lead to the enrollment of patients with a more limited spectrum of CAP severity. Hence, a selection bias against including patients with more severe illness may explain the lower mortality rates observed in the Fine class IV patients. There are too few patients of Fine class V to allow any assessments to be made regarding mortality in this group of patients.

The Applicant's proposed indication for CAP includes claims for penicillin-, clarithromycin- and cefuroxime-resistant strains of *Streptococcus pneumoniae*.

> **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including penicillin-, clarithromycin- and cefuroxime-resistant strains*)*, *Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella catarrhalis; Mycoplasma pneumoniae; Chlamydia pneumoniae; Legionella pneumophila; Staphylococcus aureus.*
> (Source: Applicant's proposed labeling for Factive (gemifloxacin), NDA 21-158)

[1] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243-50.

The efficacy data from patients with *S. pneumoniae* including data for penicillin-resistant as their baseline pathogen in CAP is summarized beginning on page 55 of this document.

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)
In the Applicant's principle ABECB studies the results support that gemifloxacin was non-inferior to its comparator agents. In addition to data in support of safety and efficacy, the Applicant also provides data regarding other findings from the ABECB studies (e.g., exacerbation free intervals, time to discharge, hospitalizations due to respiratory tract infections, time to eradication of bacterial pathogens, especially *H. influenzae*). These findings are discussed in detail in the section of this document addressing ABECB. The discussions describe the findings in the context of the objectives of the study, whether the finding is one of the pre-specified primary or one of several secondary endpoints, whether adjustments have been made for multiple comparisons, and the potential clinical implications of the finding. For more information on the results in ABECB please refer to pages 58 to 68 of this document.

Rash
During the review of the initial submission of NDA 21-158 for gemifloxacin a higher than expected rate of rash was noted in the clinical studies. The rates of rash ranged from less than 1% to higher than 25% depending upon the population or subset of the population being analyzed. Analyses of the rash data have shown that female gender, age (younger adults), and longer duration of therapy are associated with an increased rate of rash. An analysis of rate of rash by age, gender, and duration from the original NDA submission (note that the data include a number of indications in addition to ABECB and CAP) is provided in Figure 1.

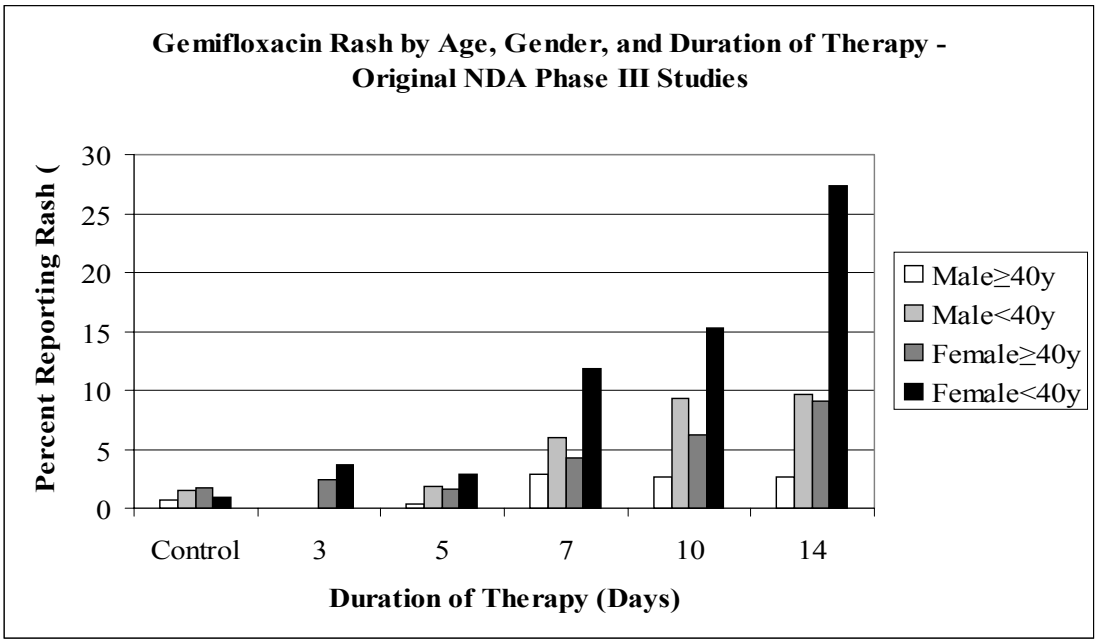

Figure 1. Gemifloxacin Associated Rash by Age, Gender, and Duration of Therapy – Original NDA Phase III Studies. Note includes Data from Phase III Studies from a number of indications. (See Appendix A, for additional information – some analysis points are derived from small numbers of patients; Source: Applicant's April 10, 2001 submission to NDA 21-158.)

Because the data in Figure 1 include data from populations beyond just the clinical studies in ABECB and CAP, it provides information about rates of rash in these other populations. This may be an important consideration because the patients outside of a clinical study (i.e., in real world clinical use) may be more heterogenous than the clinical trials population. For example, based upon data provided by the Applicant regarding antibiotic usage by age and indication, approximately one quarter of antibiotic usage for ABECB is for adults between the ages of 19 to 40 years of age.[2]

A study designed specifically to further evaluate gemifloxacin associated rash was performed (Study 344). The objectives of the study were to characterize the following:

- Clinical and histological characteristics of gemifloxacin associated rash
- Potential for cross sensitization to ciprofloxacin in subjects who experienced gemifloxacin-associated rash
- Potential for subclinical sensitization to repeat exposure to gemifloxacin in subjects not developing a rash on first exposure to gemifloxacin
- Relationship between plasma levels of gemifloxacin and N-acetyl gemifloxacin and the incidence of rash

[2] Applicant's Briefing Document for NDA 21-158, January 28, 2003, Appendix A, page 152, Table 2.

Study 344 was a double-blind, double dummy study. Healthy female subjects 18 to 40 years of age were recruited in order to enroll a population at higher risk for gemifloxacin associated rash. In Part A of the study, subjects were randomized in a 5:1 ratio to gemifloxacin 320 mg po qd or ciprofloxacin 500 mg po bid for 10 days (or until rash developed) (Figure 2). Individuals who developed rash underwent a standardized clinical and dermatological evaluation, skin biopsy, and other standardized laboratory evaluations. Four weeks after completing Part A of the study, subjects entered into Part B of the study. In Part B of the study, subjects who developed rash to gemifloxacin were randomized to receive either placebo or ciprofloxacin 500 mg po bid for 10 days. Subjects that did not develop a rash to gemifloxacin were randomized in a 3:1 ratio to receive either gemifloxacin 320 mg po qd for 10 days or placebo. Subjects who developed a rash to ciprofloxacin received placebo for 10 days in Part B (both "gemifloxacin" and "ciprofloxacin" placebo were received). Patients who did not develop a rash to ciprofloxacin in Part A received ciprofloxacin 500 mg po bid for 10 days.

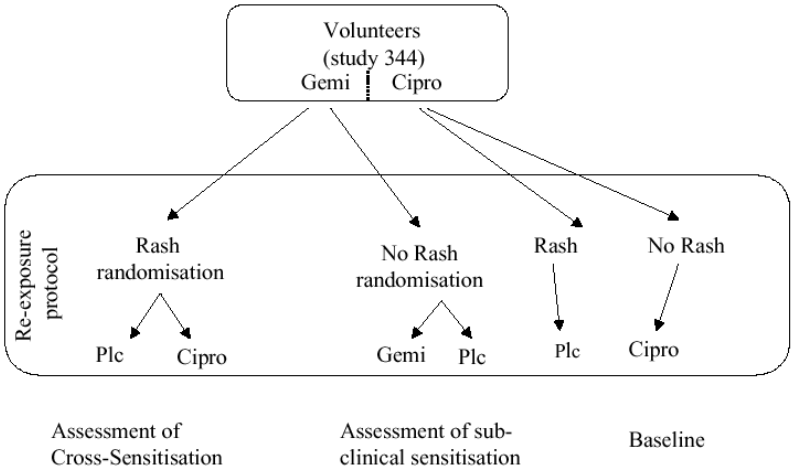

Figure 2. Study Design for Study 344
Source: Applicant's Figure 1, NDA 21-158, Report for Study 344, p. 30

A total of 1011 healthy female subjects enrolled in Part A of Study 344 of which 983 were evaluable. Of these 983 evaluable subjects, 819 received gemifloxacin and 164 received ciprofloxacin. In Part A of the study there were 25 withdrawals due to rash related AEs, all were in the gemifloxacin arm of the study. This represents approximately 3% of the patients in the gemifloxacin arm in Part A. (Note: more patients were enrolled in the gemifloxacin arm in Part A because of 5:1 randomization.)

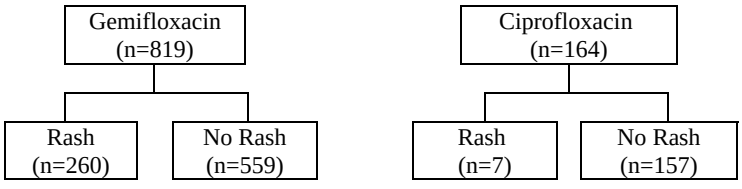

Figure 3. Summary of subject disposition in Part A
Source: Applicant's Figure 1, NDA 21-158, Report for Study 344, p. 88

In the gemifloxacin arm in Part A, 31.7% (260/819) of subjects developed rash. The rate of rash in the ciprofloxacin arm was 4.3% (7/164) (Table 5).

Table 5. Point Estimates and 95% Confidence Intervals for Incidence of Rash in Part A

Regimen	No. of Subjects	Subjects With Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemifloxacin	819	260	31.7	(28.5, 35.0)	(28.6, 35.1)
Ciprofloxacin	164	7	4.3	(0.9, 7.7)	(1.7, 8.6)

Source: Applicant's Table 14.1 from NDA 21-158 18 month Safety Update

In Part A, the median day of onset of gemifloxacin associated rash was day 9 and the median number of days of duration of gemifloxacin-associated rash was 6.

The clinical descriptions of the rashes experienced in Part A by treatment group are summarized in Table 6. The most frequently reported rash findings/symptoms were macules, papules, and pruritus.

Table 6. Summary of Description of Rash in Part A by Regimen and Severity.

Regimen	Severity			
Description	**Mild (%)**	**Moderate (%)**	**Severe (%)**	**Total (%)**
Gemi (n=260)	161/260 (62)	80/260 (31)	19/260 (7)	260/260 (100)
Macules	125 (48.1)	70 (26.9)	14 (5.4)	209 (80.4)
Papules	122 (46.9)	71 (27.3)	17 (6.5)	210 (80.8)
Plaques	15 (5.8)	11 (4.2)	3 (1.2)	29 (11.2)
Pruritus	99 (38.1)	65 (25)	16 (6.2)	180 (69.2)
Skin Tenderness	12 (4.6)	6 (2.3)	4 (1.5)	22 (8.5)
Urticaria	18 (6.9)	6 (2.3)	6 (2.3)	30 (11.5)
Cipro(n=7)	6/7 (85.7)	1/7 (14.3)	0 (0)	7/7 (100)
Macules	3 (42.9)	0 (0)	0 (0)	3 (42.9)
Papules	5 (71.4)	1 (14.3)	0 (0)	6 (85.7)
Pruritus	3 (42.9)	1 (14.3)	0 (0)	4 (57.1)

Source: Applicant's Table 14.5 fromNDA21-158 Report of Study 344 Appendix C

In Part A of the study there was a greater proportion of patients in the gemifloxacin group with larger proportions of surface area scored as covered with rash (Table 7).

Table 7. Summary of Surface Area Covered with Rash by Regimen and Severity of Rash in Part A

Regimen	Surface Area Covered	Severity			Total
		Mild	Moderate	Severe	
Gemifloxacin	Unknown	5 (1.9%)	0 (0.0%)	0 (0.0%)	5 (1.9%)
	0 - 5%	37 (14.2%)	3 (1.2%)	0 (0.0%)	40 (15.4%)
	6 - 10%	21 (8.1%)	4 (1.5%)	2 (0.8%)	27 (10.4%)
	11 - 20%	32 (12.3%)	7 (2.7%)	0 (0.0%)	39 (15.0%)
	21 - 40%	21 (8.1%)	12 (4.6%)	2 (0.8%)	35 (13.5%)
	41 - 60%	28 (10.8%)	17 (6.5%)	2 (0.8%)	47 (18.1%)
	>60%	17 (6.5%)	37 (14.2%)	13 (5.0%)	67 (25.8%)
	Total	**161 (61.9%)**	**80 (30.8%)**	**19 (7.3%)**	**260 (100.0%)**
Ciprofloxacin	Unknown	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	0 - 5%	4 (57.1%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	6 - 10%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	11 - 20%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	21 - 40%	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	41 - 60%	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
	>60%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	**6 (85.7%)**	**1 (14.3%)**	**0 (0.0%)**	**7 (100.0%)**

Source: Applicant's Table 14.6 from NDA 21-158 Report of Study 344 Appendix C

There were 16 subjects for whom mucus membrane involvement was noted among the 260 subjects who developed gemifloxacin rash (6.2%) and none in the 7 subjects who developed a rash secondary to ciprofloxacin. Review of the available case report forms revealed 5 subjects with one to a few ulcerations, erosions, papules, or vesicles inside the mouth or on the lips; 2 patients had erythema of the lips or inside the mouth, one of whom received systemic steroids; 2 additional subjects had illegible descriptions of the oral findings on the case report forms, one of whom received systemic steroids.

Patient disposition in Part B of Study 344 is summarized in Figure 4.

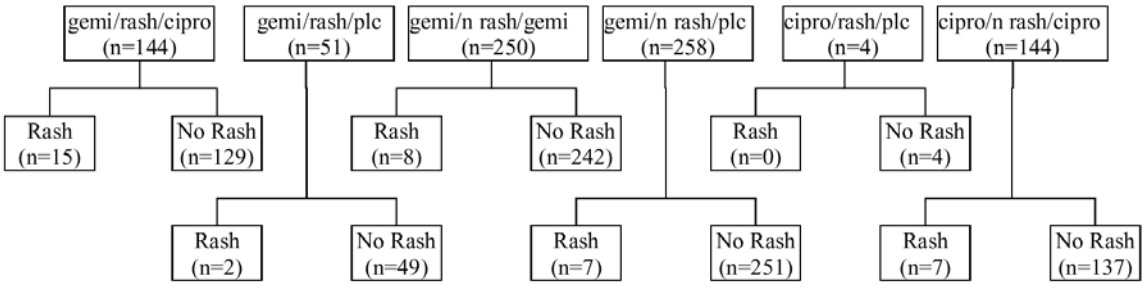

Figure 4. Patient Disposition in Part B of Study 344

The rates of rash for the Part B subjects in the Gemi/rash/cipro group was 5.9% compared to 2.0% in the Gemi/rash/placebo group (Table 8). As noted previously, one of the objectives of the study was to make an assessment of the degree of cross-sensitization of gemifloxacin to ciprofloxacin.

Table 8. Point Estimates and 95% Confidence Interval for Incidence of Rash in Part B – Excludes Center 027*

Regimen	No. of Subjects	Subjects with Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemi/rash/cipro	136	8	5.9	(1.6, 10.2)	(2.6, 11.3)
Gemi/rash/plc	50	1	2.0	(0.0, 6.9)	(0.1, 10.6)
Gemi/N rash/gemi	248	6	2.4	(0.3, 4.5)	(0.9, 5.2)
Gemi/N rash/plc	256	5	2.0	(0.1, 3.8)	(0.6, 4.5)
Cipro/rash/plc	4	0	0.0	(0.0, 12.5)	(0.0, 60.2)
Cipro/N rash/cipro	141	5	3.5	(0.1, 7.0)	(1.2, 8.1)

Data Source: Applicant's Table 21 NDA 21-158, Study Report Study 344, p. 00093.
*Excluded because of a remarkably high rate of rash and lack of corroborative evidence to support the high rash rate in Part B (e.g., photographs confirming the presence of rash)

Additional statistics and findings characterizing the rash for the different groups in Part B are provided in the body of this document.

Skin biopsies for histopathologic evaluation were obtained from 288 of the 299 total rash episodes in Parts A and B of Study 344 secondary to gemifloxacin, ciprofloxacin or occurring in the placebo arm. Punch biopsies were obtained from both affected and unaffected skin. Specimens were evaluated by routine histologic examination, immunophenotypic evaluation, and stained for immunoflourescence for IgG, IgM, IgA, and C3.

The following findings were obtained:

- Most common finding-mild superficial perivascular infiltrate.
- 10 cases of moderate superficial or deep perivascular infiltrate.
- 10 cases of eosinophils in the infiltrate (1 in unaffected skin.)
- T cell type infiltrate, both CD-4 and CD-8 with no common pattern noted.
- No evidence of vasculitis
- Activation of endothelial cells –staining for ICAM and HLA-DR.
- HLA-DR staining was noted in a significant number of cases.
- Immunoflourescence revealed faint deposits of IgM and/or C3 in dermal vessels "lumina" in some cases of unaffected and affected skin.
- One case of linear IgM along basement membrane (affected and unaffected skin)
- No bulla formation, no epidermal or eccrine necrosis.

Liver

In addition to gemifloxacin-associated rash, there have also been questions regarding the hepatic safety of gemifloxacin. In preclinical studies in dogs, gemifloxacin was associated with cholangitis and pericholangitis associated with hepatocellular degeneration and single cell necrosis. Also noted was crystalline material that had deposited in the bile ducts and bile canaliculi. Spectroscopic analysis found the deposited material to be gemifloxacin or gemifloxacin-derived material. In studies in women who received a single dose of 640 mg (twice the proposed dose of 320 mg) there was a greater proportion of patients that developed elevations of AST and ALT at the On-therapy visit compared to women receiving a ciprofloxacin comparator. (Results for ALT are shown in Table 9.)

Table 9. Number (%) of Patients with ALT Values in the Specified Ranges at the On-Therapy Visit (Gemifloxacin 640mg vs. Ciprofloxacin 250mg, Patients In-Range at Screening)

Analyte	Range	Treatment Group: Gemifloxacin 640mg Single Dose N =638		Treatment Group: Ciprofloxacin 250mg bid N = 662	
		n/N*	(%)	n/N*	(%)
ALT	<ULN	569/592	(96.1)	600/606	(99.0)
	ULN-<2xULN	14/592	(2.4)	6/606	(1.0)
	2-<4xULN	4/592	(0.7)	0/606	
	4-<6xULN	1/592	(0.2)	0/606	
	6-<8xULN	3/592	(0.5)	0/606	
	≥8xULN	1/592	(0.2)	0/606	

Data Source: Applicant Table 370 from NDA 21-158 ISS

*n/N= number of patients outside limit/number of patients evaluated for the particular parameter

In the clinical studies in the combined population, the proportion and levels of elevations of ALT and AST were similar between treatment groups. With regards to serious adverse events, there were three patients within the gemifloxacin treated patient group with the adverse event of hepatic enzymes increased. Review of these cases and other selected patients with hepatic adverse events suggest the possibility that gemifloxacin may induce elevated hepatic enzymes and raises the question whether this is a signal for the potential for more serious less frequent adverse events involving the liver.

Cardiac Repolarization

Gemifloxacin, similar to some of the other members of the quinolone class, appears to have the capacity to effect cardiac repolarization. In the NDA clinical studies in the combined population, gemifloxacin was associated with a mean degree of QT prolongation of $\leq$ 5 milliseconds.

Summary of Some Issues for Consideration: There are a variety of complex issues related to both safety and efficacy of Factive (gemifloxacin) including the following:

- The rate and characteristics of gemifloxacin-associated rash and the possibility that more serious, less frequent cutaneous adverse events may occur in the setting of larger numbers of exposed patients.
- The impact of gemifloxacin associated rash on the patient, clinical practice (e.g., because of the higher rate of rash will more patients be labeled as "quinolone allergic" and in essence have quinolones removed from their available antibiotic armamentarium), and public health.
- How the drug is likely to be used in "real world" clinical practice as opposed to a clinical trial setting.
- The *in vitro* and clinical data with regards to *S. pneumoniae* – including the Applicant's proposed resistant pathogen claims for penicillin-, clarithromycin- and cefuroxime-resistant strains of *Streptococcus pneumoniae*.
- The potential for hepatic toxicity given the findings of elevations in ALT and AST on therapy with doses greater than the proposed dose of 320 mg po qd.
- The effects on cardiac repolarization (i.e., QT effects).

We ask that the Committee consider theses issues and the overall risks versus benefits of Factive (gemifloxacin mesylate) tablets.

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I. Summary of preclinical and clinical pharmacology information

Microbiology

Gemifloxacin is a synthetic fluoroquinolone antibacterial agent. Gemifloxacin has *in vitro* activity against a number of gram-negative and gram-positive organisms. A summary of gemifloxacin's activity *in vitro* along with the activity of several other fluoroquinolones is provided in Table 10.

Table 10. *In vitro* Activity of Gemifloxacin Compared to other Fluoroquinolones (MIC_{90}* μg/mL)

Organism	**GEMI**	CIPRO	LEVO	TROV	GREP	OFL
Streptococcus pneumoniae	**0.03**	2.0	1.0	0.25	0.25	2.0
Streptococcus pyogenes	**0.03**	1.0	1.0	0.12	0.5	2.0
Streptococcus agalactiae	**0.06**	1.0	1.0	0.25	0.5	2.0
Viridans Group streptococci	**0.06**	≥4.0	1.0	0.25	0.5	4.0
Staphylococcus aureus (methicillin sensitive)	**0.06**	1.0	0.5	0.12	0.12	1.0
Staphylococcus aureus (methicillin resistant)	**≥8.0**	≥4.0	≥8.0	4.0	≥32	≥8.0
Staphylococcus epidermidis	**1.0**	≥4.0	≥8.0	4.0	≥32	≥8.0
Staphylococcus saprophyticus	**0.03**	1.0	0.5	0.12	0.12	1.0
Acinetobacter species	**≥8.0**	≥4.0	≥8.0	≥8.0	8.0	≥8.0
Enterococcus faecalis	**4.0**	≥4.0	≥8.0	≥8.0	≥32	≥8.0
Haemophilus influenzae	**0.03**	0.03	0.03	0.03	0.015	0.12
Haemophilus parainfluenzae	**0.06**	0.06	0.06	0.12	0.12	0.25
Moraxella catarrhalis	**0.015**	0.06	0.06	0.03	0.015	0.12
Escherichia coli	**0.25**	0.5	0.5	0.5	0.5	1.0
Klebsiella pneumoniae	**0.5**	1.0	1.0	1.0	1.0	4.0
Klebsiella oxytoca	**0.12**	0.25	0.25	0.12	0.12	0.5
Enterobacter aerogenes	**≥8.0**	≥4.0	≥8.0	≥8.0	≥32	≥8.0
Enterobacter cloacae	**0.25**	0.5	0.5	1.0	0.5	2.0
Morganella morganii	**0.25**	0.25	0.5	1.0	0.5	1.0
Serratia marcescens	**1-4**	0.5-4	0.5	2->16	----	----
Citrobacter freundii	**2.0**	2.0	2.0	4.0	2.0	4.0
Proteus mirabilis	**4.0**	1.0	1.0	≥8.0	16.0	4.0
Proteus vulgaris	**0.25**	0.06	0.06	0.5	0.5	0.25
Morganella morganii	**0.25**	0.25	0.5	1.0	0.5	1.0
Pseudomonas aeruginosa	**≥8.0**	≥4.0	≥8.0	≥8.0	≥32	≥8.0
Bacteroides fragilis	**2.0**	16.0	4.0	1.0	---	2.0
Fusobacterium nucleatum	**0.25**	4.0	0.5	1.0	---	2.0
Prevotella species	**2.0**	16.0	1.0	1.0	---	8.0
Clostridium species	**2.0**	---	>16.0	8.0	---	---
Peptostreptococcus species	**0.25**	4.0	4.0	0.5	---	8.0
Chlamydia pneumoniae	**0.25**	0.25-0.5	1.0	1.0	---	---
Mycoplasma pneumoniae	**0.12**	---	0.5	0.25	---	---
Legionella pneumophila	**0.015**	0.03	0.015	0.004	---	---

GEMI = gemifloxacin; CIPRO = ciprofloxacin; LEVO = levofloxacin; TROV = trovafloxacin; GREP – grepafloxacin; OFL = ofloxacin

* minimum concentration values for inhibiting 90% of the isolates

Source: Data compiled from NDA 21-158

When comparing these *in vitro* data it is important to consider that although gemifloxacin generally has much lower MIC_{90} values, especially against gram-positive aerobes, its susceptible breakpoint is 4-8 times lower than that for most other fluoroquinolones (the proposed FDA breakpoint is 0.12 μg/mL). While gemifloxacin has good activity against most gram-positive microorganisms, it is somewhat less active against a number of the gram-negative

Enterobacteriaceae (e.g. *Escherichia. coli* and *Klebsiella pneumoniae*). Like most other fluoroquinolones it has poor activity against *Pseudomonas aeruginosa, Enterococcus* species, and anaerobes.

Activity Against Key Respiratory Pathogens

Gemifloxacin's *in vitro* MIC_{90} values against *Streptococcus pneumoniae* are 4-8 times lower than those of trovafloxacin and moxifloxacin and over 16-64 times lower than the MIC_{90} values for ciprofloxacin and levofloxacin (Table 10 & Table 11). At the proposed human dose, the AUC value for gemifloxacin (8.4 μg/mL) is only about one-fourth that of most of the other fluoroquinolones. Therefore the four-fold lower gemifloxacin MIC_{90} value for *Streptococcus pneumoniae* compared to trovafloxacin or moxifloxacin is largely offset by the lower AUC values achieved with gemifloxacin at the proposed dose of 320 mg orally once daily.

Table 11. *In vitro* Activity of Gemifloxacin and Comparators Against *S. pneumoniae*

No. of Isolates	Gemifloxacin MIC_{90} (μg/mL)	Ciprofloxacin MIC_{90} (μg/mL)	Levofloxacin MIC_{90} (μg/mL)	Gatifloxacin MIC_{90} (μg/mL)	Moxifloxacin MIC_{90} (μg/mL)
6247	0.047	NT	1	NT	NT
550	0.03	2	1	0.5	0.25
1450	0.06	1	1	0.25	NT

NT = not tested

Gemifloxacin had an MIC_{90} value of 0.008 μg/mL against *Haemophilus influenzae*. Gemifloxacin's activity against *Haemophilus influenzae* was similar to that of ciprofloxacin, levofloxacin, and gatifloxacin (MIC_{90}s of 0.015 μg/mL). Moxifloxacin had a slightly higher MIC_{90} value of 0.03 μg/mL. All of these fluoroquinolones had low MIC values against *H. influenzae*. Gemifloxacin's MIC values were slightly lower but again, one should also consider that its AUC is 4-fold lower than most of the comparators (Table 12).

Table 12. *In vitro* activity of gemifloxacin and comparators against 290 *H. influenzae* isolates from U.S. hospitals

Compound	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Gemifloxacin	≤0.001-0.03	0.004	0.008
Ciprofloxacin	0.004-0.03	0.015	0.015
Levofloxacin	≤0.004-0.12	0.015	0.015
Gatifloxacin	≤0.002-0.03	0.008	0.015
Moxifloxacin	0.004-0.12	0.015	0.03

Source: Data from reference 3

Gemifloxacin had an MIC_{90} value of 0.015 μg/mL against *Moraxella catarrhalis* (Table 13). The other fluoroquinolones tested had MIC_{90} values 2 to 4 times higher. All of the fluoroquinolones tested showed good activity against *Moraxella catarrhalis*.

[3] SB-265805/RSD-101MM9/1. *In vitro* Activity of Gemifloxacin and Comparators against Recent Clinical Isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella catarrhalis.* N Scangarella and C Jakielaszek. 4 October 2001.

Table 13. *In vitro* activity of gemifloxacin and comparators against 205 *M. catarrhalis* isolates from U.S. hospitals

Compound	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Gemifloxacin	0.004-0.03	0.015	0.015
Ciprofloxacin	0.03-0.12	0.03	0.06
Levofloxacin	0.03-0.25	0.03	0.06
Gatifloxacin	0.015-0.12	0.03	0.03
Moxifloxacin	0.03-0.25	0.06	0.06

Source: Data from Reference 3

Mechanism of Action

All of the fluoroquinolones target both DNA gyrase and topoisomerase IV. Older drugs such as ciprofloxacin and levofloxacin target one enzyme to a much greater extent than they do the other enzyme. The usual preference is topoisomerase IV in Gram-positive bacteria and DNA gyrase in Gram-negative bacteria. Some studies suggest that moxifloxacin and gatifloxacin target the *gyrA* (DNA gyrase) in *Streptococcus pneumoniae*. Other studies suggest that *parC* (topoisomerase IV) is the primary target for these two drugs in *S. pneumoniae* just as it is for ciprofloxacin and levofloxacin. This apparent conflict may reflect that moxifloxacin and gatifloxacin have almost equal affinity for both enzymes. This dual mechanism (dual enzyme targets) has also been suggested for gemifloxacin. The 50% inhibitory concentration (IC_{50}) values for binding of gemifloxacin to the *parC* and *gyrA* subunits of topoisomerase IV and DNA gyrase have been assessed in a number of studies. A topoisomerase IV IC_{50} of 1.2 μg/mL and a DNA gyrase IC_{50} of 2 μg/mL for gemifloxacin have been reported in one study. A similar study, however, reported values of 1.4 μg/mL for topoisomerase IV and 47.5 μg/mL for DNA gyrase.

A single mutation in the preferred target sight (usually *parC* in *S. pneumoniae*) causes a 2-4 fold increase in the MIC for all the fluoroquinolones. This usually does not cause the MIC to reach the resistant category, except, for ciprofloxacin for which the MIC_{90} for *S. pneumoniae* is typically very close to the breakpoint. Mutations in both *parC* and *gyrA* causes a large increase in the MICs for all fluoroquinolones. This increase causes high level resistance against levofloxacin and ciprofloxacin. Although the MIC values for moxifloxacin and gemifloxacin increase 16-32 fold these values may still be around the intermediate range. Data examining the shift in MIC_{90} values for several ciprofloxacin-selected *S. pneumoniae* isolates are summarized in Table 14.

Table 14. MICs (μg/mL) of Ciprofloxacin-Selected *S. pneumoniae* Mutants

Mutation	MIC (μg/mL)			
	Gemifloxacin	Moxifloxacin	Levofloxacin	Ciprofloxacin
Wild-type	0.016	0.064	0.038	0.5
ParC S79Y	0.064	0.125	1.5	4.0
ParC S79F	0.032	0.125	1.0	2.0
ParC S79Y, *gyrA* S81Y	0.25	2.0	>32	>32
GyrA S81Y	0.023	0.125	0.75	1.0
ParC S79Y	0.064	0.125	1.0	6.0
ParC S79Y	0.047	0.064	1.0	4.0

Source: Data from reference 4

The data in Table 15 demonstrate that double-mutants are probably resistant to levofloxacin, gatifloxacin, and ciprofloxacin but may still be in the susceptible or intermediate range for moxifloxacin and gemifloxacin.

Table 15. Susceptibility of Ciprofloxacin-Intermediate and -Resistant *S. pneumoniae* to Fluoroquinolone Comparators

Strain	MIC (μg/mL)							
	Cip	Levo	Gati	Moxi	Gemi	*ParC* Change	GyrA Change	Efflux
2680	2	1	0.5	0.25	0.03	No	No	No
4610	4	1	0.5	0.25	0.06	Yes	No	No
16702	4	1	0.5	0.25	0.06	No	No	Yes
18705	4	2	0.5	0.25	0.03	Yes	No	Yes
16701	16	8	4	2	0.25	Yes	Yes	No
17012	16	8	4	2	0.12	Yes	Yes	No
18410	16	8	4	2	0.12	Yes	Yes	No

Source: Data from reference 5

In vitro Activity Against Penicillin-Resistant *Streptococcus pneumoniae*

As is the case for all fluoroquinolones, penicillin-resistance did not affect gemifloxacin MICs. The activity of gemifloxacin and other fluoroquinolones against penicillin-susceptible and -resistant *Streptococcus pneumoniae* are summarized in Table 16.

[4] SB-265805/RSD-101MND/1. Evolutionary Barriers to Resistance. SH Gillespie. 12 December 2001.
[5] SB-265805/RSD-101MNF/1. Pharmacodynamic activity of fluoroquinolones against ciprofloxacin-resistant *Streptococcus pneumoniae*. GG Zhanel, D Roberts, A Waltky, N Laing, K Nichol, T Bellyou, and DJ Hoban. 23 December 2001.

Table 16. Summary of gemifloxacin and comparator activity against Penicillin-Resistant *Streptococcus pneumoniae*

Compound	No. of Isolates	MIC Range (μg/mL)	Range of MIC_{90}s (μg/mL)	Median MIC_{90} (μg/mL)
***S. pneumoniae* (Pen-S)**				
Gemifloxacin	**261**	**≤0.004-0.25**	**0.03-0.08**	**0.06**
Moxifloxacin	196	0.06-0.25	0.25	0.25
Trovafloxacin	261	≤0.008-1	0.12-0.25	0.25
Levofloxacin	239	0.06-4	1-2	2
Ciprofloxacin	261	0.12-8	1-4	2
***S. pneumoniae* (Pen-I)**				
Gemifloxacin	**72**	**≤0.008-0.12**	**0.03-0.12**	**0.03**
Moxifloxacin	39	0.06-0.25	0.12-0.25	0.12
Trovafloxacin	72	≤0.03-0.5	0.12-0.5	0.25
Levofloxacin	59	0.12-4	1-2	2
Ciprofloxacin	72	0.25-4	1-4	2
***S. pneumoniae* (Pen-R)**				
Gemifloxacin	**51**	**≤0.004-1**	**0.03-0.12**	**0.03**
Moxifloxacin	0	0.06-0.12	0.12	NA
Trovafloxacin	51	≤0.03->8	0.12->8	0.25
Levofloxacin	41	0.5->16	1->16	1
Ciprofloxacin	51	0.25->8	1->8	1

Source: Data compiled from NDA 21-158

In vitro* Activity Against Macrolide-Resistant *Streptococcus pneumoniae

The finding that a *S. pneumoniae* isolate was macrolide (erythromycin or clarithromycin) resistant, also did not affect fluoroquinolone MICs. Macrolide-resistant strains of *S. pneumoniae* had MIC values that were about the same as macrolide-susceptible strains (Table 17).

Table 17. *In vitro* Activity of Gemifloxacin and Comparators Against Macrolide-Resistant *Streptococcus pneumoniae*

Number of Isolates (n)	Macrolide Resistant Criteria	MIC_{90} (μg/mL)			
		Gemifloxacin	Ciprofloxacin	Levofloxacin	Gatifloxacin
1505	Erythromycin MIC ≥ 1 μg/mL	0.047	NT	1	NT
115	Clarithromycin MIC ≥1 μg/mL	0.06	2	2	0.25

NT = not tested
Data from reference [6]

In vitro* Activity Against Quinolone-Resistant *Streptococcus pneumoniae

Studies were provided that tested gemifloxacin against strains with ciprofloxacin MICs ≥ 4 μg/mL and/or levofloxacin MICs ≥ 8 μg/mL. These data are summarized in Table 18. No *in vitro* studies were performed against *S. pneumoniae* strains that were shown to be resistant to moxifloxacin or gatifloxacin.

[6] SB-265805/RSD-101MM8/1. Factive Targeted Surveillance Study. J Johnson. 13 November 2001.

Table 18. Summary of Gemifloxacin and Comparator Activity Against Quinolone-Resistant* *Streptococcus pneumoniae*

Compound	No. of Isolates	MIC Range (μg/mL)	Range of MIC_{90}s (μg/mL)	Median MIC_{90} (μg/mL)
S. pneumoniae **(Quin-S)**				
Gemifloxacin	**332**	**≤0.008-0.25**	**0.06**	**0.06**
Clinafloxacin	125	0.06-0.25	0.12	NA
Trovafloxacin	332	0.016-1	0.25	0.25
Levofloxacin	332	0.12-4	2	2
Ciprofloxacin	207	0.25-4	4	NA
S. pneumoniae **(Quin-R)**				
Gemifloxacin	**160**	**≤0.03-2**	**0.25-1**	**0.5**
Clinafloxacin	57	0.25-4	1	NA
Moxifloxacin	75	0.12-8	4	NA
Trovafloxacin	160	0.25->8	4-8	4
Levofloxacin	160	0.5->32	16->32	>16
Ciprofloxacin	103	4->32	32->32	32

NA = Not applicable—Data is from one study
Data compiled from NDA 21-158
Quinolone resistance was defined in each individual study. Ciprofloxacin MIC ≥ 4 μg /mL and/or levofloxacin MIC ≥ 8 μg/mL

The data from Table 18 shows that the gemifloxacin's MIC_{90} value was ≤0.06 μg/mL, except in studies that tested quinolone-resistant strains. In studies that tested quinolone-resistant strains the MIC_{90} was 0.25-1.0 μg/mL (in the non-susceptible category for gemifloxacin). The MIC_{90} value for gemifloxacin was usually 4-8 fold lower than that of moxifloxacin or gatifloxacin. Since gemifloxacin's AUC value is about 4-8 times lower than that of moxifloxacin or gatifloxacin, these three drugs are probably about equal with regards to *in vitro* activity against "quinolone-resistant" strains. Gemifloxacin's MIC_{90} value was usually 32- to 64-fold better than that of levofloxacin or ciprofloxacin. Based upon the MIC_{90} values from the in vitro studies gemifloxacin does appear to have somewhat greater *in vitro* activity compared to levofloxacin and ciprofloxacin against *S. pneumoniae*.

Molecularly Defined Quinolone Resistance

Data were submitted to the NDA on 44 *S. pneumoniae* isolates demonstrating second step mutations in the target binding sites (Table 19). The gemifloxacin MICs were 0.5 μg/mL for 3/44 (7%) of the isolates, 0.25 μg/mL for 22/44 (50%) of the isolates, 0.125 μg/mL for 15/44 (34%) of the isolates, and ≤0.06 μg/mL for 4/44 (9%) of the isolates. If a breakpoint of ≤0.125 μg/mL is chosen (the FDA proposed breakpoint) many of these double mutants (57% of these 44 isolates) will not be susceptible but will be classified as either "intermediate" or "resistant." For these same 44 isolates the moxifloxacin MICs were 4.0 μg/mL (resistant) for 11/44 (25%) of the isolates, 2.0 μg/mL (intermediate) for 25/44 (57%) of the isolates, ≤1.0 μg/mL for 8/44 (18%) of the isolates. Gemifloxacin clearly appears to be more active *in vitro* than ofloxacin, levofloxacin, and ciprofloxacin for which the vast majority of the strains had MICs ≥16 μg/mL. Most of the gatifloxacin MICs were 4-8 μg/mL, which puts them into the resistant (≥4 μg/mL) category.

Gemifloxacin appears to have only a slight, if any, advantage over moxifloxacin if the gemifloxacin susceptible breakpoint is set at ≤ 0.125 μg/mL.

Table 19. Activity of Gemifloxacin and Comparator Quinolones against 44 *S. pneumoniae* Demonstrating Second Step Mutation

***S. pneumoniae* strain**	**MIC for Agent (μg/mL)**					
	GEM	**MOX**	**GAT**	**LEV**	**OFL**	**CIP**
203120	0.25	4	4	16	32	32
205324	0.25	2	4	16	32	32
214152	0.25	2	4	16	32	64
402123	0.25	2	4	16	32	64
403346	0.25	2	8	32	64	64
403413	0.5	4	8	32	64	64
503167	0.25	4	4	16	32	32
503244	0.25	4	8	16	32	64
509063	0.25	2	4	16	32	64
703316	0.5	4	8	32	64	32
707172	0.25	4	4	16	32	64
717146	0.25	2	4	16	32	64
100-1	0.25	4	8	16	32	64
100-2	0.25	2	4	16	32	64
119-3	0.25	2	4	16	32	32
134-26	0.25	2	8	32	64	128
136-1	0.25	4	8	16	32	64
156-5	0.25	4	4	16	32	32
185-5	0.25	4	8	16	32	32
Pt94 19061	0.125	2	4	16	32	64
Pt94 24123	0.25	2	4	16	32	64
12-1982B	0.5	2	8	16	32	64
14016S	0.25	4	8	16	32	32
205229	0.125	2	4	8	16	32
304232	0.125	1	2	8	16	32
502226	0.25	2	4	8	16	32
507103	0.06	2	4	8	16	16
717147	0.125	2	4	8	16	16
717176	0.125	2	4	8	16	16
717183	0.125	2	4	8	16	16
723084	0.125	1	2	8	16	16
34013S large	0.125	1	2	8	16	16
TPS 1	0.25	2	4	8	16	32
TPS 3	0.25	2	4	16	16	16
63-5	0.125	1	4	8	16	16
1-28B	0.125	2	4	16	16	16
1-43C	0.125	2	4	16	16	16
17-494B	0.06	2	4	8	16	16
98-641-124S	0.125	2	4	8	16	4
98-631-133S	0.016	0.5	2	8	16	4
622286	0.125	1	2	4	8	16
TPS 5	0.125	2	2	4	8	4
209165	0.125	0.25	1	2	4	8
3093S	0.06	0.125	0.5	1	2	2
MIC_{90}	**0.25**	**4**	**8**	**16**	**32**	**64**
MIC_{50}	**0.25**	**2**	**4**	**16**	**32**	**32**
Geometric Mean	**0.176**	**1.908**	**3.937**	**11.314**	**21.926**	**27.336**
Max MIC	**0.5**	**4**	**8**	**32**	**64**	**128**
Min MIC	**0.016**	**0.125**	**0.5**	**1**	**2**	**2**

GEM=gemifloxacin, MOX=moxifloxacin, GAT=gatifloxacin, LEV=levofloxacin, OFL=ofloxacin, CIP=ciprofloxacin
Source: Data from NDA 21-158

Spontaneous Emergence of Resistance

Single-step mutation frequencies for gemifloxacin and comparator quinolones were investigated against 16 *S. pneumoniae* isolates. Mutation frequency was calculated as the number of resistant colonies per inoculum at 1x, 2x, 4x, 8x, and 16x the MIC of each drug tested. The frequencies of single-step mutations with gemifloxacin ranged from 2.0×10^{-4} to $<1.0 \times 10^{-10}$. This range was equivalent to that seen with gatifloxacin (2.8×10^{-4} to $<1.0 \times 10^{-10}$) and slightly lower than that seen with moxifloxacin (3.0×10^{-4} to $<2.0 \times 10^{-9}$). Ciprofloxacin showed slightly higher frequencies with a range of $>3.0 \times 10^{-1}$ to $<5.0 \times 10^{-9}$**.** Overall, the mutation frequencies were about equal for all the fluoroquinolones tested. As expected the mutation frequencies were much higher at 1 x MIC than at 16 x MIC.

The frequency of selecting gemifloxacin-resistant *S. pneumoniae* compared with moxifloxacin, gatifloxacin, and levofloxacin was investigated. One wild-type strain and nine other strains were studied to determine the frequency of selection of mutants after exposure to multiples (2x and 4x) of the MIC either in the presence or absence of reserpine. The frequencies of mutant selection are shown in Table 20. None of the quinolones selected any mutants from the wild-type strain (M3), strain M26 (ParC Ala79), strain M126 (ParC Tyr79, GyrA Lys85), or strain M129 (Par C Asn83, GyrA Phe81). For those strains from which mutants were selected, the frequency of mutation ranged from 2×10^{-5} to 2×10^{-11}.

The highest gemifloxacin MIC was ≤ 2 μg/mL. The highest MIC seen for moxifloxacin and gatifloxacin was 16 μg/mL, 64 μg/mL for levofloxacin, and 128 μg/mL for ciprofloxacin. It must be remembered, however, that gemifloxacin has pharmacokinetic parameters that are 4-8 times lower than those of most other fluoroquinolones. A gemifloxacin MIC of 2 μg/mL is, therefore, approximately clinically equivalent to a moxifloxacin MIC of 8 to 16 μg/mL.

Reserpine inhibits an efflux pump mechanism present in *S. pneumoniae*. The presence of reserpine affected the numbers of mutants selected after exposure to each of the four agents. This can be seen in Table 20 by either a decrease in the frequency of resistance or inhibition of the selection of mutants in the presence of reserpine. These results suggest that a reserpine-susceptible efflux pump may be a step in fluoroquinolone resistance development. Moxifloxacin was affected to a much lesser extent than the other drugs tested. Many studies show that moxifloxacin is a poor substrate for the efflux pump in *S. pneumoniae.*

Table 20. Frequency of Mutant Selection

Agent	MIC Multiple	M34 ParC Ala79 GyrA Ala85		M35 ParC Ala79 GyrA Tyr81		M122 GyrA Lys85		M123 GyrA Phe81		M128 ParC Tyr79		M130 ParC Asn83	
		Conc. (μg/mL)	Freq. of resistance	Conc. (μg/mL)	Freq. of resistance	Conc. (μg/mL)	Freq. of resistance	Conc. (μg/mL)	Freq. of resistance	Conc. (μg/mL)	Freq. of resistance	Conc. (μg/mL)	Freq. of resistance
Gemi													
	X2	0.5	1.05×10^{-11}	0.5	0	0.12	4.43×10^{-6}	0.12	2.8×10^{-6}	0.06	0	1	2.05×10^{-6}
	X4	1	2.6×10^{-11}	1	0	0.25	1.68×10^{-6}	0.25	4.65×10^{-7}	0.12	0	2	0
	X2 + R	0.5	1.59×10^{-7}	0.5	0	0.12	1.07×10^{-6}	0.12	5.22×10^{-8}	0.06	0	1	6.3×10^{-8}
	X4 + R	1	0	1	0	0.25	5.7×10^{-10}	0.25	7.3×10^{-8}	0.12	0	2	0
Gati													
	X2	8	7×10^{-9}	8	0	1	0	1	0	1	0	8	1.46×10^{-6}
	X4	16	0	16	0	2	0	2	0	2	0	16	1.04×10^{-7}
	X2 + R	8	5.2×10^{-8}	8	0	1	3.8×10^{-8}	1	0	1	0	8	7.47×10^{-7}
	X4 + R	16	0	16	0	2	0	2	0	2	0	16	0
Moxi													
	X2	8	0	4	3×10^{-8}	0.5	0	0.5	1.7×10^{-6}	0.12	0	8	1.4×10^{-5}
	X4	16	0	8	0	1	2×10^{-8}	1	1.8×10^{-7}	0.25	0	16	0
	X2 + R	8	0	4	3×10^{-8}	0.5	0	0.5	8.2×10^{-7}	0.12	0	8	9.18×10^{-6}
	X4 + R	16	0	8	0	1	4.43×10^{-8}	1	7.7×10^{-10}	0.25	0	16	0
Levo													
	X2	32	0	64	0	1	0	2	5.12×10^{-10}	4	2.65×10^{-5}	16	4.67×10^{-6}
	X4	64	0	128	0	2	0	4	2.6×10^{-9}	8	3×10^{-8}	32	0
	X2 + R	32	0	64	0	1	0	2	5.12×10^{-7}	2	3×10^{-8}	16	2.2×10^{-6}
	X4 + R	64	0	128	0	2	0	4	2×10^{-9}	4	0	32	0

R = reserpine, Gemi = gemifloxacin, Gati = gatifloxacin, Moxi = moxifloxacin, Levo = levofloxacin
Data from NDA 21-158

In Vivo Models of *S. pneumoniae* Respiratory Tract Infections

The activity of gemifloxacin and comparator quinolones was examined in an experimental rat respiratory tract infection model. In these studies gemifloxacin was tested in comparison to other quinolones. Rats were infected with a standard inoculum of various strains of *S. pneumoniae*. Therapy commenced 24 hours post infection and the oral doses administered were chosen to approximate the serum and tissue concentrations measured in man following the normal human dose. For all strains with gemifloxacin MICs ≥0.125 μg/mL a different dosing regimen was used; the standard dose was divided and administered twice daily and therapy was started one hour post infection rather than 24 hours post infection**.**

The endpoint used in the study was reduction in the colony forming units (CFU) of bacteria in the lungs compared to untreated control (note: the endpoint is not complete bacterial eradication). A successful outcome was declared if there was a significant difference ($p \leq 0.01$) in the colony forming units of bacteria per gram of lung tissue compared to control. Data that will be discussed in Table 23 demonstrate that isolates with gemifloxacin MICs of ≤0.03 μg/mL had a reduction in bacterial counts to near or below the level of detection.

The data in Table 21 demonstrate that as the gemifloxacin MIC value increases the relative reduction in bacterial count decreases. The magnitude of reduction in bacterial count in the animal model that indicates clinical efficacy has not been determined. In fact one isolate (PT94254123) with a levofloxacin MIC of 16 μg/mL (levofloxacin-resistant) had a significant reduction in bacterial CFU difference from untreated control when treated with levofloxacin. Another fact not apparent from Table 21 is that dosing frequency for isolates with a gemifloxacin MIC of ≥0.125 μg/mL had to be increased to twice a day. Whereas isolates with gemifloxacin MICs of ≤0.03 μg/mL showed good results with bacterial count reduction to near or below the limit of detection with once a day dosing (Table 23).

Table 21. Activity of gemifloxacin against respiratory tract infections in rats caused by *S. pneumoniae*

S. pneumoniae Strain	Resistance profile	MIC (μg/mL)		Log_{10} CFU/Lungs		
		GEMI	LEVO	NTC	GEMI	LEVO
Treatment initiated 1-hour post infection						
1629*	Pen-S	<0.03	0.25	6.8± 1.2	<1.7[a,b]	4.3± 1.6[a]
10127*	Pen-S	<0.03	1	6.4± 1.9	1.9± 0.5 [a,b]	4.1± 1.3 [a]
L11259*	Pen-S	<0.03	1	6.4± 1.9	<1.7[a,b]	5.7± 1.1
406081*	MAC-R	<0.03	0.5	5.0± 0.9	2.2± 0.6 [a,b]	4.5± 1.8
N1387*	MAC-R	<0.03	0.5	5.1± 0.9	2.5± 1.1 [a,b]	3.5± 0.8 [a]
404053*	Pen-R	<0.03	0.5	5.9± 2.9	1.8± 0.2 [a,b]	4.0± 1.4 [a]
205118*	Pen-R	<0.03	NT	6.3± 0.6	3.6± 1.9 [a,b]	6.3± 0.7
Treatment initiated 24-hours post infection						
305313**	CIP-R	0.125	1	7.9 ± 0.4	3.3 ± 1.3[a,b]	5.7 ± 1.3[a]
622286**	CIP-R/MAC-R	0.125	4	6.4 ± 1.3	2.5 ± 1.1[a,b]	5.1 ± 1.3
PT94254123 **	CIP-R	0.25	16	8.1 ± 0.8	4.4 ± 0.7[a,b]	6.8 ± 0.6[a]
402123[+,] **	CIP-R	0.25	8	8.3 ± 0.8	5.7 ± 0.9[a,b]	7.3 ± 1.2
509063[+,] **	CIP-R	0.25	8	6.2 ± 1.6	3.5 ± 1.1[a,b]	6.2 ± 0.7
214152[+,] **	CIP-R	0.5	16	6.6 ± 1.6	3.8 ± 1.4[a]	5.0 ± 1.4
TPS 3[+,] **	CIP-R	0.5	16	6.7 ± 0.4	5.5 ± 1.8	5.9 ± 1.3
TPS 5[+,] **	CIP-R	0.5	32	6.2 ± 0.5	4.5 ± 1.2[a,b]	5.7 ± 0.5
703316[+,] **	CIP-R	0.5	>16	6.6 ± 0.4	6.2 ± 0.9	6.5 ± 0.3
42064	CIP-R	0.5	16	6.7 ± 0.3	5.4 ± 1.9	5.2 ± 1.1

MAC-R = macrolide-resistant; CIP-R = ciprofloxacin-resistant; PEN-S = penicillin-susceptible; PEN-R = penicillin-resistant

GEMI = gemifloxacin; LEVO = levofloxacin; NTC = not-treated control; NT = not tested

[a] Significant difference compared with untreated controls ($p \leq 0.01$)

[b] Significant difference compared with levofloxacin ($p \leq 0.01$)

[+] Genetically-defined second step mutants

* Dosing was once daily and started 24 hours post infection

** Dosing was BID and started 1 hour post-infection

The activity of gemifloxacin in comparison with moxifloxacin and gatifloxacin in experimental models of respiratory tract infection caused by *S. pneumoniae* was also examined. The susceptibility profiles of the strains tested to the agents are shown in Table 22.

Table 22. MICs of gemifloxacin, moxifloxacin, and gatifloxacin against *S. pneumoniae*

S. pneumoniae strain	MIC (μg/mL)		
	GEMI	MOXI	GATI
404053	≤0.03	0.06	0.125
406081	≤0.03	0.125	0.25
205118	≤0.03	0.25	1.0
305313	0.125	2.0	4.0
509063[+]	0.25	2.0	4.0
PT9424123	0.25	2.0	4.0
622286	0.125	1.0	1.0
402123[+]	0.25	2.0	4.0

[+] Genetically-defined second step mutants

GEMI = gemifloxacin, MOXI = moxifloxacin, GATI = gatifloxacin

With the exception of gatifloxacin against *S. pneumoniae* 509063, all therapies were significantly effective compared with untreated controls ($p \leq 0.01$) Table 23. Gemifloxacin showed significant improvement ($p \leq 0.05$) in the relative reduction in CFUs for two of the strains compared to moxifloxacin and gatifloxacin. The two strains for which gemifloxacin appeared to be better than moxifloxacin was a strain with gemifloxacin MIC of ≤0.03 μg/mL and another with a gemifloxacin MIC of 0.125 μg/mL, the two strains with gemifloxacin MICs of 0.25 μg/mL gave basically equivalent results with gemifloxacin and moxifloxacin. Overall it appears that except for gatifloxacin against strain 509063, that all three drugs were similar.

Table 23. Activity of gemifloxacin, moxifloxacin, and gatifloxacin against *S. pneumoniae*

S. pneumoniae strain	Log_{10} CFU/lungs			
	GEMI	MOXI	GATI	NTC
404053	≤1.7	≤1.7	≤1.7	6.5 ± 1.5
406081	≤1.7	≤1.7	≤1.7	6.8 ± 1.0
205118	1.9 ± 0.6 *,**	2.9 ± 1.6	3.7 ± 1.1	6.3 ± 1.1
305313	4.0 ± 0.8	3.5 ± 1.4	4.1 ± 1.4	6.1 ± 1.5
509063[+]	3.8 ± 1.6 *	4.6 ± 1.3	6.1 ± 1.2[c]	7.0 ± 0.4
PT 9424123	3.1 ± 0.7	3.6 ± 1.9	4.0 ± 1.4	6.8 ± 1.4
622286	2.6 ± 1.2 **	4.6 ± 2.0	3.6 ± 2.3	7.4 ± 1.4
402123[+]	3.6 ± 1.1	3.9 ± 1.3	3.1 ± 1.1	6.1 + 2.2

* significantly different compared with GATI $p<0.05$

** significantly different compared with MOXI $p<0.05$

[c] Not significantly different compared to non-treated controls (NTC) $p>0.05$

[+] Genetically-defined second step mutants

Dosing was BID and started one hour post-infusion

Clinical Pharmacology of Gemifloxacin

Absorption, distribution, metabolism, excretion
The bioavailability of gemifloxacin from the tablet formulation is about 61% of that from an IV formulation. The peak plasma concentrations of gemifloxacin after oral administration of tablet formulation are observed at about 1 hour after dosing. The steady-state volume of distribution for gemifloxacin following IV dosing (3.5 L/kg) exceeds total body water (0.60 L/kg), indicating that gemifloxacin distributes widely into tissues (see discussion below). Binding to plasma proteins is about 60 - 70%, and whole blood concentrations and plasma concentrations are similar. The gemifloxacin elimination half-life averages 7 hours. Metabolism does not contribute significantly to gemifloxacin elimination, and there is very little involvement of cytochrome P450 enzymes. Over 60% of the dose is excreted unchanged following either oral or intravenous dosing. Metabolites contribute minimally to gemifloxacin pharmacologic activity, since both metabolite concentrations and pharmacologic activity are low relative to the parent. The main metabolites are from glucuronidation, N-acetylation and isomerization. In human subjects, between-subject variability in plasma concentrations of N-acetyl-gemifloxacin was high, with AUC values ranging from 3 to 74% of the parent gemifloxacin AUC. Gemifloxacin is administered as a racemic mixture. Its (+) and (-) enantiomers have similar pharmacokinetics and pharmacologic activity. Gemifloxacin elimination occurs by both renal (60% of an IV dose) and hepatic (40% of an IV dose) routes. Gemifloxacin renal clearance (11.0 L/h) exceeded glomerular filtration rate (7 L/h), suggesting that active tubular secretion contributes significantly to gemifloxacin excretion by the kidney.

Single-dose pharmacokinetics in healthy subjects
The pharmacokinetics of gemifloxacin is linear over oral doses ranging from 20 to 800 mg. The plasma concentration-time profiles over this dose range are shown in Figure 5.

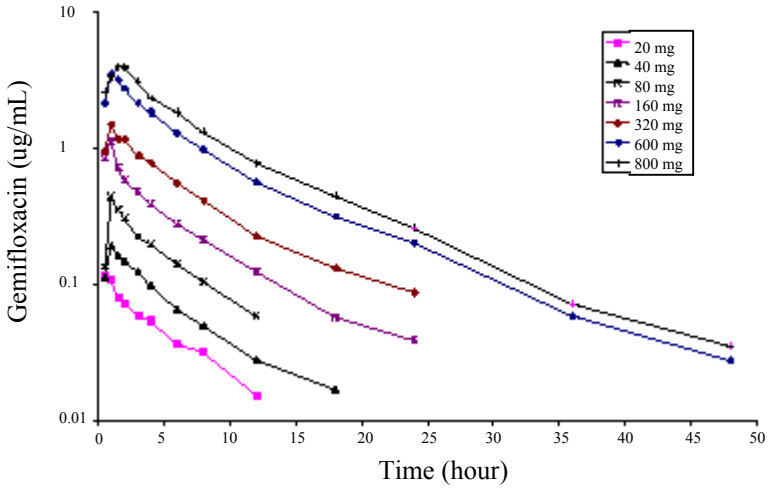

Figure 5. Gemifloxacin Concentration versus time

Steady-state pharmacokinetics
After repeat oral administration of gemifloxacin tablets for 7 days (320mg qd), gemifloxacin did not significantly accumulate in young healthy subjects; the mean observed accumulation ratios were 0.99 to 1.2. The relevant pharmacokinetic parameters of gemifloxacin at steady state are

listed in Table 24. Urinary excretion of gemifloxacin generally accounted for, on average, 25% of the administered oral dose.

Table 24. PK parameters of gemifloxacin in healthy subjects, 320 mg qd x 7 days (Mean ± SD)

AUC_{0-24} (μg·h/mL)	C_{max} (μg/mL)	T_{max} (h)	$T_{1/2}$ (h)	CL/F (L/h)	CL_r (L/h)	Ae (% dose)
9.93±3.07	1.61±0.51	1.00 (0.5-4)[a]	6.94±1.82	35.8±12	11.6±3.9	24.7±6.1

[a]: Median (range)
CL/F = apparent oral clearance; CL_r = renal clearance; Ae = amount of dose excreted in urine

Population pharmacokinetics in patients with bacterial infections
Phase III population pharmacokinetic studies showed that creatinine clearance and total body weight contribute significantly to variability in gemifloxacin pharmacokinetics. Smoking was identified as a nonsignificant covariate for CL/F, since CL/F was ~10% higher for smokers, compared with non-smokers. No other demographic variables, e.g., age, race and gender, co-existing disease or concomitantly administered medication were found to have influenced gemifloxacin disposition.

Renal impairment
A study of gemifloxacin pharmacokinetics in renal impairment as well as population pharmacokinetic analysis showed that gemifloxacin clearance is significantly lower only in severe renal impairment. Thus, it is not necessary to adjust the gemifloxacin dosage in patients with creatinine clearance >40 mL/min. However, the clinical dose of gemifloxacin should be halved (i.e. 160 mg qd) for patients with creatinine clearance <40 mL/min (including hemodialysis and continuous ambulatory peritoneal dialysis patients).

Hepatic impairment
A dosage adjustment is not considered necessary in patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B and C). In a study of gemifloxacin pharmacokinetics in subjects with severe hepatic impairment, AUC_{0-inf} and C_{max} were increased by 45 and 41%, respectively, compared with normal subjects, whereas the elimination half-life ($T_{1/2}$) was unchanged.

Drug interactions
There were no significant metabolism-based (i.e., CYP450 enzymes) pharmacokinetic interactions with gemifloxacin. In both *in vitro* and *in vivo* studies, no pharmacokinetic interactions were observed between gemifloxacin and theophylline (CYP1A2, CYP2E1), omeprazole (CYP2C19), and oral contraceptives (CYP3A4). No pharmacodynamic interaction was demonstrated when gemifloxacin was administered concomitantly with warfarin (CYP2C9). There was no pharmacokinetic interaction between gemifloxacin and digoxin.

As with other fluoroquinolones, there was significant reduction in the oral bioavailability of gemifloxacin when co-administered with products containing Mg^{2+}, Fe^{2+}, or Al^{3+} cations. Gemifloxacin can be administered with antacids/di- and trivalent cations (e.g., aluminum hydroxide, magnesium hydroxide, and ferrous sulfate) if these products are given 3 hours before or 2 hours after gemifloxacin administration. Sucralfate could be given only at 2 hours after gemifloxacin; there was still a significant reduction in gemifloxacin bioavailability at 3 hours before gemifloxacin. Co-administration with calcium (1,000 mg) resulted in ~20% reduction in oral bioavailability of gemifloxacin, regardless of timing of calcium dosing, indicating that gemifloxacin can be co-administered with 1000 mg of calcium.

Co-administration of Probenecid with gemifloxacin significantly reduced the renal clearance of gemifloxacin and increased gemifloxacin systemic exposure (AUC). This is consistent with the renal elimination pathways of gemifloxacin proposed as being comprised of both filtration and active tubular secretion. Only slight changes in gemifloxacin pharmacokinetic parameters (AUC, C_{max}, and $T_{1/2}$) occurred when gemifloxacin was given with Cimetidine (400mg qid).

Tissue distribution
Gemifloxacin is extensively distributed into body tissues and fluids. Concentrations in bronchoalveolar macrophages, bronchial mucosa, and nasal secretions exceeded those in plasma. Concentrations in epithelial lining fluid were similar to those in plasma.

Relationship between gemifloxacin and QT_c prolongation
The effect of gemifloxacin dose on the QT_c interval was also addressed by a meta analysis of 5 phase I studies in young and old healthy subjects. After single doses of 320, 480 and 640 mg, there was no clear trend between gemifloxacin dose and QT_c interval. In contrast to the single dose results, there was a dose-response in QT_c prolongation in the repeated-dose studies (qd administration). The maximum QT_c interval increased with dose. The average change for the 320 mg dose was a -5 msec decrease in maximum QT_c compared to placebo. There were average increases in maximum QT_c of 5.5 and 16 msec for the 480 mg and 640 mg repeated doses, respectively. The results of the meta analysis of QT_c interval vs. repeat doses of 320, 480 and 640 mg qd are shown in Figure 6.

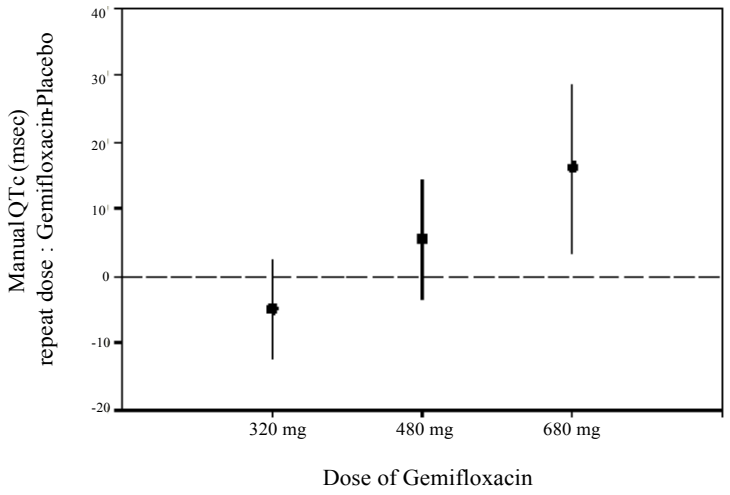

Figure 6. Meta Analysis of Maximum QTc: Repeat Dose Gemifloxacin vs Placebo

Relationship between gemifloxacin plasma exposure and rash incidence (Study 344)
After repeat oral dose of gemifloxacin (320 mg qd for 7days), population pharmacokinetic analysis was performed with data from 840 healthy female subjects participating in a double-blind, parallel group study characterizing gemifloxacin-associated rash. The pharmacokinetic parameters of gemifloxacin and its main metabolite, N-acetyl gemifloxacin, in subjects with and without rash are summarized in Table 25. Gemifloxacin and N-acetyl gemifloxacin exposure (C_{max} or AUC) parameters in subjects who experienced rash did not differ from those without rash. Thus, there were no trends for (a) higher exposure to the drug or N-acetyl gemifloxacin and (b) differences in extent of N-acetylation of gemifloxacin in subjects with rash, compared to those subjects without rash. Furthermore, there was no relationship between occurrence of rash and N-

acetyl transferase type 2 (NAT2) status. Therefore, the occurrence of rash as an adverse event does not appear to be related to the inter-individual differences in systemic exposure to gemifloxacin, its N-acetyl metabolite, or NAT2 status.

Table 25. Individual predicted PK parameters in female subjects with (n=254) and without (n=584) rash

	AUC_{0-24} (μg·h/mL)		C_{max} (Day 1) (μg/mL)		C_{max} (Day 6) (μg/mL)	
	Rash	**No rash**	**Rash**	**No rash**	**Rash**	**No rash**
Gemifloxacin						
Mean ±SD	9.14±2	8.91±2.17	1.21±0.25	1.2±0.23	1.33±0.68	1.26±0.24
Median	8.92	8.64	1.2	1.18	1.25	1.24
95% CI	5.92-13.5	5.41-13.9	0.806-1.75	0.808-1.71	0.854-1.8	0.849-1.8
N-Acetyl Gemifloxacin						
Mean ±SD	1.59±3.6	1.42±3.48	0.177±0.157	0.158±0.149	0.197±0.23	0.178±0.224
Median	0.727	0.582	0.086	0.075	0.092	0.08
95% CI	0.146-6	0.123-5.14	0.024-0.641	0.022-0.551	0.024-0.72	0.022-0.623

II. Community Acquired Pneumonia

Applicant's Proposed Indication for Community Acquired Pneumonia (CAP)

Factive is indicated for the treatment of **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including penicillin-, clarithromycin- and cefuroxime-resistant strains*)*, *Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella catarrhalis; Mycoplasma pneumoniae; Chlamydia pneumoniae; Legionella pneumophila; Staphylococcus aureus*.

The Applicant's proposed dose is one 320 mg tablet orally daily for 7 days.

Studies – Community Acquired Pneumonia

Six clinical studies were performed to investigate the efficacy of gemifloxacin in CAP. Four of the studies were controlled (three of a double-blind design and one an open study) and two studies were uncontrolled (Table 26). Five studies are complete and one, Study 287, is ongoing.

Table 26. Community Acquired Pneumonia: Controlled and Uncontrolled Studies of Gemifloxacin

Study	Treatment Regimen	Duration	N*	Geographic Region
Controlled studies				
011	gemifloxacin 320 mg po QD amoxicillin /clavulanate po 1g/125 mg tid	7 days 10 days	168 156	Europe, S. Africa
012	gemifloxacin 320 mg po QD cefuroxime 500 mg po bid /clarithromycin 500 mg po bid	7 or 14 days 7 or 14 days	319 322	U.S. Canada, Europe, S. Africa
049	gemifloxacin 320 mg po QD trovafloxacin 200 mg po QD	7 or 14 days 7 or 14 days	290 281	U.S., Mexico, Spain
185	gemifloxacin 320 mg po QD ceftriaxone 2g IV QD → cefuroxime 500 mg po bid**	7-14 days 1-7 days + 1-13 days (IV/oral = ≤14)	172 173	Australia, Europe, Guatemala, Lebanon, Philippines, Singapore and North America
Uncontrolled studies				
061	gemifloxacin 320 mg po QD	7 days	216§	World-Wide (Except N. America)
287	gemifloxacin 320 mg po QD	7 days	188	Asia, U.S., Mexico Philippines

* N refers to the number of randomized patients (enrolled for uncontrolled studies)
** comparator treatments were administered with or without a macrolide. In Study 185, 67 (38.7%) of comparator-treated patients received macrolides. Of the complete BITT dataset, 44/381 (11.5%) gemifloxacin subjects and 102/355 (28.7%) comparator subjects received additional macrolides as concomitant medications. (PP 25/280 (8.9%) gemifloxacin and 74/274 (27%) comparators).
§ Study 061 was conducted in patients with CAP or AECB. N= number of patients with CAP.

Study Design

Studies 011, 012, and 049, were randomized, multicenter, double-blind, double-dummy, parallel group studies designed to evaluate the clinical and microbiological efficacy and safety of

gemifloxacin in comparison with approved comparator antimicrobial agents (amoxicillin/clavulanate, cefuroxime axetil/clarithromycin, and trovafloxacin).

The duration of treatment was for 7 days with an option to extend to 14 days in Studies 012 and 049. Study medication could be extended to 14 days if the patient had a severe infection, if the pneumonia was confirmed or suspected to be due to an atypical pathogen (including *Legionella pneumophil*a), or at the investigator's discretion in Studies 012 and 049. All patients received 7 days of treatment with gemifloxacin in Study 011.

Study 185, the fourth controlled study, was an open label study designed to show that oral gemifloxacin (7 – 14 days) was as effective as the comparator regimen of intravenous ceftriaxone 2g once daily for a minimum of 1 day and up to a maximum of 7 days, followed by oral cefuroxime for a minimum of 1 day and up to a maximum of 13 days (total treatment duration $\leq$14 days). A macrolide could be prescribed concurrently at the screening visit for patients randomized to the comparator regimen.

Male and female patients at least 18 years of age were enrolled into all studies if they met the inclusion criteria that included new infiltrate on chest radiograph (CXR) as well as signs and symptoms of CAP. In study 011 subjects had to satisfy additional criteria that suggested that pneumococcal pneumonia was likely (sudden onset; chills; pleuritic chest pain; localized alveolar consolidation on chest radiograph; gram-positive cocci on sputum gram stain). In studies 011, 012, and 049, patients could be either out-patients or hospitalized while entry into study 185 was limited to hospitalized patients.

The two uncontrolled studies of gemifloxacin in CAP were designed to meet specific objectives in the development plan for gemifloxacin. The first study, Study 061, was conducted in patients with either CAP or ABECB and was designed to maximize the number of bacteriologically evaluable patients treated with gemifloxacin. Study 287, the second uncontrolled study remains ongoing and is being conducted in areas of the world with a high prevalence of drug-resistant respiratory pathogens.

The inclusion criteria for enrollment of CAP patients into these studies were similar to those in the controlled studies, with the exception that in study 287, patients had to have evidence of pneumococcal infection (positive urine antigen test and/or positive Gram stain for diplococci resembling *Streptococcus pneumonia*e). In both studies, patients were either out-patients or hospitalized depending on clinical need, and received open-label treatment with gemifloxacin 320 mg orally once daily for 7 days.

Primary efficacy endpoint

The primary efficacy endpoint in the four controlled clinical studies (Studies 011, 012, 049, and 185) and in uncontrolled Study 061, was clinical response at the follow-up or test of cure (TOC) visit in the per protocol (PP) population. In Study 287 (a non-comparative study) the primary objective was to demonstrate bacteriological efficacy in the treatment of CAP of suspected pneumococcal origin and so the primary endpoint in this study was the bacteriological response at the follow-up visit (TOC) in the bacteriologic ITT (intent-to treat) population.

Clinical response was also assessed at the End of Therapy visit (EOT) as a secondary endpoint. It is important to note that clinical outcome was evaluated at follow-up only if the patient was a clinical success at the EOT. Patients with a clinical outcome of clinical failure at the EOT were

carried forward to the TOC as failures. In the ITT analysis, patients with a clinical outcome of unable to determine (UTD) at the EOT were carried forward to the TOC as failures. Bacteriological response was determined for each patient from the bacteriological outcome for pathogens isolated from sputum, other respiratory samples, or blood culture. Patients with a pre-therapy pathogen but without an evaluable sample at EOT or follow-up were assigned a presumed bacteriological outcome on the basis of clinical response.

Additional secondary endpoints included therapeutic response (a composite clinical and bacteriological endpoint) and radiologic response.

In all of the CAP clinical studies there were four patient populations in whom efficacy was determined:

- **Intent to Treat (ITT):** All randomized patients who took at least one dose of study medication. (In Study 185, all randomized patients were included to reduce potential bias associated with the open design.)

- **Clinical Per Protocol (CPP):** A subset of the ITT population that excluded patients who violated the protocol to an extent that could affect treatment efficacy.

- **Bacteriology ITT (BITT):** A subset of the ITT population that included patients with evidence of infection with at least one pre-therapy pathogen identified at screening (by either culture or non-culture methods).

- **Bacteriology PP (BPP):** A subset of the BITT population that excluded patients who violated the protocol to an extent that could affect treatment efficacy.

The protocols for Studies 011, 012, 049 and 185 identified the PP populations as the primary analysis populations, with the ITT population providing confirmatory analysis. In the two uncontrolled studies, the ITT population was of primary interest. In the ITT analyses, patients with a clinical outcome of unable to determine were assigned a clinical response of failure, representing a worst case approach (these patients were excluded from the CPP population). The results from both the ITT and CPP populations are of equal importance to the Agency.

The four controlled CAP studies were designed to demonstrate that gemifloxacin was non-inferior to the active comparator. The estimation of sample size assumed 90% power to demonstrate that the lower bound of the two-sided 95% confidence interval (CI) for the difference in response rates (gemifloxacin minus comparator) was no less than a pre-defined non-inferiority limit. The planned sample size in Studies 012 and 049 was determined based on an underlying equivalent clinical response rate of 90% at follow-up. The non-inferiority limit for these studies was set at –10%. In contrast, in Studies 011 and 185 which recruited populations likely to have more severe CAP (patients with suspected pneumococcal involvement in Study 011 and hospitalized patients in study 185), a lower clinical response rate of 85% at follow-up was anticipated, and a non-inferiority limit of –15% was selected.

As stated above, the sponsor is only interested in obtaining an indication for a 7-day dosing regimen. However, 3 of the 4 controlled studies allowed dosing to continue to 14 days or up to 14 days in a non-randomized fashion based on post-randomization efficacy information. The sponsor has presented data combining the fixed 7-day regimen (controlled study 011 and uncontrolled studies 061 and 287) with the patients whose post-randomization planned duration was 7 days from the 3 other controlled studies (012, 049, and 185). It is the Agency's viewpoint

that these two types of 7-day data should not be combined. The 7-day data from the fixed 7-day regimen contain information from all patients enrolled in the studies while the 7-day data from the 7-14 day studies have patients removed who were considered by their physicians to have needed more treatment and could in general represent a more ill population. This would cause this 7-day efficacy data from these studies to be biased, most likely upwards.

In our presentation of the data, we will not combine these two groups of 7-day duration subjects. Since the Applicant is interested only in a 7-day regimen, we will consider the data from the 7 day fixed regimen as the primary data with the 7-14 days as supportive. We will present the data individually by study, by controlled studies and uncontrolled studies, and by duration as 7-day fixed regimen, 7-day from the 7-14 day studies, and 14 days from the 7-14 day studies. As cautioned by the Applicant, the 7-day efficacy data should not be directly compared to the 14-day efficacy data. Each group of gemifloxacin patients should only be compared to their respective controls.

The results of each of the individual studies were used to support the efficacy of gemifloxacin in the treatment of CAP. The fixed 7-day regimen data were presented along with 7-14 day regimen data for subgroups of interest, specifically: clinical response by gender, age, and race; clinical response by planned treatment duration and CAP characteristic (severity, hospitalized, bacteremic status, and PRSP). The bacteriological efficacy of gemifloxacin was further assessed by combining data from the 7-day fixed and 7-14 day studies to determine eradication rates of pathogens isolated at screening in the CAP studies of gemifloxacin.

For purposes of comparison, the ranges of the Test-of-Cure (TOC) visits are listed below:

- Days 24-30 (Study 011)
- 14-21 days post-therapy (Studies 012 and 049)
- 21-28 days post-therapy (Study 185)
- Days 21-28 (Study 061)
- Days 28-35 (Study 287)

The mean day of evaluation fell within the prespecified ranges for all studies except for study 185 where the window was extended to days 19 – 41. The mean day of assessment was day 31 in study 287 but this was within the prespecified range (Table 27).

Table 27. Mean Day of Assessment for the Test-of-Cure Visit

Study Number	**Gemifloxacin**				**Comparators**			
Per Protocol	**N**	**Mean (Day)**	**Median (Day)**	**Min-Max (Day)**	**N**	**Mean (Day)**	**Median (Day)**	**Min-Max (Day)**
011	114	28	28	24 - 36	113	28.2	28	13 - 50
012	249	25.3	24	20 - 37	257	25.3	24	17 - 36
049	214	26.3	26	19 - 36	205	26.3	26	20 - 45
061	166	24.3	24	20 - 24	-	-	-	-
185	116	35.9	36	27 - 56	119	35.1	35	28 - 56
287	144	31.5	31	24 - 54	-	-	-	-

Patient Disposition

In the CAP studies, a total of 1349 patients received treatment with gemifloxacin 320 mg po once daily and 927 patients received treatment with an active comparator.

In the four randomized, controlled studies (Studies 011, 012, 049 and 185), 947 patients were treated with gemifloxacin and 927 received a comparator. Four hundred two (402) patients received treatment with gemifloxacin 320 mg po once daily in the uncontrolled studies (Table 28).

A similar proportion of patients withdrew from the controlled and uncontrolled studies. In the combined controlled study population, the incidence of withdrawal for the combined gemifloxacin group was 16.3% compared with the combined comparator group rate of 15.9%. A similar rate of withdrawal (16.6%) was observed in the combined uncontrolled study population.

Table 28. Patient Disposition: CAP Combined Controlled and Uncontrolled Studies (All Randomized Patients)

	Controlled Studies Studies 011, 012, 049 and 185		Uncontrolled Studies Studies 061 and 287	All Studies Controlled + Uncontrolled	
	Gemifloxacin 320 mg QD	Pooled Comparators	Gemifloxacin 320 mg QD	Gemifloxacin 320 mg QD	Pooled Comparators
	n	n	n	n	n
Randomized	949	932	404	1353	932
Received study medication (ITT)	**947**	**927**	**402**	**1349**	**927**
Completed study, n (%)*	794 (83.7)	784 (84.1)	337 (83.4)	1131 (83.4)	784 (84.1)
Withdrawal reason, n (%):					
Adverse event	73 (7.7)	66 (7.1)	18 (4.5)	91 (6.7)	66 (7.1)
Insufficient therapeutic effect	20 (2.1)	16 (1.7)	8 (2.0)	28 (2.1)	16 (1.7)
Protocol deviation	23 (2.4)	16 (1.7)	12 (3.0)	35 (2.6)	16 (1.7)
Lost to follow-up	27 (2.8)	43 (4.6)	21 (5.2)	48 (3.5)	43 (4.6)
Other reason	12 (1.3)	7 (0.8)	8 (2.0)	20 (1.5)	7 (0.8)
Total withdrawn, n (%)	155 (16.3)	148 (15.9)	67 (16.6)	222 (16.4)	148 (15.9)
Populations for Analysis					
Clinical PP end of therapy	755	762	335	1090	762
Clinical PP follow-up	697	698	315	1012	698
Bacteriology ITT	381	355	171	552	355
Bacteriology PP end of therapy	305	303	142	447	303
Bacteriology PP follow-up	280	274	135	415	274

* Patients were considered to have completed the study if they were not actively withdrawn from the study.

For inclusion in the BITT population, patients were required to have at least one respiratory pathogen identified at screening from an evaluable sample (by either culture or non-culture methods). In the ITT population of the combined controlled studies, 40.2% (381/947) of the combined gemifloxacin group and 38.3% (355/927) of the combined comparator group were in this category. In the ITT population of the combined uncontrolled studies, 42.5% (171/402) satisfied this criteria.

Demographics

In the ITT population there were more male than female patients (combined gemifloxacin: 53.5% male; combined comparators: 57.9% male), the average age was approximately 53.2 for gemifloxacin and 53.5 for comparators years and the majority of the patients were white (combined gemifloxacin: 71%; combined comparators: 88.8%). Of note, the demographic profile for the combined uncontrolled studies showed a slightly higher proportion of female patients (53.2%), an average age of 51 years and the most predominant racial group was Oriental (40.5%). There were no major differences evident between the ITT population and the CPP population in any of the individual studies or the combined study datasets.

The following table gives the demographics of patients in the ITT populations broken down by 7-day fixed regimen and 7- and 14-day planned duration from the 7-14 day studies.

Table 29. FDA Demographics and Baseline Characteristics Controlled CAP Studies – ITT Population

Characteristic	7-Day Fixed			7 – 14 Day Studies			
	Study 011		Uncontrolled Studies	7 Days		14 Days	
	Gemifloxacin	Comparator	Gemifloxacin	Gemifloxacin	Comparator	Gemifloxacin	Comparator
	N = 167	N = 153	N = 402	N = 468	N = 457	N = 312	N = 317
Gender							
Male	107 (64.1)	96 (62.8)	188 (46.8)	272 (58.1)	256 (56.0)	155 (49.7)	185 (58.4)
Female	60 (35.9)	57 (37.2)	214 (53.2)	196 (41.9)	201 (44.0)	157 (50.3)	132 (41.6)
Race							
White	138 (82.6)	120 (78.4)	109 (27.1)	435 (93.0)	419 (91.7)	276 (88.5)	284 (89.6)
Black	17 (10.2)	26 (17.0)	11 (2.7)	16 (3.4)	21 (4.6)	18 (5.8)	18 (5.7)
Oriental	7 (4.2)	3 (2.0)	163 (40.5)	8 (1.7)	7 (1.5)	3 (1.0)	7 (2.2)
Other	5 (3.0)	4 (2.6)	119 (29.6)	9 (1.9)	10 (2.2)	15 (4.8)	8 (2.5)
Age							
Mean (SD)	53.3 (20.4)	55.3 (19.8)	51.1 (18.3)	53.4 (18.2)	51.9 (18.3)	55.7 (17.8)	54.9 (18.0)
Range	18-97	18-86	18 - 89	18-94	18-93	18-90	18-97
CAP Severity							
Mild	120 (71.9)	93 (60.8)	320 (79.6)	345 (73.7)	342 (74.8)	211 (67.6)	218 (68.8)
Moderate	27 (16.2)	44 (28.8)	61 (15.2)	78 (16.7)	79 (17.3)	58 (18.6)	56 (17.7)
Severe	20 (12.0)	16 (10.5)	21 (5.2)	45 (9.6)	36 (7.9)	43 (13.8)	43 (13.6)
Hospitalized	152 (91.0)	149 (97.4)	204 (50.7)	229 (48.9)	193 (42.2)	175 (56.1)	197 (62.2)
Bacteremic	11 (6.6)	16 (10.5)	15 (3.7)	11 (2.4)	17 (3.7)	25 (8.0)	20 (6.3)
Severe CAP, Hospitalized or Bacteremic	152 (91.0)	151 (98.7)	213 (53.0)	239 (51.1)	209 (45.7)	180 (57.8)	203 (64.0)
Patients with PRSP	4 (2.4)	0	7 (1.7)	2 (0.4)	2 (0.4)	1 (0.3)	2 (0.6)

Severity of CAP

Severity was determined by categorizing patients according to the mortality risk classes published by Fine, *et al*.[7] Patients were assigned to one of five classes (I, II, III, IV, and V) with respect to risk of death within 30 days, firstly according to an algorithm (class I) and then on the basis of a total points score (classes II-V). A prediction rule assigned points based on age and the presence of co-existing disease, abnormal physical findings, and abnormal laboratory findings at presentation. For most of the CAP studies the severity classification was performed retrospectively, not all of the data elements that contribute to the total points score were available. The Applicant classified patients based upon the data that was available. Because some data was not available, patients were more likely classified to a lower risk class than if all data were available. Only in Study 287 were these criteria applied prospectively.

Based on the assigned risk class, patients were classified as having mild (class I or II), moderate (class III), or severe (class IV or V) CAP.

In the ITT population for the combined controlled studies, the majority of patients had CAP of mild severity (risk class I and II); 71.4% in the gemifloxacin group compared with 70.4% of patients in the comparator group. In Study 011, there were more patients with mild CAP randomized to gemifloxacin (71.9%) compared to the comparator (60.8%) [Table 29]. Approximately 10.5% of patients in the ITT population had severe CAP (classes IV and V). Of note, however, of the 129 ITT patients with severe disease, 125 had class IV disease including 2 with PRSP. The remaining 4 had class V disease. In the PP population, the respective numbers were 89 with class IV disease and 2 with class V disease. Again there were 2 subjects with severe disease with PRSP and both were class IV patients.

A further review of demographic data on all subjects by degree of severity (data not shown), revealed that those subjects with mild disease had a mean age of 45 – 46 years whereas those with moderate and severe disease were much older with a mean age of 69 for the moderately ill gemifloxacin-treated subjects (70 comparator), and a mean age of 76 for the severe group of gemifloxacin-treated subjects (comparator, 74). Additionally in the 7-14 day studies, as severity increased the percentage of gemifloxacin patients receiving 14 days of therapy (38% for mild, 43% for moderate, and 49% for severe) increased. This raised concerns that not enough patients with severe disease were treated with a 7-day regimen.

[7] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243-50.

Efficacy Analyses - Results

Primary Parameter of Efficacy

An analysis of clinical success rates at follow-up for the CPP and ITT populations is presented below for each study. The results of study 011 show that the clinical efficacy of gemifloxacin at follow-up was at least as good as (non-inferior to) the comparator regimen of amoxicillin/clavulanate in both the clinical per protocol and the ITT populations since the lower limit of the 95% CI exceeded the pre-specified non-inferiority margin of -15%. The results for the 7 – 14 days comparative studies and 7-day fixed uncontrolled studies support this conclusion.

Table 30. Summary of Clinical Response at Follow-Up: CAP Controlled and Uncontrolled Studies 011, 012, 049, 185, 061 and 287

	Success Rate		Treatment Difference**
	Gemifloxacin % (n/N)	Comparator* % (n/N)	% (95% CI)**
Clinical PP Population			
Controlled Studies			
Study 011	88.7% (102/115)	87.6% (99/113)	1.1 (-7.3, 9.5)
Study 012	87.6% (220/251)	92.6% (238/257)	-5.0 (-10.1, 0.2)
Study 049	94.0% (202/215)	89.9% (186/207)	4.1 (-1.1, 9.3)
Study 185	92.2% (107/116)	93.4% (113/121)	-1.15 (-7.73, 5.43)
Uncontrolled Studies			
Study 061	91.7% (154/168)	-	(86.1, 95.2)
Study 287	89.8% (132/147)	-	(84.9, 94.7)
Intent-to-Treat			
Controlled Studies			
Study 011	77.2% (129/167)	79.1% (121/153)	-1.8 (-10.9, 7.2)
Study 012	78.4% (250/319)	84.7% (272/321)	-6.4 (-12.4, -0.4)
Study 049	87.5% (253/289)	81.1% (227/280)	6.5 (0.5, 12.4)
Study 185	75.6% (130/172)	78.6% (136/173)	-3.03 (-11.89, 5.83)
Uncontrolled Studies			
Study 061	82.9% (179/216)	-	(77.0, 87.5)
Study 287	78.5% (146/186)	-	(72.6, 84.4)

* Comparators were amoxicillin/ clavulanate 1g/125 mg tid (011), clarithromycin 500 mg/cefuroxime 500 mg bid (012), trovafloxacin 200 mg QD (049), and ceftriaxone/cefuroxime 2g iv QD/500 mg bid (185).

** The difference and 95% confidence intervals are calculated as Gemifloxacin – Comparator. Non-inferiority limit was prospectively defined as -10% for Studies 012 and 049; -15% for Studies 011 and 185. For the uncontrolled studies, the 95% CI around the success rate is shown.

Clinical Response by Duration of Treatment

Analyses of clinical response by duration of treatment were performed. Subjects were divided into those that received a planned duration of treatment of 7 days or less and those that received a planned duration between 8 and 14 days. The decision to extend the duration of treatment was not made at the time of randomization but at the On-Therapy visit. If subjects were improved, the investigator had the option of extending the treatment duration. If patients were failing at the On-Therapy visit, they were removed from study treatment and classified as failures. Thus an element of bias was introduced as no patient failing treatment at the On-Therapy visit could have been included in the 14-day group but only in the 7-day group. As per the Applicant, only subjects doing well at the On-Therapy visit could have had their treatment extended beyond 7 days. Thus the 14-day group results were artificially inflated and the 7-day results deflated in

comparison to the 14-day group. Comparisons therefore between the 7- and 14-day groups of the same treatment arm should not be made.

From the Agency's standpoint, it could only be assumed that the investigator would have more often extended the treatment of more ill patients to 14 days, while less ill patients would be given only 7 days. When looking at demographics and baseline characteristics, it was noted that patients in the 14-day group were a few years older on average and that as the severity of disease increased, a larger proportion of subjects received 14 days of treatment.

When the allowed comparisons between treatment groups are made, for both the 7-day fixed and the 7 – 14 day studies gemifloxacin clinical success rates were similar to those of the respective comparators.

Table 31. FDA Analysis of Clinical Response at Follow-up by Duration of Therapy

	Treatment Group	
	Gemifloxacin n/N (%)	**Comparators n/N (%)**
Clinical Per Protocol Population		
7-day Fixed studies*		
Controlled (011)	102/115 (88.7)	99/113 (87.6)
Uncontrolled (061, 287)	286/315 (90.8)	
Combined (Controlled and Uncontrolled)	388/430 (90.2)	
"7 - 14" day studies**		
7 days	329/363 (90.6)	319/348 (91.7)
14 days†	200/219 (91.3)	218/237 (92.0)
All patients	529/582 (90.9)	537/585 (91.8)
Intent-to-Treat Population		
7-day Fixed studies*		
Controlled (011)	129/167 (77.2)	121/153 (79.1)
Uncontrolled (061, 287)	325/363 (90.6)	
Combined (Controlled and Uncontrolled)	454/569 (79.8)	
"7 - 14" day studies**		
7 days	375/468 (80.2)	371/457 (81.2)
14 days†	258/312 (82.7)	264/317 (83.3)
All patients	633/780 (81.2)	636/774 (82.0)

* includes Studies 011, 061, and 287

** includes Studies 012, 049, and 185 – all were controlled studies

† note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

Other Parameters of Efficacy

Bacteriological Response at Follow-Up

Bacteriologic response (success or failure) at the follow-up visit was a secondary efficacy variable in the four controlled CAP studies (012, 049, 011, and 185) and in uncontrolled Study 061. In uncontrolled Study 287, bacteriological response at follow-up was the primary efficacy variable. In these analyses, gemifloxacin was similar to the comparators.

Table 32. Bacteriological Response at Follow-Up CAP All Studies 011, 012, 049, 185, 061 and 287

	Success Rate		Treatment
	Gemifloxacin % (n/N)	Comparator* % (n/N)	Difference** % (95% CI)
Bacteriology PP Follow-Up Population			
Controlled Studies			
Study 011	87.2% (41/47)	89.1% (41/46)	-1.9 (-15.0, 11.2)
Study 012	89.9% (71/79)	88.9% (80/90)	1.0 (-8.3, 10.3)
Study 049	87.8% (79/90)	89.3% (67/75)	-1.6 (-11.3, 8.2)
Study 185	90.6% (58/64)	87.3% (55/63)	3.3 (-7.6, 14.2)
Uncontrolled Studies			
Study 061	87.3% (48/55)	-	(74.9, 94.3)
Study 287	90.0% (72/80)	-	(83.4, 96.6)
Bacteriology Intent-to-Treat			
Controlled Studies			
Study 011	75.0% (54/72)	76.2% (54/72)	-1.2 (-15.7, 13.3)
Study 012	80.4% (82/102)	86.1% (93/108)	-5.7 (-15.8, 4.4)
Study 049	84.0% (100/119)	80.4% (82/102)	3.6 (-6.5, 13.8)
Study 185	76.1% (67/88)	79.3% (65/82)	-3.13 (-15.6, 9.4)
Uncontrolled Studies			
Study 061	77.9% (60/77)	-	(66.8, 86.3)
Study 287	84.0% (79/94)	-	(76.6, 91.4)

* Comparators were amoxicillin/ clavulanate 1g/125 mg tid (011), clarithromycin 500 mg/cefuroxime 500 mg bid (012), trovafloxacin 200 mg QD (049), and ceftriaxone/cefuroxime 2g iv QD/500 mg bid (185).
** The difference and 95% confidence intervals are calculated as Gemifloxacin – Comparator. For the uncontrolled studies, the 95% CI around the success rate is shown.

Other Analyses

Analyses were provided for clinical and bacteriologic response at the EOT, radiologic response at the EOT and at follow-up, combined clinical and radiological response rates at the EOT and at follow-up, and therapeutic response at the EOT and follow-up. In these analyses, gemifloxacin was shown to be similar to the comparators.

Bacteriological Response by Pathogen

In the BPP follow-up population, 88.5% (461/521) of initial pathogens in the combined gemifloxacin group were either eradicated or presumed eradicated as compared with 89.9% (301/335) of initial pathogens in the combined comparator group. By pathogen eradication rates are shown in Table 33.

Streptococcus pneumoniae and *Mycoplasma pneumoniae*, the most frequently isolated pathogens in this combined study population of CAP patients, had eradication rates in the gemifloxacin group of 90.7% and 88.7%, respectively (BPP population). For the pooled comparator group the corresponding rates for these pathogens were 92.9% and 87% respectively.

Table 33. Pre-Therapy Pathogens Eradicated or Presumed Eradicated at Follow-Up CAP Combined Principal and Supportive Studies 012, 049, 011, 185 and 287, 061

	Combined CAP studies 012, 049, 011, 061, 185, 287							
	Bacteriology PP**				Bacteriology ITT			
	Gemifloxacin		All Comparators		Gemifloxacin		All Comparators	
Follow-Up	**N=415**		**N=274**		**N=552**		**N=355**	
	n/N*	**%**	***n/N****	**%**	***n/N****	**%**	***n/N****	**%**
All Pathogens	461/521	(88.5)	301/335	(89.9)	552/702	(78.6)	361/445	(81.1)
S. pneumoniae	117/129	(90.7)	65/70	(92.9)	136/168	(81.0)	76/94	(80.9)
M. pneumoniae	102/115	(88.7)	94/108	(87.0)	126/153	(82.4)	109/129	(84.5)
C. pneumoniae	51/54	(94.4)	41/45	(91.1)	62/77	(80.5)	48/59	(81.4)
H. influenzae	51/58	(87.9)	25/28	(89.3)	60/75	(80.0)	30/37	(81.1)
S. aureus	24/28	(85.7)	8/9	(88.9)	30/41	(73.2)	11/16	(68.8)
L. pneumophila	12/16	(75)	12/14	(85.7)	13/26	(50.0)	17/21	(81.0)
C. burnetii	9/9	(100.0)	8/8	(100.0)	10/10	(100.0)	11/13	(84.6)
M. catarrhalis	13/14	(92.9)	3/3	(100.0)	15/16	(93.8)	4/4	(100.0)
K. pneumoniae	17/19	(89.5)	4/4	(100.0)	23/29	(79.3)	4/4	(100.0)
H. parainfluenzae	15/19	(78.9)	7/7	(100.0)	16/23	(69.6)	9/10	(90.0)

Note: failures at end of therapy are carried forward into the follow-up analysis by applying the following algorithms:
(1) failures and 'unable to determines' at end of therapy are added to the denominator at follow-up
(2) successes at end of therapy with missing data at follow-up are NOT added to the denominator at follow-up.
* *n/N* = number of pathogens eradicated or presumed eradicated / number of pathogens.
** Bacteriology PP follow-up population.

The following table gives rates by fixed 7-day regimen studies (011, 061 and 287) and 7-day duration from the 7-14 day studies (012, 049, 185) (Table 34). The rates in the 7-day fixed studies had lower rates for *S. pneumoniae* in the gemifloxacin arm than in the comparator arm, though higher rates for *M. pneumoniae*. Note that in Study 011 alone, the rates for *S. pneumoniae* and *M. pneumoniae* for gemifloxacin arm and the comparator are 17/20 (85%) gemifloxacin vs. 18/19 (94.7%) comparator and 13/14 (92.6%) gemifloxacin vs. 13/16 (81.3%) comparator per organism, respectively.

Table 34. Bacterial Response by Pathogen for Patients who Received 7-days of Treatment – Bacteriology Per Protocol Population

	Fixed 7-Day Regimen Studies Studies 011, 061, 287		7-Day Planned Duration from the 7-14 Day Studies Studies 012, 049, 185	
	Gemifloxacin n/N (%)	Comparator* n/N (%)	Gemifloxacin n/N (%)	Pooled Comparators** n/N (%)
All pathogens	196/225 (87.1)	51/57 (89.5)	136/157 (86.6)	115/133 (86.5)
S. pneumoniae	68/77 (88.3)	18/19 (94.7)	22/22 (95.5)	23/26 (88.5)
M. pneumoniae	21/22 (95.5)	13/16 (81.3)	48/59 (81.4)	45/54 (83.3)
H. influenzae	30/35 (85.7)	5/5 (100.0)	13/14 (92.9)	5/7 (71.4)
C. pneumoniae	13/14 (92.9)	3/3 (100.0)	18/18 (100.0)	18/20 (90.0)
S. aureus	11/15 (73.3)	1/1 (100.0)	4/4 (100.0)	2/2 (100.0)
K. pneumoniae	14/16 (87.5)	2/2 (100.0)	2/2 (100.0)	-
H. parainfluenzae	5/6 (83.3)	1/1 (100.0)	1/4 (25.0)	1/1 (100.0)
L. pneumophila	3/5 (60.0)	5/6 (83.3)	7/9 (77.8)	4/5 (80.0)
M. catarrhalis	10/10 (100.0)	-	1/1 (100.0)	1/1 (100.0)

* Study 011 was the only fixed 7-day study with a comparator arm (amoxicillin / clavulanate po 1g/125 mg tid). Note the bacteriologic response rates for comparator among atypical organisms.

** Comparators were clarithromycin 500 mg/cefuroxime 500 mg bid (012), trovafloxacin 200 mg QD (049), and ceftriaxone/cefuroxime 2g iv QD/500 mg bid (185).

Treatment Failures

Forty-seven of 415 (11%) gemifloxacin treated CAP controlled and uncontrolled patients in the BPP population at follow-up were classified as treatment failures as compared to 31 of 274 (11%) comparator-treated patients.

Eleven of the 47 treatment failures in the gemifloxacin group (23%) had documented microbiological evidence of persistence at the EOT or recurrence/new infection at follow-up; in the remainder of cases bacteriological failure was presumptive based on clinical response. Pathogens that persisted at End of Therapy in individual patients were *Mycoplasma pneumoniae* (2 patients), *Klebsiella pneumoniae, beta-hemolytic Streptococcus group G* and *Pseudomonas aeruginosa*. At follow-up, the following pathogens recurred: *Streptococcus pneumonia*e, *Mycoplasma pneumoniae* (3 patients), *Klebsiella pneumoniae,* and *Serratia marcescens.*

Twelve patients who failed treatment in the BPP population had *Streptococcus pneumoniae* identified at screening; ten isolates were penicillin-susceptible and 2 isolates were penicillin-intermediate. With one exception, CAP due to *Streptococcus pneumoniae* in these treatment failures was monomicrobial. Two treatment failures with *Streptococcus pneumoniae* were bacteremic, three patients had CAP of moderate severity and one patient had severe CAP.

Among the 47 gemifloxacin-treated patients who were treatment failures in the BPP population, five patients were bacteremic at screening and two patients had severe CAP. Among the 31 comparator patients who failed treatment, four patients were bacteremic and seven patients had severe CAP. Patients who were hospitalized comprised 60% (28/47) of treatment failures in the gemifloxacin group and 68% (21/31) of treatment failures in the combined comparator group.

Special Populations

There was no evidence that age or gender had any effect on the clinical response to gemifloxacin. The majority of patients were white and clinical success rates for the small number of black, oriental, and other race patients did not indicate any differential responses compared with the

overall study population although the numbers of subjects was too small to allow for valid comparisons.

Table 35. FDA Analysis of Clinical Response at Follow-up Clinical Per Protocol Population

	Fixed 7-Day (Study 011)		7 – 14 Day (Studies 012, 049, 185)			
			7 Days		14 Days	
	Gemifloxacin N=115	Comparator N=113	Gemifloxacin N=363	Comparators N=338	Gemifloxacin N=219	Comparators N=237
Gender						
Male	67/76 (88.2)	62/70 (88.6)	193/210 (91.9)	178/185 (96.2)	103/115 (89.6)	122/135 (90.4)
Female	35/39 (89.7)	37/43 (86.0)	136/153 (88.9)	141/153 (92.2)	97/104 (93.3)	96/102 (94.1)
Race						
White	87/98 (88.8)	75/88 (85.2)	311/344 (90.4)	304/329 (92.7)	182/199 (91.5)	198/216 (91.7)
Black	9/9 (100.0)	18/19 (94.7)	10/10 (100.0)	9/12 (75.0)	9/9 (100.0)	8/9 (88.9)
Oriental	3/4 (75.0)	2/2 (100.0)	3/4 (75.0)	3/3 (100.0)	3/3 (100.0)	5/5 (100.0)
Other	3/4 (75.0)	4/4 (100.0)	5/5 (100.0)	3/4 (75.0)	6/8 (75.5)	7/7 (100.0)
Age						
18 to <40	31/33 (93.9)	29/31 (93.5)	94/103 (91.3)	93/104 (89.4)	41/43 (95.3)	45/48 (93.8)
40 to < 65	36/44 (81.8)	28/35 (80.0)	127/142 (89.4)	125/136 (91.9)	80/90 (80.9)	97/104 (93.3)
65 to <75	15/18 (83.3)	14/18 (77.8)	68/75 (90.7)	61/65 (93.8)	37/41 (90.2)	50/54 (92.6)
≥75	20/20 (100.0)	28/29 (96.6)	40/43 (93.0)	40/43 (93.0)	42/45 (93.3)	26/31 (83.9)

Clinical Response by Severity

Fine Criteria

In the Applicant's analysis, clinical response rates for the controlled studies in the CPP population of severe CAP patients treated with gemifloxacin, were higher than those seen for patients classified as having mild to moderate disease. This difference was not seen on the comparator arm or in the ITT analysis. In the ITT analysis the severely ill patients had the lower response rates. Note that this analysis combined the 7-day fixed and the 7 – 14 day populations.

Table 36. Rates of Clinical Success at Follow-Up by Severity of CAP: CAP Combined Controlled Studies

	Success Rate	
	Gemifloxacin	**Comparator**
	% *(n/N)*	**% *(n/N)***
CLINICAL RESPONSE		
CAP Severity[§]		
Clinical PP Follow-Up	**N=697**	**N=698**
Mild	90.2% (449/498)	91.9% (453/493)
Moderate	89.3% (108/121)	91.3% (126/138)
Severe	94.9% (74/78)	85.1% (57/67)
ITT	**N=947**	**N=927**
Mild	80.9% (547/676)	82.8% (541/653)
Moderate	79.8% (130/163)	81.6% (146/179)
Severe	78.7% (85/108)	72.6% (69/95)

Notes: N = number of patients in the analysis population; *n* = number of patients who were a success, *N* = number of patients included in the subgroup.

As noted in previous sections subjects in the "severe" group were on average older and received more prolonged durations of treatment. As can be seen in the following table, although efficacy in all severely ill subjects was high, there were very few patients treated with the 7-day fixed regimen. Also as noted previously, the 7-day group of the 7 –14 day studies cannot be added to the fixed 7-day patient population and additionally, comparisons cannot be made between the 7 and 14 day regimens. Thus, the data currently available on severe patients are quite limited.

Table 37. FDA Analysis of Clinical Response at Follow-up for Severe Patients by Duration of Therapy

	Treatment Group	
	Gemifloxacin n/N (%)	**Comparators n/N (%)**
Clinical Per Protocol Population		
7-day Fixed studies*		
Controlled (011)	13/13 (100.0)	10/11 (90.9)
Uncontrolled (061, 287)	11/13 (84.6)	
Combined (Controlled and Uncontrolled)	24/26 (92.3)	
"7 - 14" day studies**		
7 days	30/31 (96.8)	22/26 (84.6)
14 days†	31/34 (91.2)	25/30 (83.3)
All patients	61/65 (93.8)	47/56 (83.9)
Intent-to-Treat Population		
7-day Fixed studies*		
Controlled (011)	15/20 (75.0)	13/16 (81.3)
Uncontrolled (061, 287)	16/21 (76.2)	
Combined (Controlled and Uncontrolled)	31/41 (75.6)	
"7 - 14" day studies**		
7 days	37/43 (86.0)	26/36 (72.2)
14 days†	33/45 (73.3)	30/43 (69.8)
All patients	70/88 (79.5)	56/79 (70.9)

* includes Studies 011, 061, and 287

** includes Studies 012, 049, and 185 – all were controlled studies

† note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

Hospitalization

In addition to the classification of subjects by the Fine criteria, the applicant also assessed clinical response in hospitalized subjects to assess the effectiveness of gemifloxacin in more severe cases of CAP. However, as the decision to hospitalize or not was investigator-driven in all studies except study 185, it would not appear that the presence or absence of this factor can be used as a determinant of severity of illness. Additionally, in study 185 where all subjects were hospitalized (gemifloxacin N= 172, comparator N = 173), only 36 of the 172 gemifloxacin subjects were classified to Fine classes IV and V. Approximately 80% of the subjects in that study that were hospitalized had mild to moderate disease, thus again raising the question of the appropriateness of using hospitalization alone as a criterion for severe CAP.

The applicant provided further details on these subjects regarding intubation status, use of pressors or respiratory treatments. None of the subjects had documented use of any of these treatments at the time of enrollment. Six subjects required at least one of these concomitant treatments during the study and all were ultimately categorized as failures.

As can be seen in the following table, the response rates of hospitalized patients were comparable between treatment arms.

Table 38. FDA Analysis of Clinical Response at Follow up Hospitalized Patients by Duration of Therapy

	Treatment Group	
	Gemifloxacin n/N (%)	**Comparators n/N (%)**
Clinical Per Protocol Population		
7-day CAP studies*		
Controlled (011)	90/103 (87.4)	97/111 (87.4)
Uncontrolled (061, 287)	141/157(89.8)	
Combined (Controlled and Uncontrolled)	231/260 (88.8)	
"7 - 14" day CAP studies**		
7 days	147/163 (90.2)	129/147 (87.8)
14 days†	118/130(90.8)	142/153 (92.8)
All patients	265/293 (90.4)	271/300 (90.3)
Intent-to-Treat Population		
7-day CAP studies*		
Controlled (011)	114/152 (75.0)	118/149 (79.2)
Uncontrolled (061, 287)	161/204(78.9)	
Combined (Controlled and Uncontrolled)	275/356 (77.2)	
"7 - 14" day CAP studies**		
7 days	169/229 (73.8)	146/193 (75.6)
14 days†	143/175 (81.7)	163/197 (82.7)
All patients	312/404 (77.2)	309/309 (79.2)

* includes Studies 011, 061, and 287

** includes Studies 012, 049, and 185 – all were controlled studies

† note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

Bacteremia

As an additional assessment of the effectiveness of gemifloxacin in severe disease, the applicant elected to provide a separate analysis of outcome in bacteremic subjects. In the combined all studies dataset (CPP), 4.7% (48/1012 patients) of the gemifloxacin group had a positive blood culture at screening. These patients had a clinical success rate at follow-up of 89.6% (CPP) and 89.4% for bacteriological response (BPP).

For the ITT population of bacteremic patients, the clinical success rate was comparable between the combined gemifloxacin group (67.6%) and combined comparator group (69.7%).

In the Agency's analysis of bacteremic subjects, though clinical response rates were comparable between treatment arms, the sample size was too small to allow for valid comparisons.

Table 39. FDA Analysis of Clinical Response at Follow up in Bacteremic Patients by Duration of Therapy

	Treatment Group	
	Gemifloxacin n/N (%)	**Comparators n/N (%)**
Clinical Per Protocol Population		
7-day Fixed studies*		
Controlled (011)	8/8 (100.0)	10/11 (90.9)
Uncontrolled (061, 287)	9/13 (69.2)	
Combined (Controlled and Uncontrolled)	17/21 (81.0)	
"7 - 14" day studies**		
7 days	4/4 (100.0)	9/12 (75.0)
14 days†	22/23 (95.7)	14/14 (100.0)
All patients	26/27 (96.3)	23/26 (88.5)
Intent-to-Treat Population		
7-day fixed studies*		
Controlled (011)	9/11 (81.8)	12/16 (75.0)
Uncontrolled (061, 287)	10/15 (66.7)	
Combined (Controlled and Uncontrolled)	19/26 (73.1)	
"7 - 14" day studies**		
7 days	6/11 (54.5)	11/17 (64.7)
14 days†	24/25 (96.0)	18/20 (90.0)
All patients	30/36 (83.3)	29/37 (78.4)

* includes Studies 011, 061, and 287

** includes Studies 012, 049, and 185 – all were controlled studies

† note: "14-days" includes all patients who were to receive a planned duration of therapy of >7 days.

Thirty-seven of the 48 bacteremic gemifloxacin-treated subjects had *Streptococcus pneumoniae.* Twenty of these subjects received more than 7 days of treatment. Clinical success rates in these subjects were 35/37 PP (94.5%). In the > 7-day group the rate was 19/20 (95%).

Mortality

The clinical review team requested that the applicant provide tables of risk class specific mortality for all ITT patients and for in- and outpatients separately. Overall mortality was similar between the gemifloxacin and comparator-treated groups as well as between the gemifloxacin controlled and uncontrolled study patients with 12 deaths (1.3%) in the gemifloxacin controlled study patients, 13 deaths (1.4%) in the comparator-treated patients, and 5 deaths (1.2%) in the gemifloxacin-treated uncontrolled study patients. There were 17 deaths (1.3%) in all gemifloxacin-treated patients.

When mortality was assessed in the ITT population by in or outpatient status, it was apparent that most of the deaths occurred in the inpatients with 14 of 17 gemifloxacin deaths in inpatients (11 controlled and 3 uncontrolled) as compared to 12 of 13 deaths on the comparators arm.

When deaths were assessed by Fine class, it appeared that mortality rates for Class I, II, and III patients mortality rates were consistent with what was expected based on the publication by Fine

et al.[8] In class IV subjects the mortality rates in the clinical studies appeared to be somewhat less than what was reported for Fine Class IV patients. There were too few class V subjects in the dataset to draw any conclusions for this class (Table 40). (The mortality risk for class IV subjects ranges from 9 – 12%, whereas for class V subjects it is in the 30% range in the publication by Fine *et al*.)

[8] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243-50.

Table 40. For All Patients – Risk Class Specific Mortality Rates - CAP studies/ITT

Fine Class (score)*	Fine pneumonia Validation cohort		Comparative Studies				Non-Comparative Studies		All	
	Mortality		gemifloxacin		comparators		gemifloxacin		gemifloxacin	
	# of patients	% who died	# of patients	% who died	#of patients	% who died	# of patients	% who died	# of patients	% who died
			n	%	n	%	n	%	n	%
I	772	0.1	347	1 (0.3%)	369	3 (0.8%)	154	0	501	1 (0.2%)
II (≤70)	477	0.6	330	2 (0.6%)	287	2 (0.7%)	166	3 (1.8%)	496	5 (1.0%)
III (71-90)	326	0.9	164	4 (2.4%)	181	3 (1.7%)	63	2 (3.2%)	227	6 (2.6%)
IV (91-130)	486	9.3	104	5 (4.8%)	90	4 (4.4%)	21	0	125	5 (4.0%)
V (>130)	226	27.0	4	0	5	1 (20.0%)	0	0	4	0
Total	2287	5.2	949	12 (1.3%)	932	13 (1.4%)	404	5 (1.2%)	1353	17 (1.3%)

***** Inclusion in risk class I was based upon the absence of all predictors identified in step 1 of the Fine prediction rule.
Inclusion in risk classes II, III, IV, and V was determined by a patient 's total risk score, which was computed according to the Fine scoring system.
Table design adapted from Table 3. in Fine MJ et al. N Engl J Med 1997;336:243-50.

Penicillin –resistant *Streptococcus pneumoniae* (PRSP)

There were 12 patients in the combined gemifloxacin group with penicillin-resistant *Streptococcus pneumoniae* isolated at screening (penicillin MIC of $\geq$ 2 mcg/mL) in the BPP population at follow-up. There were 14 patients in the BITT population with PRSP isolated at screening. There were a total of 126 PP and 165 ITT subjects with *Streptococcus pneumoniae* (12/126, 9.5%). Thirty-seven subjects were bacteremic with *Streptococcus pneumoniae.*

All 12 patients with PRSP in the BPP population in the combined gemifloxacin group were successfully eradicated (confirmed eradication or presumed eradication based on clinical success). The clinical and bacteriological success rates associated with PRSP were 100% (12/12). In the BITT population, there was one PRSP case that was not eradicated in the combined gemifloxacin group; the pathogen eradication rate and the associated clinical and bacteriological response rates for the BITT population was 13/14 (92.8%). Four patients in the combined comparator group of the gemifloxacin CAP studies had PRSP, which were successfully eradicated with a corresponding 100% clinical and bacteriological success rates.

Of the 14 bacteriologically evaluable ITT CAP patients (12 in the BPP follow-up population) with PRSP, 2 patients were assessed as having severe CAP and 3 patients had CAP of moderate severity. Three patients were bacteremic including 2 patients with severe CAP. In total, ten of the PRSP patients were hospitalized. All but one patient received 7 days of treatment with gemifloxacin.

Of the PP subjects, there were 2 subjects with severe disease as well as 2 bacteremic subjects, one of who had severe disease. Eight subjects were hospitalized. The duration of treatment in 1 subject was 14 days.

Clinical success rates for all subjects with *Streptococcus pneumoniae* were 117/129 (91%) and 136/168 (81%) in the gemifloxacin and the combined comparator arms, respectively.

A comparison with publicly available information from other antimicrobials that sought this indication revealed the following:

Levofloxacin: 15 PP subjects were identified with PRSP from a total of 250 total subjects with CAP due to *Streptococcus pneumoniae*. Six of the levofloxacin PRSP patients had severe disease and 6 PRSP subjects were bacteremic [total # of bacteremic subjects with *Streptococcus pneumoniae* (55)]. Clinical success was attained in all subjects with PRSP (100%). Subjects with severe disease were defined as those with hypotension (diastolic BP < 60 mm Hg in the absence of volume depletion), subjects with mental status changes, subjects who required mechanical ventilation, subjects with bacteremia, and subjects with a baseline RR of > 28/min. This differentiation was utilized to determine mode of treatment (IV or PO) and duration of treatment at the time of randomization.

Telithromycin: Twenty-seven Per Protocol subjects were identified with PRSP of 318 total subjects with CAP due to *Streptococcus pneumoniae*. Eighty-two telithromycin-treated subjects were bacteremic with *Streptococcus pneumoniae.* Clinical success was achieved in 19/27 (70.3%) PRSP subjects and in 300/318 (94%) of patients with pneumococcal pneumonia as well as in 5/7 bacteremic subjects with PRSP.

Clarithromycin -Resistant *Streptococcus pneumoniae* (MRSP)

The Applicant presented data on 36 BITT gemifloxacin-treated patients with MRSP isolated as baseline of whom 25 were in the BPP population. There were 14 BITT comparator-treated subjects with MRSP of whom 12 were in the BPP and CPP populations.

Of the 25 BPP gemifloxacin MRSP cases, 10 (40%) were also PRSP. In the BITT population 11 of 36 (30%) of the MRSP cases were also penicillin-resistant. All subjects with combined penicillin and macrolide resistant *Streptococcus pneumoniae* (PR & MRSP) were clinical successes with presumed eradication at follow-up. Of the ten cases with combined PR & MRSP, 8 had mild disease, one had moderate disease, and one had severe disease. A total of 3 Per Protocol MRSP subjects were bacteremic, of whom 2 had mild disease and 1 had severe disease. All 3 were successfully treated with presumed eradication. There were an additional 2 BITT subjects who were bacteremic, both were severe and outcome was not determined in either case. Of note, there were 2 Per Protocol subjects with moderate disease and the remaining subjects were classified as mild or in the cases of the subjects from the original submission, as not severe.

Overall clinical success and bacteriologic success rates for patients with MRSP on the gemifloxacin arm were 22/25 (88%) for the BPP population. For the MRSP ITT gemifloxacin-treated population, 27/36 (78%) of patients achieved clinical successes. For the 9 patients in the ITT population that were not successes, 4 were failures and 5 were "unable to determine." Similar results were obtained for the BITT population, with 3 isolates presumed persistent and 6 "unable to determine."

Of the 12 BPP comparator-treated MRSP subjects, 4 were bacteremic. All were clinical successes with presumed eradication. Two of the bacteremic subjects had non-severe disease, and 2 were considered severe. The overall clinical and bacteriological success rates for the comparators was 11/12 (91.6%). Three of the 12 MRSP isolates from BPP subjects were also PRSP.

Streptococcus pneumoniae resistant to other antibacterials

In addition, to the data provided on penicillin and clarithromycin resistant *S. pneumoniae*, the applicant also provided information regarding the clinical and bacteriological efficacy of gemifloxacin at follow-up for isolates of *Streptococcus pneumoniae* from gemifloxacin-treated patients in CAP studies that were resistant to cefuroxime and quinolones (ofloxacin and levofloxacin).

Cefuroxime -Resistant *Streptococcus pneumoniae*

In the combined CAP gemifloxacin group (BPP population) there were

- 18 patients with *Streptococcus pneumoniae* resistant to cefuroxime with an MIC of ≥ 4 mcg/mL.
- 12 of the 18 cefuroxime-resistant isolates were also penicillin resistant (3 with an MIC of 4 mcg/mL and 9 with an MIC of 2 mcg/mL).
- 15 of the 18 cefuroxime-resistant isolates were also clarithromycin resistant (10 with MICs of 16 mcg/mL or greater, 1 with an MIC of 4 mcg/mL, 3 with an MIC of 3 mcg/mL and 1 with an MIC of 1 mcg/mL.
- 4 subjects had severe disease, 3 had moderate disease, and 11 had mild disease.
- 2 severe subjects were bacteremic. One subject with mild disease was also bacteremic.

Clinical success and bacteriological eradication/presumed eradication rates at follow-up for the BPP population with cefuroxime-resistant isolates of *Streptococcus pneumonia*e were 17/18 (94.4%). The

failure was in a subject with mild disease who was not bacteremic but was hospitalized. This subject's isolate was clarithromycin-resistant (MIC 2 mcg/mL) but penicillin sensitive (MIC 1 mcg/mL).

On the comparators arm there were 7 subjects in the Per Protocol (PP) population with *S. pneumoniae* isolates resistant to cefuroxime that were all successfully treated. Four of these isolates were also penicillin-resistant and 5 were also clarithromycin resistant. Two subjects had severe disease, 1 had moderate disease, and 4 had mild disease. Three subjects were bacteremic including 1 with severe disease and 2 with mild disease.

Quinolone -Resistant *Streptococcus pneumoniae*
In the gemifloxacin group of the combined studies population, there were no pathogens resistant to ofloxacin and levofloxacin as identified by NCCLS breakpoints. There was 1 resistant isolate on the all comparators arm that was a clinical and bacteriological failure.

In the gemifloxacin group there were 4 isolates of *Streptococcus pneumoniae* with an MIC against ciprofloxacin of 4 ug/mL (all 4 isolates were from patients with a planned treatment duration of 7 days). The clinical and bacteriological success rate associated with these isolates was 100%. There were 2 PP and 3 ITT isolates with ciprofloxacin MIC's of 4 mcg/mL (2 isolates) and >16 mcg/mL (1 isolate). One PP isolate was successfully treated and the others were associated with clinical failure.

III. Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

The Applicant presents data from 11 clinical studies in ABECB to support the safety and efficacy of gemifloxacin in the treatment of ABECB. Eight of the studies used a dose of 320 mg po qd for 5 days, two studies used a dose of 320 mg po qd for 7 days, and one dose ranging study that was performed early in the clinical development program used a treatment duration of 10 days. In the review of the Applicant's original submission from December of 1999, the Agency concurred with the applicant's conclusion that gemifloxacin was efficacious for the treatment of ABECB at a dose of 320 mg po qd for 5 days, however there were unresolved safety issues and questions regarding the overall risk benefit for this indication. In the sections that follow, the principle and supportive studies will be discussed followed by a discussion of the proposed claims made by the sponsor.

Applicant's Proposed Labeling Claim

The Applicant's Indication for ABECB is as follows:

> **INDICATIONS AND USAGE**
> *Factive* is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.
>
> **Acute bacterial exacerbations of chronic bronchitis** caused by *Streptococcus pneumoniae*; *Haemophilus influenzae*; *Haemophilus parainfluenzae; Moraxella catarrhalis.*

The proposed dosage regimen is one 320 mg orally daily for 5 days.

Acute Bacterial Exacerbation of Chronic Bronchitis: Principal Studies

The three principal studies (Study 068, 070, 212) were randomized, double blind, double-dummy, parallel group studies, that compared the clinical and microbiological efficacy and safety of oral gemifloxacin 320mg once daily for 5 days with an approved antibacterial comparator given for 7 days. The inclusion criteria targeted an ABECB study population that represented patients who would benefit from antibacterial therapy but were appropriate for oral therapy.

Clinical response, based on the resolution of signs and symptoms of ABECB in the Clinical Per Protocol Population (CPP) at follow-up (FU), served as the primary efficacy parameter in the principal clinical studies. Secondary endpoints included bacteriological and clinical responses in the patients with an identified pathogen (the Bacteriology intent to treat (BITT) and Bacteriology Per Protocol Population (BPP)). None of the studies were designed to test non-inferiority for secondary endpoints. The following table summarizes the key design elements and the outcomes for the principal studies in ABECB.

Table 41. Efficacy Results for Gemifloxacin in ABECB: Principal Studies

	Study 068		**Study 070**		**Study 212**	
DESIGN:	randomized, double-blind, double-dummy, multicenter, parallel group		Same as 068		Same as 068	
Gemifloxacin regimen	320 mg qd x 5 days		Same as 068		Same as 068	
Comparators	Clarithromycin 500 mg bid x 7 days		Amoxicillin/clavulanate 500/125 mg tid daily x 7 days		Levofloxacin 500 mg qd x 7 days	
Countries	Europe, USA and Canada		Europe		Europe and USA	
Primary Efficacy Analysis	Clinical response in the clinical per protocol population at follow-up (PP FU)		Same as 068		Same as 068	
Prootocol-specified non-inferiority limit	-10		-10		-13	
Number of centers	93		112		62	
Number of patients randomized to gemifloxacin	340		304		182	
OUTCOME						
	Gemifloxacin 320mg qd 5 days	Clarithromycin 500mg bid 7 days	Gemifloxacin 320mg qd 5 days	Augmentin 500/125mg tid 7 days	Gemifloxacin 320mg qd 5 days	Levofloxacin 500mg od 7 days
Clinical response CPP FU	86.0%	84.8%	93.6%	93.2%	88.2%	85.1%
Difference (95% CI)	1.2 (-4.7, 7.0)		0.3 (-3.9, 4.6)		3.0 (-4.7, 10.7)	
Bacteriological response PP FU	85.0%	72.7%	90.9%	79.5%	78.4%	85.7%
Difference (95% CI)	12.3 (-4.9, 29.5)		11.4 (-3.3, 26.0)		-7.3 (-23.8, 9.2)	

Demographic characteristics were equally balanced between treatment arms for all studies. The study population generally consisted of middle aged, white, long-term smokers, with a mean 12-year history of ABECB and 1-4 exacerbations of AECB in the past year. Males and females were equally represented in the principal studies. About a third of patients in Studies 070 and 212 had a FEV1<50% of predicted. Patients with severe ABECB (stage 3) were a minority.

The per pathogen bacteriologic outcomes in the bacteriological per protocol population are summarized in Table 42.

Table 42. Per Pathogen Bacteriologic Response in the Pivotal ABECB Studies*(excludes recurrences)

Pathogen	**Gemifloxacin**		**Comparator**	
Hemophilus influenzae	n/N	%	n	%
068	11/12	91.7	6/6	100
070	14/14	100	14/15	93.3
212	7/7	100	10/11	90.9
TOTAL	**32/33**	**97.0**	**30/32**	**93.7**
Streptococcus pneumoniae				
068	6/7	85.7	5/5	100
070	6/6	100	8/8	100
212	4/4	100	4/5	80
TOTAL	**16/17**	**94.1**	**17/18**	**94.4**
Moraxella catarrhalis				
068	5/5	100	5/5	100
070	13/14	92.8	12/12	100
212	5/6	83.3	14/14	100
TOTAL	**23/25**	**92.0**	**31/31**	**100**
Hemophilus parainfluenzae				
068	6/6	100	5/5	100
070	2/2	100	0	0
212	7/7	100	5/6	83.3
TOTAL	**15/15**	**100**	**10/11**	**90.9**
Staphylococcus aureus				
068	4/4	100	5/6	83.4
070	1/1	100	7/7	100
212	4/4	100	4/5	80
TOTAL	**9/9**	**100**	**16/18**	**88.9**
In the analyses in this table successful response refers to proven and presumed eradication only.				

Acute Exacerbation of Chronic Bronchitis: Supportive Studies

Two clinical trials, Study 069 and 207, provided additional supportive evidence of the efficacy and safety of gemifloxacin 320 mg po qd for 5days in the treatment of ABECB. Study 069 was of identical design as the principal studies, however, the dose of the comparator, Trovan (trovafloxacin), utilized in Study 069 was based on the approved dose in Europe (200mg qd for 5 days) whereas the approved dose in the United States is 100mg qd for 7-10 days. Hence, Study 069 was considered as a supportive rather than a principle study. The population of patients recruited into Study 069 was was very similar to the patient populations in the principal clinical studies in ABECB in terms of baseline characteristics and severity of AECB.

Study 207 was designed to investigate the safety and efficacy of gemifloxacin in hospitalized patients with ABECB and the impact of oral versus parenteral therapy on time to discharge and cost. Compared to the study population in the pivotal trials, patients in Study 207 were slightly older and had more frequent exacerbations of ABECB in the last 12 months. Many required oxygen and were treated with systemic corticosteroids, indicators that the patients may have been considered to have more severe ABECB. However, these indicators have not been shown to correlate with the need for parenteral antimicrobial therapy. This study was not blinded (open-label) and patients in Study 207 were recruited from centers in Europe, Mexico and South Africa, and did not include patients in the United States.

Table 43. Selected Demographic and Baseline Characteristics in the Supportive ABECB Studies

	Study 068		Study 070		Study 212		Study 069		Study 207	
	Gemi N=340	**Clari** N=351	**Gemi** N=304	**Amox/Clav** N=296	**Gemi** N=182	**Levo** N=179	**Gemi** N=302	**Trova** N=314	**Gemi** N=138	**Ceftr IV /Cefurox po** N=136
Age										
Mean Age (SD)	58.8 (12.0)	58.6 (11.9)	64.2 (11.7)	63.9 (12.1)	61.6 (11.6)	63.4 (10.5)	60.8 (11.0)	62.4 (11.2)	68.1 (9.8)	67.1 (10.3)
Exacerbations (past 12 months)										
0	65 (19)	66 (18.8)	19 (6.3)	24 (8.1)	25 (13.7)	20 (11.2)	31 (10.3)	36 (11.5)	0	0
1-4	236 (69.4)	245 (69.8)	226 (74.3)	231 (78.0)	143	136 (76.0)	230 (76.2)	240 (76.4)	98 (71.0)	90 (66.2)
>4	36 (10.6)	40 (11.4)	58 (19.1)	41 (13.9)	14 (7.7)	23 (12.8)	38 (12.6)	37 (11.8)	40 (29.0)	46 (33.8)
Use of Supplemental Oxygen, n (%)										
Yes	32 (9.4)	23 (6.6)	14 (4.6)	9 (3.0)	18 (9.9)	19 (10.7)	8 (2.6)	12 (3.8)	34 (24.6)	33 (24.3)
Use of Systemic Steroids in last year, n (%)										
Yes	72 (21.2)	75 (21.4)	76 (25.0)	72 (24.3)	50 (27.5)	52 (29.2)	73 (24.2)	96 (30.6)	65 (47.1)	61 (44.9)
Current Smoker*, n(%)	*smoked regulary in last month		*smoked regularly in last month		*Currently smoke		*Smoked regulary in last month		*Current smoker	
Yes	146 (42.9)	161 (45.9)	130 (33.9)	117 (39.5)	81 (44.5)	67 (37.5)	114 (37.7)	117 (37.3)	27 (19.6)	30 (22.1)
Number of Pack Years patients has smoked n (%)										
0	72 (21.2)	80 (22.8)	96 (31.6)	96 (32.4)	38 (20.9)	39 (21.9)	99 (32.8)	83 (26.4)	28 (20.3)	30 (22.1)
>0-30	123 (36.2)	123 (35.0)	112 (36.8)	113 (38.2)	62 (34.1)	43 (24.2)	120 (39.7)	142 (45.2)	61 (44.2)	58 (42.6)
>30	143 (42.1)	147 (41.9)	92 (30.3)	82 (27.7)	82 (45.1)	96 (53.9)	83 (27.5)	89 (28.3)	49 (35.5)	48 (35.3)

In Study 069 the response rate in the Clinical Per Protocol Population (CPP) at follow-up (FU) was 91.5% for gemifloxacin and 87.6% for comparator (Table 44). The clinical response rate in the CPP at FU in Study 069 were similar to those observed in the principal clinical studies. In Study 207 the clinical response rate in the CPP at FU was 86.8% for gemifloxacin and 81.3% in comparator. The respone rates in Study 207, which enrolled hospitalized patients were lower than the success rates observed for the principal studies.

Table 44. Clinical and Bacteriological Response at Follow-Up in the Supportive ABECB Studies

	Success Rate		
	Gemifloxacin	**Comparator**	**Treatment Difference**
	% (n/N)	**% (n/N)**	**% (95% CI)**
Clinical Response in the Clinical PP Population			
069	91.5 (249/272)	87.6 (241/275	3.9 (-1.2,9.0)
207	86.8 (105/121)	81.3 (91/112)	5.5 (-3.9,14.9)
Clinical Response in the Clinical ITT Population			
069	89.4 (270/302)	83.1 (261/314)	6.3 (0.9, 11.7)
207	82.6 (114/138)	72.1 (98/136)	10.5 (0.7, 20.4)
Response in the Bacteriology PP Population			
069 Bacteriological	86.8 (46/53)	82.4 (42/51)	4.4 (-9.4,18.3)
207 Clinical	80.9 (38/47)	87.0 (40/46)	-6.1 (-21.0, 8.8)
Bacteriological	63.8 (30/47)	68.3 (28/41)	-4.5 (-24.3, 15.3).
Response in the Bacteriology ITT Population			
069 Bacteriological	83.6 (46/55)	74.1 (43/58)	9.5 (-5.4, 24.4)
207 Clinical	81.3 (39/48)	82.4 (42/51)	-1.1 (-16.3, 14.1)
Bacteriological	62.5 (30/48)	60.8 (31/51)	1.7 (-17.4, 20.9)

Additional Studies in ABECB Evaluating Other Outcomes

The Applicant conducted additional studies of gemifloxacin in ABECB to evaluate several other outcomes beyond safety and efficacy. These additional outcomes include the following:

- Exacerbation-free intervals (Study 112, 105, 139)
- Time to discharge in patients requiring hospitalization (Study 207)
- Number of hospitalizations due to RTI-related episodes (Study 139)
- Time to eradication of bacterial pathogens (especially *H. influenzae*) (Study 105 & 068)

These additional studies performed from which the data were derived to investigate these additional outcomes are as follows:

- Study 105 - small PK/PD study (n=163) conducted in patients at risk for recurrence
- Study 112 - a large multinational study (n=1805) evaluating time to next exacerbation out to 4 months post therapy
- Study 139 - a longer term follow-up study added on to Study 068 (n=438). In Study 139 patients were followed for 26 weeks to evaluate time to next exacerbation.

In addition to data from these three studies (Studies 105, 112, and 139), data from the Study 068 and Study 207 were also used to provide information in support of these additional outcomes.

Study 105
Study 105 was designed to investigate the pharmacokinetic and pharmacodynamic properties of gemifloxacin versus clarithromycin in patients with ABECB at risk of early recurrence. The study also attempted to characterize the cytokine response, the role of nasopharyngeal (NP) colonization in ABECB recurrences, the change in quality of life as measured by the St George Respiratory Questionnaire (SGRQ), and other indicators of clinical and bacteriologic response. There were no primary efficacy parameters for this exploratory study. The protocol stated that no formal statistical testing will be carried out, and results will be for descriptive purposes only. The Applicant did not provide any adjustment for the type one error rate. The following 10 efficacy parameters were listed in the protocol:

- Clinical response at end of therapy and at follow-up
- Bacteriological response at end of therapy and at follow-up
- Time to bacterial eradication over all pathogens and by pathogens
- Change in clinical signs and symptoms
- Change in response to the sGRQ from screening
- Change in percent predicted FEV1
- Change in inflammatory parameters
- Proportion of patients with eradication of NP colonizing organisms (S. pneumoniae, S. aureus, M. catarrhalis, and H. influenzae) on Day 1, Day 4, end of therapy and follow-up
- Time from the follow-up visit to next episode of AECB
- Change in sputum cytology

Given that there are approximately 31 comparisons accounting for the different pathogens and time points for analysis, there would be a very high probability of seeing a statistically significant result by chance alone.

Study 112
Study 112 was a randomized, double-blind, double-dummy, multicenter study conducted in 10 countries. The objective of the study was to establish superiority of gemifloxacin 320 mg once daily for 5 days over clarithromycin 500 mg bid for 7 days in time to next exacerbation of chronic bronchitis. Secondary efficacy parameters included clinical response at Visit 2 and Visit 3 (Visit 3 was scheduled 16-18 weeks after Visit 2) and time to resolution of initial episode of ABECB. This study also collected a number of pharmacoeconomic and health related quality of life measures.

Study 139
Study 139 was a double-blind, observational parallel/ follow-on study to study 068 to assess the proportion of patients who had resolved from their initial episode and remained recurrence free for ABECB. Following the first 4 to 5 weeks of study 068 in the USA and Canada, patients were recruited to attend two further visits, at Weeks 12 and 26 (following the screening visit for study 068). Patients would be assessed for recurrence of ABECB at Visit 2 (day 28-35), Visit 3 (week 12) and Visit 4 (week 26). Investigators telephoned patients between visits at Week 8, Week 17 and Week 21 to check on the patient's status. The primary analysis compared the proportion of patients who had not yet had a recurrence of ABECB across treatments at each visit and call. This approach results in a total of 6 analyses. No adjustment for the type 1 error rate was made. Secondary parameters included the number of recurrences, quality of life measures, use of resources measures, and indirect cost measures.

Prolonged exacerbation-free intervals (Study 112, 105, 139)
Three studies measured the time to recurrence of ABECB. The results from these studies regarding this outcome were as follows. Study 139 concludes that gemifloxacin provides an advantage in the proportion of recurrence free patients (primary endpoint), whereas Study 112 finds no such advantage in time to next exacerbation (primary efficacy endpoint). Study 105 evaluated time to recurrence as one of 12 efficacy parameters. Study 105 found that therapy with gemifloxacin resulted in more patients with recurrences as well as an earlier time to recurrence.

For study 139, the Applicant states that the proportion of patients who were recurrence free was statistically higher for gemifloxacin with a difference in point estimates of 12%. However, this endpoint was not statistically significant using a Bonferroni adjustment (limit = 0.008 = 0.05/6). The results of this analysis are provided in Table 45.

Table 45. Proportion of patients resolved and with no recurrence Study 139

Visit/Call	Gemifloxacin	Clarithromycin	P-value
Visit 2 (week 4-5)	176/202 (87.1)	173/214 (80.8)	0.081
Call 1 (week 8)	165/195 (84.6)	159/197 (80.7)	0.039
Visit 3 (week 12)	148/183 (80.9)	131/176 (74.4)	0.143
Call 2 (week 17)	135/179 (75.4)	118/176 (67.0)	0.084
Call 3 (week 21)	117/160 (73.1)	97/156 (62.2)	0.110
Visit 4 (week 26)	120/169 (71.0)	100/171 (58.5)	0.016

Study 112 did not find any difference in recurrence rates between gemifloxacin and clarithromycin in time to next exacerbation. The risk for recurrence was not significantly different between treatment groups (hazard ratio 0.98, 95% CI 0.84, 1.15) as can be seen in the following Kaplan Meier plot (Figure 7).

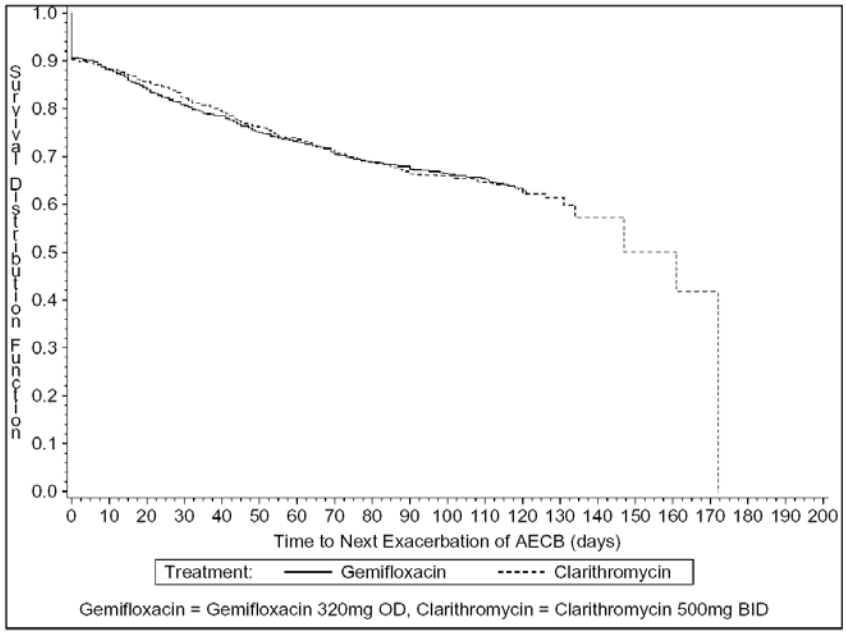

Figure 7. Kaplan – Meier Plot: Time to Next Exacerbation of Chronic Bronchitis (ITT Population) – (Source: Applicant's Figure 2 from Study Report for Study 112)

The following table gives the results of the proportion of patients remaining recurrence free. There was not a statistically significant different between the two arms.

Table 46. Proportion of patients remaining recurrence free Study 112

ITT analysis	Gemifloxacin	Clarithromycin	P-value
By 17-20 weeks after end of therapy	595/903 (65.9)	586/896 (64.5)	0.827

As stated above, study 105 also looked at time to recurrence as one of its many endpoints. Recurrence rate of ABECB was higher for gemifloxacin (60%, 50/83) than for clarithromycin (53%, 42/80) and occurred earlier in the gemifloxacin treatment group (median time to recurrence 22 vs. 46 days for gemifloxacin and clarithromycin, respectively). The following table gives the proportion of patients for whom ABECB resolved and who remain recurrence-free.

Table 47. Proportion of patients resolved and with no recurrence - Study 105

ITT population	Gemifloxacin	Clarithromycin	P-value
Week 11 (approx.)*	33/83 (39.8)	38/80 (47.5)	0.319

Source: Data from Table 43 of sponsor's study report. page 121/1646

*Patients were seen at follow-up on Day 21-25 and at four post-follow-up visits (every 2 weeks after the follow-up visit). Patients who withdrew before an exacerbation were censored.

The Kaplan Meier plots for time to next episode of ABECB for the ITT population both including (Figure 8) and excluding (Figure 9) (respectively) patients who had a time to next episode of 0 days from Study 105.

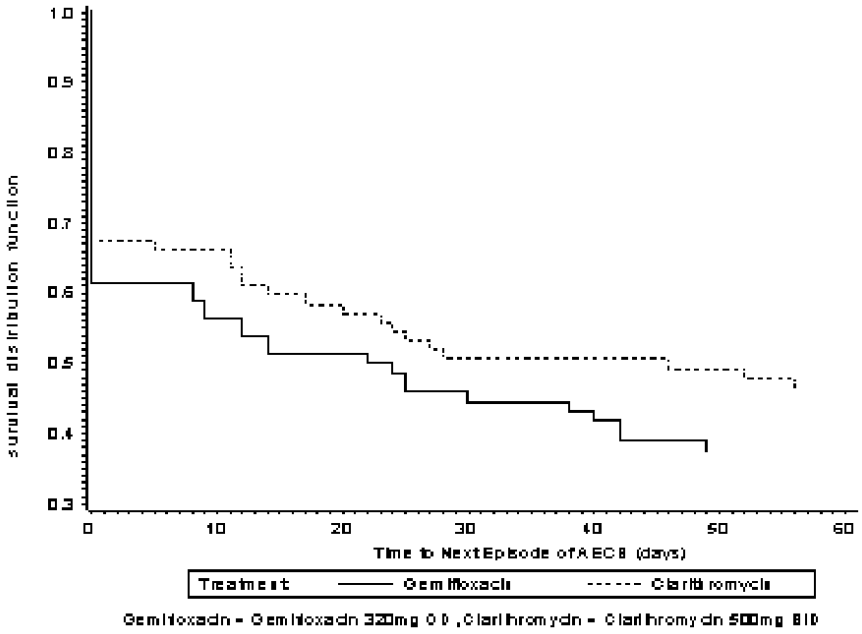

Figure 8. Time to Next Episode of ABECB – Kaplan Meier Plot (ITT Population) – Source: Applicant's figure 3 from the Study Report for Study 105

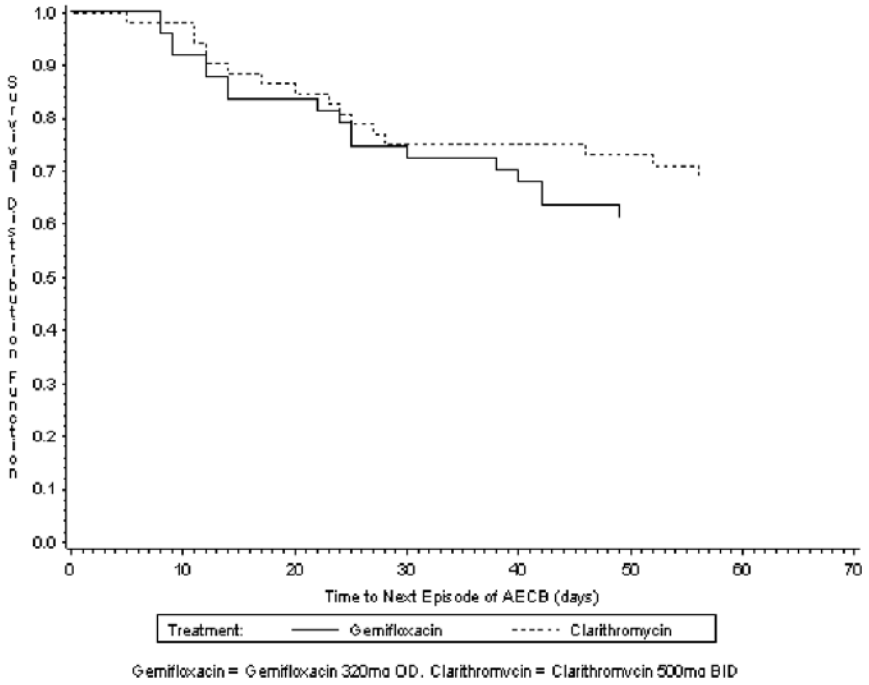

Figure 9. Time to Next Episode of ABECB – Kaplan Meier Plot – Clinical Success (Intent to Treat) Applicant's figure 3 from the Study Report for Study 105

In summary, of the 3 studies that measured the endpoint time to next episode of ABECB, one study favored gemifloxacin, one study favored clarithromycin, and one study showed no difference.

Time to discharge in patients requiring hospitalization (Study 207)

In Study 207, a supportive open-label study, the sponsor also evaluated the duration of hospitalization in inpatients with ABECB along with its primary endpoint of clinical response at follow-up. This endpoint was one of four secondary endpoints with no adjustment for multiple comparisons proposed. This study compared gemifloxacin 320mg for 5 days with parenteral ceftriaxone followed by oral cefuroxime axetil in the treatment of hospitalized adult patients. The Applicant's analysis shows that patients who received gemifloxacin had a median time to discharge that was 2 days shorter than that of the comparator. The Applicant determined that there was a statistically significant difference in time to discharge based on a Wilcoxon p-value of 0.04. However, the hazard ratio of 0.83 is not statistically significantly different from one (0.83, 95% C.I. 0.64, 1.07) and the log-rank p-value is 0.16. The difference in means between the two groups is 0.5 days (11.1 vs. 10.6). The Kaplan Meier plot of this data is provided in Figure 10.

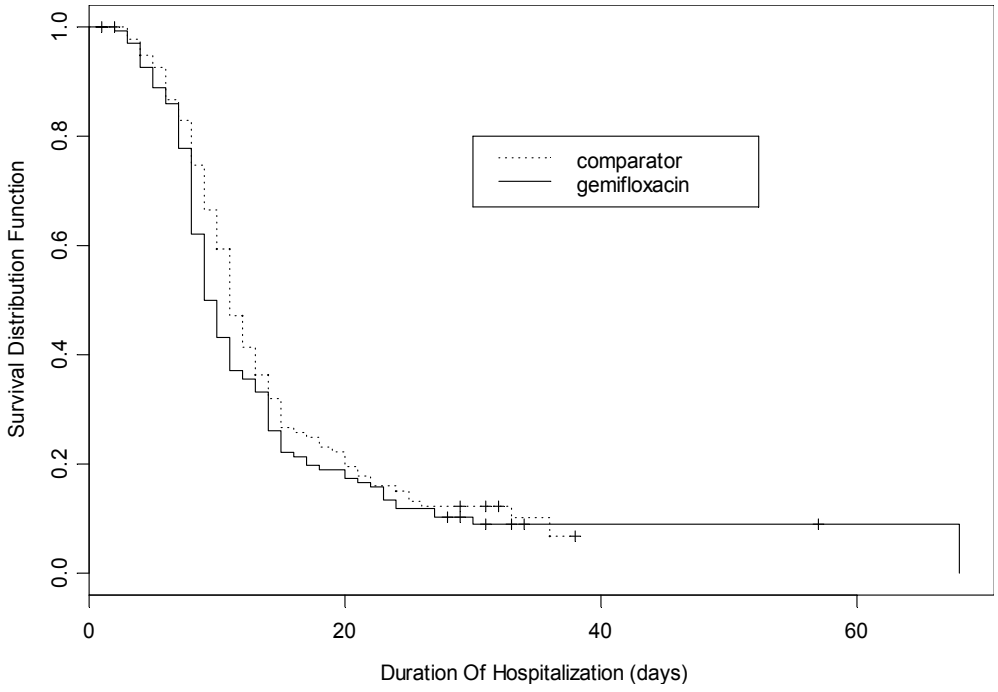

Figure 10. Time to Discharge – Kaplan Meier Plot Intent-To-Treat Population – (Source: Applicant's Study Report for Study 207 Figure 13.01)

Note that patients in the IV group received at least one dose of intravenous medication and that preparation for intravenous administration of therapy alone could explain the difference in the mean time to discharge. Furthermore, resolution of symptoms, resource utilization, quality of life and readmissions did not differ between study arms.

As part of a pharmacoeconomics analysis, the sponsor also conducted an analysis of duration of hospitalization using a general linear model. Treatment was not a statistically significant variable in the model ($p = 0.55$).

Hospitalizations due to respiratory tract infection (RTI) - related episodes (Study 139)

The number of patients hospitalized for an RTI-related episode over the 26-week study period was one of many secondary endpoints under the category of use of resources in Study 139. The number of patients with an RTI-related hospital episode by Visit number is provided in Table 48. Note that there was not a significant difference between treatment groups in the number of patients with an RTI-related hospital episode.

Table 48. Study 139 Number of Patients with an RTI-related Hospital Episode at Each Visit

Visit	Gemifloxacin N=214 n/N (%)	Clarithromycin N=224 n/N (%)	Difference (95% CI)	P-value
Visit 2	1/202 (0.5)	5/214 (2.3)	-1.8 (-4.1. 0.4)	0.217
Visit 3	2/183 (1.1)	4/176 (2.3)	-1.2 (-3.9, 1.5)	0.441
Visit 4	3/169 (1.8)	5/179 (2.9)	-1.1 (-4.4, 2.1)	0.723
Total	5/214 (2.3)	14/224 (6.3)	-3.91 (-7.67,-0.15)	0.059

Source: NDA 21-158, Study Report for Study 139, Tables 28 and 29

Additional secondary "resource utilization" endpoints included length of RTI-related hospital stay, number of days on antibiotic therapy, number of days on RTI-related antibiotic therapy, and number of RTI-related physician visits. None of these endpoints showed a difference between treatments.

Time to eradication of bacterial pathogens - (especially *H. influenzae*) - (Study 105 and 068)

The time to bacterial eradication of *H. influenzae* was evaluated in two clinical studies – Study 105 and Study 068. The results from each of these two studies are summarized in the sections that follow.

Study 105

In Study 105 the Applicant found that bacterial pathogens were more rapidly eradicated in patients treated with gemifloxacin compared to those treated with clarithromycin. By day 6, only 2% (1/66) of gemifloxacin treated patients had persistently positive sputum cultures, compared to 28% 16/58 in the clarithromycin group. The median time to bacteriological eradication of all pathogens was 1 day for gemifloxacin and 2.5 days for clarithromycin. Results from this study for *H. influenzae* showed that on Day 1 the bacterial eradication rates of *H. influenzae* on gemifloxacin was 18/23 (78%) compared to 13/31 (42%) for clarithromycin. The median time to eradication of *H. influenzae* was 1 day for gemifloxacin and 2 days for clarithromycin. Again, this was based on one of many efficacy parameters analyzed in this study for descriptive purposes.

The following two tables show the number of patients with continued clinical success at the six time points for this study for both the subset of patients with any pathogen (Table 49) and the subset of patients with *H. influenzae* (Table 50). When taking this finding into consideration within the context of the clinical and bacteriological outcomes in the principal clinical studies which demonstrated non-inferiority of gemifloxacin to its comparators its not clear that the time to bacterial eradication has an impact on ultimate patient outcomes in ABECB.

Table 49. Sustained Clinical Success in Patients with Pathogens at Baseline - Study 105

Clinical Success (ITT) n (%)	Gemifloxacin N=66	Clarithromycin N=58
EOT	55 (83.3%)	45 (77.6%)
Follow-up	38 (57.6%)	39 (67.2%)
Visit 1	30 (45.5%)	33 (56.9%)
Visit 2	25 (37.9%)	27 (46.6%)
Visit 3	20 (30.3%)	27 (46.6%)
Visit 4	19 (28.8%)	24 (41.4%)

Table 50. Sustained Clinical Success in Patients with *H. influenzae* - Study 105

Clinical Success (ITT) n (%)	Gemifloxacin N=23	Clarithromycin N=31
EOT	19 (82.6%)	24 (77.4%)
Follow-up	16 (69.6%)	21 (67.7%)
Visit 1	12 (52.2%)	18 (58.1%)
Visit 2	8 (34.8%)	14 (45.2%)
Visit 3	7 (30.4%)	14 (45.2%)
Visit 4	6 (26.1%)	13 (41.9%)

Study 068

Study 068, one of the principal studies, also contained a sub-study to evaluate the time to *H. influenzae* eradication, which was one of the 6 listed secondary analyses. This analysis was restricted to the subgroup of patients enrolled in the sub-study who had *H. influenzae* cultured at baseline (n=24). These patients had their bacteriological outcome determined daily from days 1 to 6. An outcome of eradication, persistence, or unable to be determined was given at each time point. Time to bacterial eradication was defined as the time in days to the first outcome of bacterial eradication. Kaplan Meier plots of time to eradication were presented along with the two pre-specified analyses of time to eradication and an analysis of proportion of patients with eradication on Day 1.

The number and percent of *H. influenzae* eradicated by treatment group at Days 1 through Day 3 are summarized in Table 51. The proportion of patients with bacteria eradicated at Day 1 was not statistically significantly different between the two treatment arms. However, the difference in time to bacterial eradication was statistically significant (p=0.02 based on a log-rank test).

Table 51. Number and Percent of *H. Influenzae* Eradicated by Study Day - Study 068 Sub-study

	Treatment Group	
	Gemifloxacin 320 mg po qd x 5 days N = 12	**Clarithromycin 500 mg po bid x 7 days N = 12**
Day 1	7 (58%)	3 (25%)
Day 2	11(92%)	7 (58%)
Day 3	11 (92%)	8 (67%)
	1 subject was censored on day 0	1 subject was censored on day 0 1 subject was censored on day 3 2 subjects were censored on day 4

The Kaplan-Meier plot for the time to eradication of *H. influenzae* by treatment group is provided in Figure 11**.**

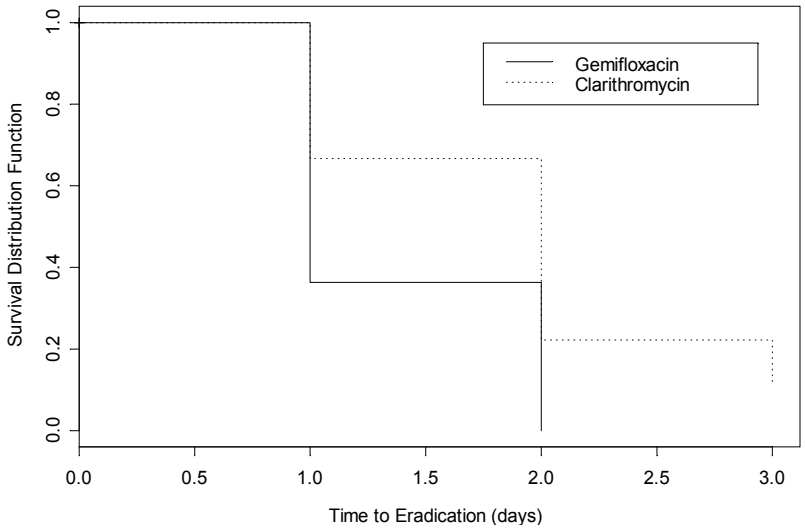

Figure 11. Time to Eradication for *H. influenzae* – Kaplan-Meier Plot – Bacterial Eradication Analysis Population: Source- Study Report for Study 068, Figure 13.01

As noted previously in the discussion of the results of Study 105 the clinical and bacteriological outcomes in the principal clinical studies demonstrated non-inferiority of gemifloxacin to its comparators; it is not clear that the time to bacterial eradication has an impact on ultimate patient outcomes in ABECB. In Study 068, the clinical cure rates for gemifloxacin were less than or equal to clarithromycin at the time points evaluated with the exception of the per protocol analysis at follow-up (Table 52).

Table 52. Clinical Cure in Patients with *H. influenzae* - Study 068 sub-study

Clinical Cure	Gemifloxacin	Clarithromycin
PP at EOT	8/10 (80%)	10/12 (83%)
PP at follow-up	8/10 (80%)	8/12 (67%)
ITT at EOT	8/12 (67%)	10/12 (83%)
ITT at follow-up	8/12 (67%)	8/12 (67%)
ITT at long-term follow-up	6/12 (50%)	7/12 (58%)

The sponsor showed in two studies (Studies 105 and 068 (sub-study) that eradication of *H. influenzae* in the sputum occurs sooner for gemifloxacin than for clarithromycin. Though, these results were based on analyses that were not adjusted for multiple comparisons, they are consistent across the two studies. However, this earlier eradication of *H. influenzae* has not been shown to translate into a clinical benefit.

IV. Safety

Extent of Exposure and Demographics

Safety data derived from the gemifloxacin clinical studies will be presented to describe the safety profile of gemifloxacin. In addition to data from the clinical studies, data from a study to evaluate rash in healthy women (Study 344) and data from relevant clinical pharmacology studies will be presented where these data complement the data from the clinical studies data. The safety experience in the clinical studies is derived from data from 12,023 patients: 6775 of whom received gemifloxacin 320 mg po qd and 5248 received comparators (this population is referred to as the Combined Population). The duration of exposure to gemifloxacin for the patients in the clinical studies are summarized in Table 53.

Table 53. Duration of Exposure to Study Medication in Clinical Studies (Combined Population)

Duration of Exposure	Gemifloxacin 320mg qd N = 6775		All Comparators N = 5248	
	n	(%)	n	(%)
0 days*	1	(0.0)	0	
1 day	55	(0.8)	41	(0.8)
2 to 3 days	553	(8.2)	456	(8.7)
4 to 5 days	3009	(44.4)	464	(8.8)
6 to 7 days	1911	(28.2)	1903	(36.3)
8 to 10 days	812	(12.0)	1766	(33.7)
11 to 14 days	356	(5.3)	526	(10.0)
15+ days	22	(0.3)	33	(0.6)
Unknown	56	(0.8)	59	(1.1)

Data Source: Applicant's Table 3.5 from p. 99 NDA 21-158 18 month safety update
*In the NDA population, 1 patient (011.038.05278) was reported as having 0 days of therapy. This patient received 1 dose of study medication (placebo) and was withdrawn prior to receiving active study medication (gemifloxacin)

The average age for patients that received gemifloxacin in the combined population was approximately 53 years of age. The populations were relatively evenly divided between males and females. In the gemifloxacin treatment group, 87% of the patients were white, 4.4% were black, 3.4% were oriental, and 5.6 % were categorized as other (Table 54). The patients that comprise the Combined Population were derived from clinical studies in a variety of indications as listed in Table 54.

Table 54. Demographic Characteristics in Clinical Studies (Gemifloxacin 320 mg versus All Comparators) (Combined Population)

Demographic Characteristics	Treatment Group: Gemifloxacin 320mg qd N=6775		Treatment Group: All Comparators N=5248	
Age (years) n (%)				
≥16 - <18	22	(0.3)	8	(0.2)
≥18 - <40	1689	(24.9)	1029	(19.6)
≥40 - <65	3000	(44.3)	2398	(45.7)
≥65 - <75	1285	(19.0)	1126	(21.5)
≥75	779	(11.5)	687	(13.1)
Mean (SD)	52.8 (17.98)		55.1 (17.19)	
Median	54		57	
Range	16-97		16-99	
Gender n (%)				
Male	3278	(48.4)	2511	(47.8)
Female	3497	(51.6)	2737	(52.2)
Race n (%)				
White	5871	(86.7)	4825	(91.9)
Black	298	(4.4)	192	(3.7)
Oriental	227	(3.4)	43	(0.8)
Other	379	(5.6)	188	(3.6)
Region				
North American countries	2693	(39.7)	2402	(45.8)
European countries	3611	(53.3)	2745	(52.3)
Other countries	471	(7.0)	101	(1.9)
Indication				
AECB	2847	(42.0)	2591	(49.4)
ABS	1397	(20.6)	521	(9.9)
CAP	1160	(17.1)	926	(17.6)
cUTI	758	(11.2)	729	(13.9)
uUTI	430	(6.3)	444	(8.5)
NGU	144	(2.1)	0	
uSSSI	39	(0.6)	37	(0.7)

Data Source: Applicant's Table 4.3 from p. 107 NDA 21-158 18 month safety update

ABS = Acute bacterial sinusitis; AECB = Acute exacerbation of chronic bronchitis; CAP = Community-acquired pneumonia; cUTI = Complicated urinary tract infection; NGU = Non -gonococcal urethritis; SD = Standard deviation; uSSSI = Uncomplicated skin and skin structures infection.

Adverse Experiences (AEs)

In the clinical studies combined population, 44.7% of patients treated with gemifloxacin reported having at least one AE in comparison to 47.5% for comparator. Diarrhea, headache and nausea were the three most common AEs reported for both groups, all with a slightly higher incidence in the comparator arm. Rash was the fourth most common AE in gemifloxacin treated patients at 3.6% in contrast to 1.1% in comparator (Table 55).

Table 55. Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences in Either Treatment Group (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Preferred Term	**n**	(%)	**n**	**(%)**
Patients with at least one AE	3029	(44.7)	2492	(47.5)
Diarrhea	343	(5.1)	325	(6.2)
Headache	304	(4.5)	273	(5.2)
Nausea	265	(3.9)	237	(4.5)
Rash*	241	(3.6)	59	(1.1)
Abdominal Pain	157	(2.3)	116	(2.2)
Vomiting	123	(1.8)	106	(2.0)
Dizziness	117	(1.7)	134	(2.6)
Rhinitis	105	(1.5)	74	(1.4)
Insomnia	100	(1.5)	92	(1.8)
Hyperglycemia	98	(1.4)	70	(1.3)
Injury	96	(1.4)	60	(1.1)
Back Pain	93	(1.4)	75	(1.4)
Creatinine Phosphokinase Increased	90	(1.3)	64	(1.2)
Sinusitis	84	(1.2)	69	(1.3)
Constipation	73	(1.1)	62	(1.2)
Flatulence	69	(1.0)	40	(0.8)
Myalgia	67	(1.0)	45	(0.9)
SGPT Increased	67	(1.0)	49	(0.9)
Dyspepsia	66	(1.0)	74	(1.4)
Fatigue	66	(1.0)	57	(1.1)
Bronchitis	64	(0.9)	75	(1.4)
Upper Respiratory Tract Infection	58	(0.9)	67	(1.3)
Pharyngitis	57	(0.8)	73	(1.4)
Moniliasis Genital	48	(0.7)	57	(1.1)
Mouth Dry	33	(0.5)	51	(1.0)
Taste Perversion	21	(0.3)	108	(2.1)

Data Source: Applicant's Table 4.3 from p. 125 NDA 21-158, 18 month safety update
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular and rash pustular.

The most common AE's in the gemifloxacin treated patients with a suspected or probable relationship (based upon the investigator's assessment) to gemifloxacin were diarrhea, nausea, rash, headache, and vomiting (Table 56). The rate of rash with a suspected or probable relationship to study drug was 2.8% for gemifloxacin and 0.6% for comparators.

Table 56. Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences of Suspected or Probable Relationship to Study Medication in Either Treatment Group (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE of suspected or probable relationship to study medication	1179	(17.4)	1047	(20.0)
Diarrhea	244	(3.6)	242	(4.6)
Rash*	192	(2.8)	34	(0.6)
Nausea	182	(2.7)	168	(3.2)
Headache	81	(1.2)	80	(1.5)
Abdominal Pain	60	(0.9)	58	(1.1)
Vomiting	58	(0.9)	57	(1.1)
Dizziness	55	(0.8)	80	(1.5)
Taste Perversion	18	(0.3)	101	(1.9)

Data Source :Applicant's Table 5.7 from NDA 21-158 18 month Safety Update

Deaths

In the combined population of clinical studies there were 33 deaths in the gemifloxacin treated population and 30 deaths in the all comparators group during the on therapy plus 30 day post therapy period. Most of the deaths in both groups were secondary to cardiorespiratory or respiratory causes and all were deemed by the investigators to be unrelated or unlikely to be related to the study drugs. The adverse events associated with death are summarized in Table 57. All deaths were associated with at least one adverse event.

Table 57. Most Commonly Reported (≥ 2 Patients in Either Treatment Group) Adverse Experiences Associated With Death During the On-Therapy Plus 30 Days Post-Therapy Interval (Combined Population)

Preferred Term	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
	N	**(%)**	**N**	**(%)**
Patients with Adverse Events Associated with Death	33	0.1	30	0.6
Cardiac Arrest	5	0.1	4	0.1
Respiratory Insufficiency	5	<0.1	5	0.1
Cardiac Failure	3	<0.1	5	0.1
Sudden Death	3	<0.1	0	<0.1
COPD	2	<0.1	1	<0.1
MI	2	<0.1	5	0.1
Pneumonia	2	<0.1	0	0.0
Lung Cancer	2	<0.1	2	0.1
Pulmonary Edema	2	<0.1	1	0.1
Acute Renal Failure	2	<0.1	0	0.0
Dyspnea	1	<0.1	2	<0.1
Suicide Attempt	0	0.0	2	<0.1

Data Source: Applicant's Table 6.2 from NDA 21-158 18 month Safety Update

Serious Adverse Experiences (SAEs)

The percentage of patients in the Combined Population who experienced serious SAE's during the interval on therapy to 30 days post therapy was 3.6% (247/6775) in the gemifloxacin 320 mg qd group and was 4.3% (228/5248) in the all comparator group. There was no single SAE which occurred in greater than 1% of the patients in either group.

Rash, increase in hepatic enzymes, pyelonephritis, sudden death, and injury are noteworthy SAE's which occurred more frequently in the gemifloxacin population than in the all comparators group. Whereas in the comparator group, the SAEs of myocardial infarction, diarrhea, and abscess were reported more frequently (Table 58).

Table 58. Number (%) of Patients (≥3 Patients in Either Treatment Group) With Serious Adverse Experiences by Preferred Term (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one SAE	247	(3.6)	228	(4.3)
Pneumonia	21	(0.3)	25	(0.5)
Chronic Obstructive Airways Disease	14	(0.2)	17	(0.3)
Bronchitis	13	(0.2)	16	(0.3)
Dyspnea	13	(0.2)	10	(0.2)
Pulmonary Carcinoma	13	(0.2)	8	(0.2)
Respiratory Insufficiency	12	(0.2)	10	(0.2)
Injury	10	(0.1)	3	(0.1)
Therapeutic Response Increased	10	(0.1)	5	(0.1)
Respiratory Disorder	8	(0.1)	8	(0.2)
Cardiac Arrest	6	(0.1)	5	(0.1)
Cardiac Failure	6	(0.1)	8	(0.2)
Chest Pain	6	(0.1)	2	(0.1)
Pleural Effusions	5	(0.1)	1	(0.1)
Pyelonephritis	5	(0.1)	2	(<0.1)
Rash*	6	(0.1)	1	(<0.1)
Fever	4	(0.1)	2	(<0.1)
GI Hemmorrhage	4	(0.1)	2	(<0.1)
Myocardial Infarction	4	(0.1)	10	(0.2)
Neoplasm NOS	4	(0.1)	1	(<0.1)
Pleurisy	4	(0.1)	1	(<0.1)
Renal Failure Acute	4	(0.1)	2	(<0.1)
Angina Pectoris	3	(<0.1)	2	(<0.1)
Cerebrovascular Disorder	3	(<0.1)	3	(0.1)
Coughing	3	(<0.1)	0	(0.0)
Dehydration	3	(<0.1)	3	(0.1)
Atrial Fibrillation	3	(<0.1)	2	(<0.1)
Hepatic Enzymes Increased	3	(<0.1)	0	(0.0)
Sudden Death	3	(<0.1)	0	(0.0)
Suicide Attempt	3	(<0.1)	3	(0.1)
Vomiting	3	(<0.1)	1	(<0.1)
Asthma	2	(<0.1)	4	(0.1)
Abdominal Pain	1	(<0.1)	5	(0.1)
Abscess	1	(<0.1)	6	(0.1)
Angina Pectoris Aggravated	1	(<0.1)	3	(0.1)
Embolism Pulmonary	1	(<0.1)	3	(0.1)
Hemoptysis	1	(<0.1)	3	(0.1)
Infection TBC	1	(<0.1)	5	(0.1)
Myelomatosis Multiple	1	(<0.1)	3	(0.1)
Sepsis	1	(<0.1)	4	(0.1)
Diarrhea	0	(0.0)	4	(0.1)

Data Source: Adapted from NDA 21-158, 18 month Safety Update, Table 025c, p.004646.

*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, rash pustular.

Serious Adverse Events With a Suspected or Probable Relationship to Study Medication

In the combined population the percentage of patients with at least one SAE with suspected or probable relationship to study medication (based upon the investigator's assessment) during the on therapy plus 30 day post therapy period was 0.4% (29/6775) in the gemifloxacin 320 mg group and in the all comparator group was also 0.4% (19/5248) (Table 59). The most frequent SAE's with a suspected or probable relationship to study medication in the gemifloxacin treated group included rash, increased hepatic enzymes or altered hepatic function, pneumonia, and increased therapeutic response. The SAE of diarrhea was reported in only comparator treated patients. Further discussion of the adverse events of rash, and hepatic and cardiac safety will be provided in sections within this document to follow that specifically address these issues.

Table 59. Number (%) of Patients (≥3 in Either Treatment Group) Reporting a Serious Adverse Experience With a Suspected or Probable Relationship to Study Medication (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least 1 SAE of suspected or probable relationship to study medication	29	(0.4)	19	(0.4%)
Rash*	7+	(0.1)	1	(<0.1)
Hepatic Enzymes Increased	3	(<0.1)	0	
Pneumonia	3	(<0.1)	2	(<0.1)
Therapeutic Response Increased	3	(<0.1)	3	(<0.1)
Diarrhea	0		3	(<0.1)

Data Source: Table 7.5, NDA 21-158, 18 month Safety Update, Table 7.5, p. 155
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, rash pustular.
+Includes PID 206.003.28549, which had a preferred term serum sickness-like reaction SAE associated with a maculo-papular rash

Withdrawals Due to Adverse Experiences

Clinical Studies

In gemifloxacin treated patients the most common adverse experiences leading to withdrawal were rash, nausea, and diarrhea. Urticaria was also reported as an adverse event leaing to withdrawal in 0.2% of gemifloxacin treated patients and 0.1% of comparator treated patients. The AE's most often associated with withdrawal for patients treated with comparator were diarrhea, nausea, vomiting, abdominal pain and rash. The major AE's leading to withdrawal in the gemifloxacin group were related to skin or allergic complications whereas gastrointestinal side effects were more prominent in patients treated with comparator agents.

Table 60. Number (%) of Patients (≥5 in Either Treatment Group) Withdrawn Due to Adverse Experiences (Gemifloxacin 320mg qd vs All Comparators) – On Therapy Plus 30 Days Post Therapy (Combined Population)

	Treatment group			
	Gemifloxacin 320mg qd N = 6775		All comparators N = 5248	
Preferred term*	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE leading to withdrawal	264	(3.9)	226	(4.3)
Rash+	64	(0.9)	15	(0.3)
Nausea	23	(0.3)	20	(0.4)
Diarrhea	22	(0.3)	25	(0.5)
Urticaria	15	(0.2)	4	(0.1)
Vomiting	15	(0.2)	16	(0.3)
Pneumonia	12	(0.2)	12	(0.2)
Dyspnea	8	(0.1)	7	(0.1)
Headache	6	(0.1)	4	(0.1)
Respiratory insufficiency	6	(0.1)	6	(0.1)
Abdominal pain	5	(0.1)	15	(0.3)
Cardiac arrest	5	(0.1)	5	(0.1)
SGPT increased	5	(0.1)	2	(<0.1)
Chronic obstructive airways disease	4	(0.1)	8	(0.2)
Dizziness	4	(0.1)	8	(0.2)
Bronchitis	3	(<0.1)	6	(0.1)
Cardiac failure	2	(<0.1)	5	(0.1)
Respiratory disorder	2	(<0.1)	10	(0.2)
Sinusitis	2	(<0.1)	5	(0.1)
Vertigo	1	(<0.1)	9	(0.2)
Creatinine clearance decreased	0	(0.0)	5	(0.1)

Data Source: NDA 21-158, 18 month Safety Update, Table 8.6, p. 171

* Adverse events are sorted by decreasing frequency in the gemifloxacin 320mg qd group.

+ The term rash includes AEs recorded with the preferred terms rash, rash erythematous, rash maculopapular, and rash pustular.

Cutaneous Adverse Events: Rash

During the review of the original submission of the Factive (gemifloxacin mesylate) NDA, a high rate of rash was noted in the gemifloxacin clinical studies, particularly among women. This section of the background document will summarize the data from the clinical studies Combined Population regarding the adverse event of rash. Following the discussion of the data from the clinical studies population, data from Study 344 will be discussed. Study 344 was a special study conducted to specifically characterize gemifloxacin associated rash including histopathology, potential for cross-sensitization, and subclinical sensitization to gemifloxacin.

Clinical Studies

The incidence of all AE's of the skin and appendage body system was 5.8% in gemifloxacin treated patients and 2.6% in comparator treated patients (Table 61). Within the skin and body system category, rash was the most frequently reported adverse event with 3.6% of gemifloxacin treated and 1.1% of comparator treated patients reporting rash. Urticarial reactions were seen in 36 (0.5%) of gemifloxacin treated patients compared to 11 (0.2%) of comparator patients. Six cases of facial edema were reported but upon review none appeared to represent angioedema.

Table 61. Number (%) of Patients in the Combined Population (≥ 3 Patients in Either Treatment Group) Reporting Adverse Experiences by Preferred Term in the Skin and Appendages Body System (On-Therapy plus 30 Days Post-Therapy Interval)

Preferred Term	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
	n	(%)	n	(%)
Patients With At Least One AE in the Skin and Appendages Body System	396	(5.8)	137	(2.6)
Rash* - (Composite term)	241	(3.6)	59	(1.1)
Rash	159	(2.3)	43	(0.8)
Rash Erythematous	57	(0.8)	12	(0.2)
Rash Maculo-Papular	28	(0.4)	4	(0.1)
Rash Pustular	3	(<0.1)	0	(0.0)
Pruritus	47	(0.7)	23	(0.4)
Urticaria	36	(0.5)	11	(0.2)
Dermatitis	25	(0.4)	3	(0.1)
Eczema	13	(0.2)	9	(0.2)
Pruritus, Genital	18	(0.3)	6	(0.1)
Dermatitis, Fungal	7	(0.1)	3	(0.1)
Acne	4	(0.1)	6	(0.1)
Skin Hypertrophy	3	(<0.1)	0	(0.0)
Skin Discoloration	3	(<0.1)	0	(0.0)
Skin Dry	6	(0.1)	6	(0.1)
Skin Ulceration	3	(<0.1)	5	(0.1)
Photosensitivity Reaction	3	(<0.1)	1	(0.0)
Bullous Eruption	1	(<0.1)	3	(0.1)
Skin Disorder	1	(<0.1)	3	(0.1)

Data Source: Tables 012b & Table 219a; NDA #21-158, 18 month Safety Update, pp.4090-4102 and 6210.
*Rash as a composite term includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.
Note: One patient (049.080.11311) in the gemifloxacin treatment group had an AE of erythema multiforme (NDA population).

The rates of rash that were reported in patients varied by gender and duration of therapy. Tables illustrating the range of rates of rash in the clinical study safety database by gender, duration of therapy, and indication for therapy are summarized in Appendix A.

Time and Rash

The timing of the onset of rash by treatment group was examined (Table 62). The results show that two-thirds of comparator treated patients have onset of the rash in the first 7 days while two-thirds of the gemifloxacin treated patients have rash onset after 7 days with 35% having onset on days 8, 9, or 10.

Table 62. Time to Onset of Rash (Combined Populations)

	Treatment Group			
	Gemifloxacin 320mg qd		All Comparators	
Patients with Rash*	N=241		N=59	
Time to Rash Onset (days)	**n**	**(%)**	**n**	**(%)**
1	9	(3.7)	6	(10.7)
2	19	(7.9)	9	(15.3)
3	14	(5.8)	10	(16.9)
4	10	(4.1)	6	(10.2)
5	12	(5.0)	3	(5.1)
6	7	(2.9)	2	(3.4)
7	6	(2.5)	2	(3.4)
8	36	(14.9)	1	(1.7)
9	46	(19.1)	4	(6.8)
10	38	(15.8)	3	(5.1)
11	19	(7.9)	1	(1.7)
12-14	11	(4.6)	2	(3.4)
15-19	7	(2.9)	5	(8.5)
20-24	2	(0.8)	2	(3.4)
25-29	2	(0.8)	2	(3.4)
≥30	3	(1.2)	1	(1.7)

Data Source: Applicant's Table 14.14 from NDA 21-158 18 month Safety Update.
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

The duration of rash by treatment group was also evaluated (Table 63). In general there appears to be a trend toward longer duration of rash in gemifloxacin treated patients than in comparator treated patients reporting rash.

Table 63. Duration of Rash (Combined Populations)

	Treatment Group			
	Gemifloxacin 320mg qd		All Comparators	
Patients with Rash*	N=241		N=59	
Duration of Rash (days)	**n**	**(%)**	**n**	**(%)**
1	4	(1.7)	4	(6.8)
2	19	(7.9)	11	(18.6)
3	30	(12.4)	5	(8.5)
4	39	(16.2)	7	(11.9)
5	22	(9.1)	3	(5.1)
6	17	(7.1)	3	(5.1)
7	11	(4.6)	4	(6.8)
8	13	(5.4)	1	(1.7)
9	9	(3.7)	2	(3.4)
10-14	30	(12.4)	3	(5.1)
15-19	10	(4.1)	4	(6.8)
20-24	7	(2.9)	1	(1.7)
25-29	4	(1.7)	0	(0.0)
≥30	5	(2.1)	1	(1.7)
Unknown/Ongoing	21	(8.7)	10	(16.9)

Data Source: Applicant's Table 14.13 from NDA 21-158 18 month Safety Update.
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

The frequency of rash by severity across treatment arms is summarized in Table 64. The frequency of rash of all severities was greater among gemifloxacin treated patients. Among the patients with rash, there is a slightly greater rate of more severe rash among gemifloxacin treated patients.

Table 64. Frequency of Rash by Severity in Either Treatment Group (Combined Populations)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		All Comparators N=5248	
	n	**(%)**	**n**	**(%)**
Patients with AE of Rash*	**241**	**(3.6)**	**59**	**(1.1)**
Mild	123	(1.8)	34	(0.6)
Moderate	90	(1.3)	22	(0.4)
Severe	33	(0.5)	4	(0.1)

Data Source: Adapted from Applicant's Table 14.16 from NDA 21-158 18 month Safety Update.
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular, and rash pustular.

Risk Factors for Rash Development

In order to investigate factors that may be related to the adverse event of rash, the data from the clinical studies database (Combined Population) were examined stratifying by a number of factors. The rates of rash vary across indications, reflecting in part the differences in the patient populations enrolled in the studies (age and gender) and the duration of therapy (Table 65). The rates of rash by indication consistently reveal higher rates of rash in the gemifloxacin treated patients compared to comparator treated patients.

Table 65. Number (%) of Patients With Rash by Therapeutic Indication (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		**All Comparators N=5248**	
Indication	**n**	**(%)**	**n**	**(%)**
AECB	44/2847	(1.5)	21/2591	(0.8)
CAP	55/1160	(4.7)	19/926	(2.1)
ABS	73/1397	(5.2)	5/521	(1.0)
cUTI	48/758	(6.3)	11/729	(1.5)
uUTI	14/430	(3.3)	2/444	(0.5)
uSSSI	5/39	(12.8)	1/37	(2.7)
NGU	2/144	(1.4)	0/0	(0.0)

Data Source: Tables 105a, 105b, 105c, 105d, 105e, 105f, 105g.
Source: Applicant's Table 14.20 from NDA 21058 18 month Safety Update

Rash was noted more frequently in female than male patients in both treatment groups (Table 66). Age less than 40 years was associated with higher rates of gemifloxacin associated rash. In general, longer duration therapy was associated with increasing rates of rash. For both treatment arms rash rates were higher in the North American and US sites than the Non North American sites.

Table 66. Number (%) of Patients With Rash by Gender, Age, Duration of Treatment, and Country (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=6775		**All Comparators N=5248**	
	n/N	**(%)**	**n/N**	**(%)**
Gender				
Male	78/3278	(2.4)	20/2511	(0.8)
Female	163/3497	(4.7)	39/2737	(1.4)
Age, yrs				
<40	115/1711	(6.7)	13/1037	(1.3)
≥40	126/5064	(2.5)	46/4211	(1.1)
Duration of Treatment, n (%)				
3	14/501	(2.8)	2/444	(0.5)
5	37/2991	(1.2)	3/334	(0.9)
7	112/2113	(5.3)	22/1985	(1.1)
10	55/858	(6.4)	25/2240	(1.1)
14	23/312	(7.4)	7/245	(2.9)
Country				
North America*	125/2693	(4.6)	42/2402	(1.7)
United States	99/2283	(4.3)	34/2086	(1.6)
Non North America+	116/4082	(2.8)	17/2846	(0.6)

Source: Applicants' Tables 14.21-14.24 from NDA 21-158 18 month Safety Update

Logistic regression was used to analyze the effects of several explanatory variables (indication, gender, grouped country, age, and planned treatment duration) on the development of rash in gemifloxacin treated patients. The results of the analysis examining the individual explanatory variables found an association of rash with female gender, indication, age less than 40, enrollment in a North American site, and duration of treatment.

Additional analyses were performed to determine if oral contraceptive use and/or hormone replacement therapy were associated with the development of gemifloxacin associated rash. In the population of female patients less than 40 years of age, oral contraceptive (OC) use was not associated; 8.6% of oral contraceptive users developed a rash and 7.9% of women under 40 who did not use OCs experienced a rash. In the population of female patients 40 years of age and older, hormone replacement therapy (HRT) did appear to have a correlation with gemifloxacin associated rash; for gemifloxacin treated patients, 5.6% of HRT users developed a rash in comparison to 2.8% of nonusers.

The Applicant examined the safety database to evaluate the rates of rash in gemifloxacin-treated patients with prior gemifloxacin exposure, prior other quinolone exposure, and quinolone exposure subsequent to gemifloxacin exposure. While these data probably represent selected populations and the number of patients available for analyses was limited in some categories, the analyses did not reveal any striking findings.

Table 67. Effect of Prior or Subsequent Quinolone Usage on the Development of Rash

Exposure Category	% Incidence of Rash
Prior Gemifloxacin Exposure (41/4659-0.5%)	0
Prior Other Quiolone Exposure (181/7659-2.45)	3/181 (1.7%)
Subsequent Quinolone Exposure N=13	0

Source: From text and tables 14.28 and 14.28 from NDA 21-158 18 month Safety Update

The data from the clinical studies were also reviewed to investigate rates of rash in patients with other adverse events that might suggest a systemic syndrome. Rates of rash in patients who had increased liver function tests, fever, arthralgia, or arthralgia and lymphadenopathy are summarized in Table 68.

Table 68. Rates of Rash in Gemifloxacin Treated Patients with Signs of Potential Systemic Syndromes

Sign	Number of Patients Exhibiting Sign n/N (%)	Number of Patients with Sign Reporting an AE of Rash n/N (%)
Increased Liver Function Tests or Eosinophilia	38/6775 (0.6)	2/38 (5.3)
Fever	52/6775 (0.8)	3/52 (5.8)
Arthralgia	45/6775 (0.7)	3/45 (6.7)
Arthralgia and Lymphadenopathy	4/6775 (0.06)	1/4 (25.0)

Adapted from the text and tables, NDA 21-158, 18 month safety update, pp. 383-387.

One patient did experience a serum sickness like reaction. This patient's course is summarized in the following section.

Patient number 206.003.28549 was a 42 y.o. Caucasian female resident of the United States. She had a history of allergic rhinitis and asthma. She was entered into study 202 for the treatment of Acute Bacterial Sinusitus and received gemifloxacin 320 mg po qd for 5 days. Thirteen days after completing therapy she developed a generalized maculopapular rash, fever, chills, joint pains and cough. Her liver function test and hematologic parameters stayed within normal limits. She was

treated with Vicodin and decadron. The rash cleared in approximately 26 days and the other symptoms were resolved by 2 months.

STUDY 344

Design

The factors associated with the increased likelihood of rash in the clinical studies database for gemifloxacin were female gender, age less than 40, and gemifloxacin use longer than 7 days. Study 344 was designed to further characterize gemifloxacin-associated rash in a population predisposed to the development of rash (women under 40 years of age receiving gemifloxacin for 10 days). Study 344 was a clinical pharmacology study enrolling healthy female volunteers under the age of 40 who were randomized in Part A using a 5:1 ratio to receive either gemifloxacin 320 mg po qd for 10 days or ciprofloxacin 500 mg po bid for 10 days, respectively (Figure 12). After a washout period of 4-6 weeks, subjects entered Part B of the study as shown in the study schema. Subjects who developed gemifloxacin rash were randomized to either ciprofloxacin or placebo in a 3:1 ratio; subjects who did not develop a rash to gemifloxacin treatment were randomized to receive a second course of gemifloxacin or placebo. The subjects who received ciprofloxacin in Part A received placebo in Part B if they developed a rash to ciprofloxacin in Part A, or a second course of ciprofloxacin if the subject did not develop a rash to ciprofloxacin in Part B. The objectives of the study were to characterize the following:

- Clinical and histological characteristics of gemifloxacin associated rash
- Potential for cross sensitization to ciprofloxacin in subjects who experienced gemifloxacin-associated rash
- Potential for subclinical sensitization to repeat exposure to gemifloxacin in subjects not developing a rash on first exposure to gemifloxacin
- Relationship between plasma levels of gemifloxacin and N-acetyl gemifloxacin and the incidence of rash

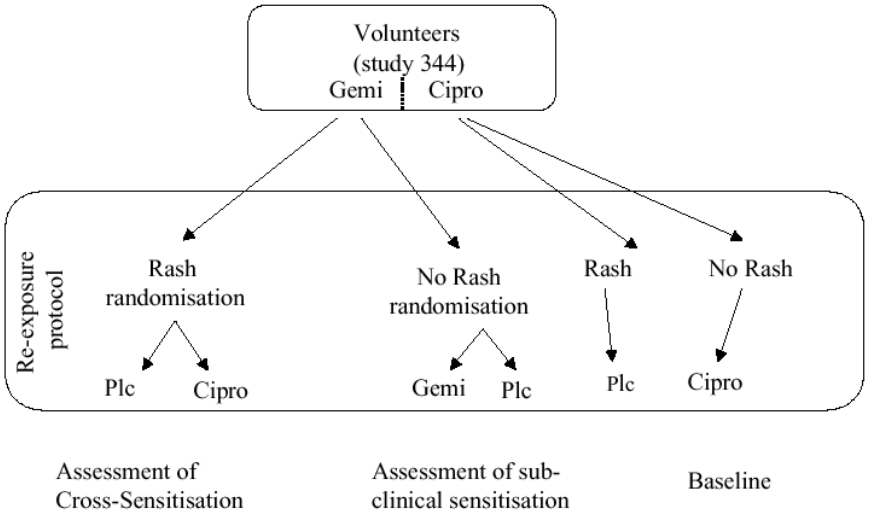

Figure 12. Schema for Study 344

In Part A of the study, there were 819 evaluable subjects that received gemifloxacin and 164 that received ciprofloxacin (Figure 13). In the gemifloxacin group 31.7% (260/819) of women developed rash and 4.3% (7/164) developed rash to ciprofloxacin (Table 69).

Part A

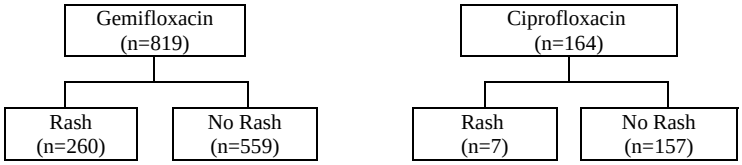

Figure 13. Summary of subject disposition in Part A

Table 69. Point Estimates and 95% Confidence Intervals for Incidence of Rash in Part A

Regimen	No. of Subjects	Subjects With Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemifloxacin	819	260	31.7	(28.5, 35.0)	(28.6, 35.1)
Ciprofloxacin	164	7	4.3	(0.9, 7.7)	(1.7, 8.6)

Source: Applicant's Table 14.1 from NDA 21-158 18 month Safety Update

In Part B of the study, subjects were randomized or assigned to further gemifloxacin, placebo, or ciprofloxacin therapy depending on their outcome in Part A and according to the study schema in Figure 12. Subject disposition in the Part B portion of the study is shown in Figure 14. The results for rates of rash in each of the groups in Part B of the study are summarized in Table 70. For subjects that developed rash to gemifloxacin in Part A, 10.4% of these subjects randomized to ciprofloxacin in part B developed a rash compared to 4.9% of the subjects who recieved placebo. For the subjects who received gemifloxacin in Part A and did not develop a rash, 3.2% of subjects randomized to a second course of gemifloxacin in Part B developed rash compared to 2.7% of their placebo counterparts in Part B.

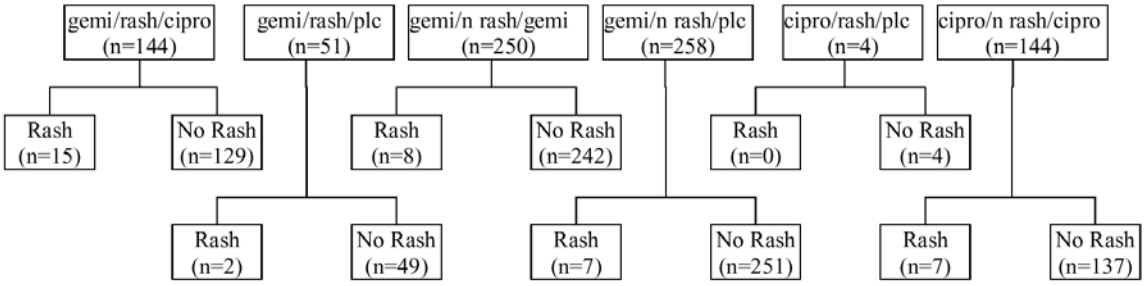

Figure 14. Summary of Subject Disposition in Part B

Table 70. Point Estimates and 95% Confidence Intervals for Incidence of Rash in Part B

Regimen	No. of Subjects	Subjects With Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
gemi/rash/cipro	144	15	10.4	(5.1, 15.8)	(5.9, 16.6)
gemi/rash/plc	51	2	3.9	(0.0, 10.2)	(0.5, 13.5)
gemi/N rash/gemi	250	8	3.2	(0.8, 5.6)	(1.4, 6.2)
gemi/N rash/plc	258	7	2.7	(0.5, 4.9)	(1.1, 5.5)
cipro/rash/plc	4	0	0.0	(0.0, 12.5)	(0.0, 60.2)
cipro/N rash/cipro	144	7	4.9	(1.0, 8.7)	(2.0, 9.8)

Source: Applicant's Table 14.2 from NDA 21-158 18-month safety update

The point estimates and their 95% confidence intervals for differences in incidence rates for rash in several groups of interest are provided in Table 71.

Table 71. Point Estimates and 95% Confidence Intervals for Differences in Incidence of Rash

Regimen	Point Estimate(%)	95% C.I.*
(gemi/rash/cipro/rash) – (cipro/N rash/cipro/rash)*	5.6	(-1.2, 12.4)
(gemi/rash/cipro/rash) – (gemi/rash/plc/rash)**	6.5	(-2.1, 15.1)
(gemi/rash/cipro/rash) – (cipro/rash)***	6.1	(-0.4, 12.7)

* Difference in incidence of rash for dosing with ciprofloxacin Part B following gemifloxacin associated rash in Part A relative to dosing with ciprofloxacin in Part B following ciprofloxacin without rash in Part A.

** Difference in incidence of rash for dosing with ciprofloxacin Part B following gemifloxacin associated rash in Part A relative to dosing with placebo in Part B following gemifloxacin associated rash in Part A.

*** Difference in incidence of rash for dosing with ciprofloxacin Part B following gemifloxacin associated rash in Part A relative to dosing with ciprofloxacin in Part A.

Source: Adapted from Applicant's Table 14.3 from NDA 21-158 18 month safety update

In Part B, one of the study centers had remarkably high incidence of rash in Part B (>66%) with all 3 subjects receiving placebo reported as having a rash. Therefore additional analyses were performed examining rates of rash in Part B excluding results from this one center (Table 72). The rash rate for the group gemi/rash/cipro was 5.9% and the rash rate in the gemi/rash/placebo group was 2.0% when data from this one center was excluded.

Table 72. Point Estimates and 95% Confidence Interval for Incidence of Rash in Part B – Excluding Center 027

Regimen	No. of Subjects	Subjects with Rash	Point Estimate (%)	95% C.I. Normal Approximation	Exact Method
Gemi/rash/cipro	136	8	5.9	(1.6, 10.2)	(2.6, 11.3)
Gemi/rash/plc	50	1	2.0	(0.0, 6.9)	(0.1, 10.6)
Gemi/N rash/gemi	248	6	2.4	(0.3, 4.5)	(0.9, 5.2)
Gemi/N rash/plc	256	5	2.0	(0.1, 3.8)	(0.6, 4.5)
Cipro/rash/plc	4	0	0.0	(0.0, 12.5)	(0.0, 60.2)
Cipro/N rash/cipro	141	5	3.5	(0.1, 7.0)	(1.2, 8.1)

Data Source: Applicant's Table 21 NDA 21-158, Study Report Study 344, p. 00093.

The preceding tables demonstrate the high incidence of rash in Part A of 31.7% in the gemifloxacin treated subjects in comparison to the rate of 4.3% in the ciprofloxacin treated subjects. In part B subjects who had rash to gemifloxacin in Part A had either 10.2 or 5.9% (if Center 027 is excluded) incidence of rash possibly suggesting some cross sensitization.

Rash Characteristics – Part A

The rashes observed in Parts A and B were characterized by examining the description, surface area involved, day of onset, and duration of rash. Since there were only 7 rashes in the ciprofloxacin arm in Part A it is difficult to make significant comparisons between the groups. However, the information gathered provided important detail on the nature of the rash and can also be compared to what was seen in the clinical trials group and what would be expected overall.

The following tables and graphics depict the characteristics of the rash in Parts A and B.

The rash in Part A of Study 344 appears to have a later onset and longer duration similar to what was observed in the combined clinical trials population. Eighty percent of subjects who developed a rash to gemifloxacin did so on days 8, 9, or 10 (Table 73). The average duration for gemifloxacin rash was 7 days in comparison to 4 days for rashes secondary to ciprofloxacin treatment (Table 74).

Table 73. Day of Onset of Rash in Part A

Day of Onset	Gemifloxacin	Ciprofloxacin
1	10 (3.8%)	0 (0.0%)
2	6 (2.3%)	2 (28.6%)
3	2 (0.8%)	1 (14.3%)
4	2 (0.8%)	1 (14.3%)
5	2 (0.8%)	0 (0.0%)
6	3 (1.2%)	0 (0.0%)
7	5 (1.9%)	0 (0.0%)
8	54 (20.8%)	1 (14.3%)
9	109 (41.9%)	0 (0.0%)
10	50 (19.2%)	1 (14.3%)
11	10 (3.8%)	0 (0.0%)
12	3 (1.2%)	0 (0.0%)
13	0 (0.0%)	0 (0.0%)
14	1 (0.4%)	0 (0.0%)
15	1 (0.4%)	0 (0.0%)
16	1 (0.4%)	0 (0.0%)
17	1 (0.4%)	1 (14.3%)
Total	260 (100.0%)	7 (100.0%)

Source: Applicant's Table 12.3 from NDA 21-158 18 month safety update

Table 74. Summary Statistics for Duration of Rash in Part A

Regimen	n	Mean	S.D.	Median	Min	Max
Gemifloxacin	258	7	5.3	6	1	52
Ciprofloxacin	7	4	1.1	3	2	5

Source : Applicant's Table 12.6 from NDA 21-158 Report of Study 344

The amount of surface area involved and the intensity of the rash secondary to gemifloxacin in Part A are both greater than what was seen in the ciprofloxacin arm in Study 344. Over 25% had a rash covering >60% of body surface area and 7.3% were classified as having a severe rash while none of the ciprofloxacin subjects had a severe rash. In addition 11.5% who developed rash to gemifloxacin had an urticarial component to that rash while none of the ciprofloxacin rashes did so.

Table 75. Summary of Description of Rash in Part A by Regimen and Severity.

Regimen	Severity			
Description	**Mild (%)**	**Moderate (%)**	**Severe (%)**	**Total (%)**
Gemi (n=260)	161/260 (62)	80/260 (31)	19/260 (7)	260/260 (100)
Macules	125 (48.1)	70 (26.9)	14 (5.4)	209 (80.4)
Papules	122 (46.9)	71 (27.3)	17 (6.5)	210 (80.8)
Plaques	15 (5.8)	11 (4.2)	3 (1.2)	29 (11.2)
Pruritus	99 (38.1)	65 (25)	16 (6.2)	180 (69.2)
Skin Tenderness	12 (4.6)	6 (2.3)	4 (1.5)	22 (8.5)
Urticaria	18 (6.9)	6 (2.3)	6 (2.3)	30 (11.5)
Cipro(n=7)	6/7 (85.7)	1/7 (14.3)	0 (0)	7/7 (100)
Macules	3 (42.9)	0 (0)	0 (0)	3 (42.9)
Papules	5 (71.4)	1 (14.3)	0 (0)	6 (85.7)
Pruritus	3 (42.9)	1 (14.3)	0 (0)	4 (57.1)

Source: Applicant's Table 14.5 fromNDA21-158 Rpoert of Study 344 Appendix C

Table 76. Summary of Surface Area Covered with Rash by Regimen and Severity of Rash in Part A

	Surface Area	Severity			
Regimen	**Covered**	**Mild**	**Moderate**	**Severe**	**Total**
Gemifloxacin	Unknown	5 (1.9%)	0 (0.0%)	0 (0.0%)	5 (1.9%)
	0 - 5%	37 (14.2%)	3 (1.2%)	0 (0.0%)	40 (15.4%)
	6 - 10%	21 (8.1%)	4 (1.5%)	2 (0.8%)	27 (10.4%)
	11 - 20%	32 (12.3%)	7 (2.7%)	0 (0.0%)	39 (15.0%)
	21 - 40%	21 (8.1%)	12 (4.6%)	2 (0.8%)	35 (13.5%)
	41 - 60%	28 (10.8%)	17 (6.5%)	2 (0.8%)	47 (18.1%)
	>60%	17 (6.5%)	37 (14.2%)	13 (5.0%)	67 (25.8%)
	Total	**161 (61.9%)**	**80 (30.8%)**	**19 (7.3%)**	**260 (100.0%)**
Ciprofloxacin	Unknown	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	0 - 5%	4 (57.1%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
	6 - 10%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	11 - 20%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	21 - 40%	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
	41 - 60%	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
	>60%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	**6 (85.7%)**	**1 (14.3%)**	**0 (0.0%)**	**7 (100.0%)**

Source: Applicant's Table 14.6 from NDA 21-158 Report of Study 344 Appendix C

Characteristics of Rash-Part B

There were much smaller numbers of subjects to compare in the arms in Part B. However, the tendency for rashes secondary to gemifloxacin to occur later and last longer were still present but less pronounced. There were 8 Gemi/Nrash/gemi subjects with a mean onset of rash of 6 days and mean duration of 7 days while there were 15 Gemi/rash/cipro subjects with rash with a mean

onset of 4 days and mean duration of 5 days. Overall, the rashes in Part B were milder and involved less surface area than the rashes in Part A.

Table 77. Summary Statistics for Day of Rash Onset in Part B

Regimen	n	Mean	S.D.	Median	Min	Max
gemi/rash/cipro	15	4	2.9	2	1	10
gemi/rash/plc	2	6	4.9	6	2	9
gemi/N rash/gemi	8	6	5.7	5	1	18
gemi/N rash/plc	7	6	7.9	2	1	23
cipro/rash/plc	0					
cipro/N rash/cipro	7	6	2.6	6	3	10

Source: Applicant's Table 12.19 from NDA 21-158 Report of Study 344

Table 78. Summary Statistics for Duration of Rash in Part B

Regimen	n	Mean	S.D.	Median	Min	Max
gemi/rash/cipro	15	5	6.0	3	2	26
gemi/rash/plc	2	3	0.7	3	2	3
gemi/N rash/gemi	8	7	5.6	6	2	19
gemi/N rash/plc	7	4	1.8	5	1	6
cipro/rash/plc	0					
cipro/N rash/cipro	7	5	3.6	4	2	12

Source: Applicant's Table 12119 from NDA 21-158 Report of Study 344

Table 79. Summary of Surface Area Covered with Rash by Regimen and Severity of Rash in Part B

	Surface Area	Severity			
Regimen	Covered	Mild	Moderate	Severe	Total
gemi/rash/cipro	0 - 5%	13 (86.7%)	2 (13.3%)	0 (0%)	15 (100%)
gemi/rash/plc	0 - 5%	2 (100%)	0 (0%)	0 (0%)	2 (100%)
gemi/N rash/gemi	0 - 5%	4 (50%)	0 (0%)	0 (0%)	4 (50%)
	6 - 10%	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	11 - 20%	1 (12.5%)	1 (12.5%)	0 (0%)	2 (25%)
	21 - 40%	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	41 - 60%	1 (12.5%)	0 (0%)	0 (0%)	1 (12.5%)
gemi/N rash/plc	0 - 5%	6 (85.7%)	0 (0%)	0 (0%)	6 (87.5)
	6 - 10%	1 (14.3%)	0 (0%)	0 (0%)	1 (14.3%)
cipro/N rash/cipro	0 - 5%	5 (71.4%)	0 (0%)	0 (0%)	5 (71.4%)
	6 - 10%	2 (28.6%)	0 (0%)	0 (0%)	2 (28.6%)

Source: Applicant's Table 12.26 from NDA 21-158 Report of Study 344

Mucus membrane involvement

As noted in Table 62 there were 16 cases of mucus membrane involvement among the 260 subjects who developed gemifloxacin rash (6.2%) and none in the 7 subjects who developed a rash secondary to ciprofloxacin. The three cases of reported eye involvement consisted primarily of dry eyes and the one case of involvement of the genitalia was in a subject with "total body rash" with no specific lesions other than extension of a macular papular rash.

Eleven case reports of subjects with mucus membrane involvement of the mouth were reviewed. Five of these reports describe one to a few ulcerations, erosions, papules, or vesicles inside the mouth or on the lips. For 2 of these subjects no therapy was prescribed, 2 were prescribed topical steroids, and 1 was treated with topical steroids and oral antihistamines. Two subjects were

described as having erythema on the lips and/or inside the mouth-one of these subjects required treatment with systemic steroids. Two subjects' CRFs are unreadable for the description of the mouth involvement but one of these also required treatment with systemic steroids. Two subjects were reported to have petechiae on lips: neither required any therapy.

Table 80. Summary of Mucous Membrane Involvement by Regimen and Severity of Rash in Part A

	Mucous Membrane	Severity of Rash			
Regimen	**Involvement**	**Mild**	**Moderate**	**Severe**	**Total**
Gemifloxacin (n=260)	None	152 (58.5%)	72 (27.7%)	17 (6.5%)	241 (92.7%)
	Eyes	3 (1.2%)	0 (0.0%)	0 (0.0%)	3 (1.2%)
	Genitalia	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
	Mouth	3 (1.2%)	7 (2.7%)	2 (0.8%)	12 (4.6%)
Ciprofloxacin (n=7)	None	6 (85.7%)	1 (14.3%)	0 (0.0%)	7 (100.0%)
	Eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Genitalia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mouth	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Applicant's Table 12.11 from NDA 21-158 Report of Study 344

Histopathology Results

Histopathology specimens were obtained from 288 of the 299 total rash episodes in Parts A and B of Study 344 secondary to gemifloxacin, ciprofloxacin or occuring in the placebo arm. Punch biopsies were obtained from both affected and unaffected skin. Specimens were evaluated by routine histologic examination, immunophenotypic evaluation, and stained for immunoflourescence for IgG, Igm, IgA, and C3.
The following findings were obtained:

- Most common finding-mild superficial perivascular infiltrate.
- 10 cases of moderate superficial or deep perivascular infiltrate.
- 10 cases of eosinophils in the infiltrate (1 in unaffected skin.)
- T cell type infiltrate, both CD-4 and CD-8 with no common pattern noted.
- No evidence of vasculitis
- Activation of endothelial cells –staining for ICAM and HLA-DR.
- HLA-DR staining was noted in a siginificant number of cases.
- Immunoflourescence revealed faint deposits of IgM and/or C3 in dermal vessels "lumina" in some cases inlvolving unaffected and affected skin.
- One case of linear IgM along basement membrane (affected and unaffected.)
- No bulla formation, no epidermal or eccrine necrosis.

Hepatic Safety Assessments

Pre-Clinical Studies

Pre-clinical studies in dogs with gemifloxacin using repeat oral doses of 28 days, 3 months and 6 months duration noted cholangitis/pericholangitis accompanied by hepatocellular degeneration and single cell necrosis. The lowest effect dose was 23mg/kg/day (mean Cmax 1.1μg/mL, AUC 7.6 μg.h/mL for combined sexes). These findings were associated with deposits of crystalline drug-related material, also containing magnesium, in bile canaliculi and bile ducts. Elevated hepatic enzymes, most consistently ALT and alkaline phosphatase, but also GGT and AST, were also associated with the liver histopathology. The abnormalities in hepatic enzymes returned to normal following a four week off-dose period. The no-effect dose for hepatic effects after 28 days was 96 mg/kg/day (mean Cmax 4.1μg/mL, AUC 29.2 μg.h/mL for combined sexes), and after 6 months was 8 mg/kg/day (mean Cmax 0.64 μg/mL, AUC 3.0 μg.h/mL). The values for humans dosed with 320 mg of gemifloxacin orally are C_{max} 1.2 μg/mL and AUC 8.4 μg.h/mL, respectively.

Clinical Pharmacology - Oral Gemifloxacin-NDA

In clinical pharmacology studies, repeat doses of gemifloxacin 320mg were well tolerated, but repeat doses of 480mg and 640mg resulted in an increase in the rate of asymptomatic elevations of ALT and AST relative to the 320mg dose. These abnormalities returned to normal within 48 hours following cessation of dosing. All of the abnormalities in LFTs in these studies at all doses were considered of mild or moderate severity by the investigators.

Table 81. Incidence of Flagged LFT's at Various Doses on Gemifloxacin in a Clinical Pharmacolgy Study

Parameter	Flag	Gemifloxacin dose (mg)				
		<320	320	480-600	≥640	All doses
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
ALT	High	0/16 (0.0)	0/79 (0.0)	5/16 (31.2)	1/8 (12.5)	6/119 (5.0)
AST	High	0/16 (0.0)	1/79 (1.2)	3/16 (18.7)	1/8 (12.5)	5/119 (4.2)

Source: Adapted from Table DS16B from NDA 21-158 ISS

In single dose studies with gemifloxacin 320mg, the only LFT with F3 transitions was high total bilirubin [3/373 subject sessions (0.8%)]. Subject 066.001.00015 had a total bilirubin value of 7.5 mg/dL (normal range: 0-1.0 mg/dL) 7 days after single dose gemifloxacin 320mg. The increase was 7.5 x ULN and was suspected to be related to study medication. It was therefore reported as an adverse experience (bilirubinemia). At screening, the subject's total bilirubin was normal (0.8 mg/dL). The subject also had mildly elevated bilirubin 7 days after dosing with ofloxacin 400mg (1.7 mg/dL), which occurred before the gemifloxacin dosing session. At follow-up, the subject's bilirubin value had returned to just outside the normal reference range (1.1 mg/dL), but was not considered clinically significant by the investigator. The patient was asymptomatic. Two further subjects (084.001.00034 and 084.001.00035) had high total bilirubin F3 transitions after single dose gemifloxacin 320mg, each less than 2 x ULN, which were not considered clinically significant by the investigators.

Four subjects were withdrawn from study 005, a pK study of healthy elderly subjects who received repeat dosing of 480 mg of gemifloxacin, because of asymptomatc elevations in ALT (range 121-333 IU).

Clinical Studies

NDA population

Included in the NDA submission 21-158 are studies of uncomplicated UTI where single doses of 640 mg were compared to ciprofloxacin 250 mg po bid for 3 days in primarily otherwise healthy young women. The LFT abnormalities by treatment arm are shown in the table below. For all LFT measurements there were higher rates of abnormalities in the gemifloxacin arm. These differences had mostly resolved by the end of therapy (note-gemifloxacin was administered as a single dose.)

Table 82. Number (%) of Patients with Liver Function Values in the Specified Ranges at the On-Therapy Visit (Gemifloxacin 640mg vs Ciprofloxacin 250mg, Patients In-Range at Screening)

		Treatment Group			
Functional Group/ Variable	Range	Gemifloxacin 640mg Single Dose N =638		Ciprofloxacin 250mg bid N = 662	
		n/N*	(%)	n/N*	(%)
ALT	<ULN	569/592	(96.1)	600/606	(99.0)
	ULN-<2xULN	14/592	(2.4)	6/606	(1.0)
	2-<4xULN	4/592	(0.7)	0/606	
	4-<6xULN	1/592	(0.2)	0/606	
	6-<8xULN	3/592	(0.5)	0/606	
	≥8xULN	1/592	(0.2)	0/606	
AST	<ULN	578/593	(97.5)	602/607	(99.2)
	ULN-<2xULN	10/593	(1.7)	5/607	(0.8)
	2-<4xULN	3/593	(0.5)	0/607	
	4-<6xULN	1/593	(0.2)	0/607	
	6-<8xULN	0/593		0/607	
	≥8xULN	1/593	(0.2)	0/607	
ALK-P	<ULN	599/606	(98.8)	622/625	(99.5)
	ULN-<2xULN	7/606	(1.2)	3/625	(0.5)
	2-<4xULN	0/606		0/625	
	4-<6xULN	0/606		0/625	
	6-<8xULN	0/606		0/625	
	≥8xULN	0/606		0/625	
Total Bilirubin	<ULN	596/600	(99.3)	610/615	(99.2)
	ULN-<2xULN	4/600	(0.7)	5/615	(0.8)
	2-<4xULN	0/600		0/615	
	4-<6xULN	0/600		0/615	
	6-<8xULN	0/600		0/615	
	≥8xULN	0/600		0/615	

Data Source: Applicant Table 370 from NDA 21-158 ISS

*n/N= number of patients outside limit/number of patients evaluated for the particular parameter

(Note: 2/4 patients treated with gemifloxacin and 0/5 patients treated with ciprofloxacin who had bilirubin elevations to 2-4xULN had treatment emergent elevations.

The remainder of the LFT abnormalities from the clinical studies will be discussed as part of the combined population.

The Clinical Studies Combined Population

During the On-Therapy visit in the combined population, 0.8% of the gemifloxacin treated patients had ALT elevations >2xULN in comparison to 0.5% for comparator. Only 1 patient in each arm had an ALT value >4xULN with the comparator patient's level being higher than

8xULN (Patient number 011.015.05219). At the On-Therapy visit, 0.7% of gemiloxacin patients had AST levels >2xULN while 0.4% of comparator patients achived this level of abnormality. Two gemifloxacin patients had AST values >4xULN (008.042.12183 and 008.044.12476) while one comparator did so (012.135.17939). There was only 1 gemifloxacin patient (013.101.02888) with an alkaline phosphatase >4xULN and no comparator treated patients. There were 3 gemifloxacin treated patients with bilirubin elevations of >2xULN in comparison to none for comparator (Table 83).

In the Combined Population 2 patients in each treatment group (gemifloxacin and comparator) had end of therapy treatment emergent elevations of >4xULN for ALT.

Table 83. Number (%) of Patients with Liver Function Tests Within Specified Ranges at the On-Therapy Visit - Patients In-Range at Screening (Combined Population)

Functional Group/ Variable	Range	Treatment Group			
		Gemifloxacin 320mg qd N=6681*		All Comparators N=5174*	
		n/Np+	(%)	n/Np+	(%)
ALT	<ULN	3800/3989	(95.3)	3443/3588	(96)
	ULN-<2xULN	162/3989	(4.1)	127/3588	(3.5)
	2-<4xULN	26/3989	(0.7)	15/3588	(0.4)
	4-<6xULN	1/3989	(<0.1)	2/3588	(0.1)
	6-<8xULN	0/3989		0/3588	
	≥8xULN	0/3989		1/3588	(<0.1)
AST	<ULN	3824/3990	(95.8)	3512/3633	(96.7)
	ULN-<2xULN	141/3990	(3.5)	106/3633	(2.9)
	2-<4xULN	25/3990	(0.6)	14/3633	(0.4)
	4-<6xULN	1/3990	(<0.1)	1/3633	(<0.1)
	6-<8xULN	1/3990	(<0.1)	0/3633	
	≥8xULN	0/3990		0/3633	
Alkaline Phosphatase	<ULN	4007/4075	(98.3)	3607/3672	(98.2)
	ULN-<2xULN	61/4075	(1.5)	62/3672	(1.7)
	2-<4xULN	7/4075	(0.1)	3/3672	(0.1)
	4-<6xULN	1/4075	(<0.1)	0/3672	(<0.1)
	6-<8xULN	0/4075		0/3672	
	≥8xULN	0/4075		0/3672	
Total Bilirubin	<ULN	4046/4087	(99)	3621/3655	(99.1)
	ULN-<2xULN	38/4087	(0.9)	34/3655	(0.9)
	2-<4xULN	3/4087	(0.1)	0/3655	
	4-<6xULN	0/4087		0/3655	
	6-<8xULN	0/4087		0/3655	
	≥8xULN	0/4087		0/3655	

Data Source: Table 206a.

* N = total number of patients with in-range (<ULN) values at screening.

+ n/Np = number of patients within the specified range/number of patients evaluated for the laboratory parameter.

Source: Adapted from Applicant's Table 17.27 from NDA 21-158, 18-month Safety Update

Patients with Baseline Liver Disease (All Therapeutic Indications)

Patients with an ongoing medical history of liver disease or a baseline AE suggestive of active liver disease were included in a population of patients defined as having liver disease at baseline. Patients were excluded from the population of patients with liver disease if they had a past history of liver disease but did not have active liver disease at baseline.

In the Combined population, 58.7% (138/235) of patients with baseline liver disease in the gemifloxacin group and 54.8% (92/168) of patients with baseline liver disease in the all-comparators group reported at least one adverse experience (AE). Adverse experiences associated with the hepatobiliary system were reported in 16.6% (39/235) of patients in the gemifloxacin group and 11.3% (19/168) of patients in the all-comparators group. The most frequently reported AEs among patients with baseline liver disease in the gemifloxacin group were SGPT increased (7.2%), SGOT increased (5.1%), abdominal pain (4.7%), diarrhea (4.7%), and thrombocythemia (4.7%) (Table 84).

The hepatobiliary AE's for which there were differences between the gemifloxacin group and comparator group include hepatic enzymes increased and SGPT increased, alkaline phosphatase increased (10% for gemifloxacin patients and 0% for comparator), and bilirubinemia (2.1% for gemifloxacin group and 0.6% for comparator).

The non hepatobiliary AE's which were more prominent in the gemifloxacin group included anemia, myalgia, CPK increased, hypokalemia, and leukopenia. The AE's which were more prominent in the comparator group were diarrhea, vomiting, and dizziness.

Table 84. Number (%) of Patients with the Most Frequently Occurring (≥1%) Adverse Experiences in Patients with Baseline Liver Disease (Combined)

	Treatment Group			
	Gemifloxacin 320mg qd N=235		All Comparators N=168	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least 1 AE	138	(58.7)	92	(54.8)
SGPT Increased	17	(7.2)	8	(4.8)
SGOT Increased	12	(5.1)	8	(4.8)
Abdominal Pain	11	(4.7)	4	(2.4)
Diarrhea	11	(4.7)	21	(12.5)
Thrombocythemia	11	(4.7)	4	(2.4)
Hyperglycemia	10	(4.3)	4	(2.4)
Phosphatase Alkaline Increased	10	(4.3)	0	
Headache	9	(3.8)	3	(1.8)
Hepatic Enzymes Increased	8	(3.4)	0	
Rash	8	(3.4)	5	(3.0)
Anemia	7	(3.0)	2	(1.2)
Nausea	7	(3.0)	6	(3.6)
Myalgia	6	(2.6)	1	(0.6)
Back Pain	5	(2.1)	2	(1.2)
Bilirubinemia	5	(2.1)	1	(0.6)
Chest Pain	5	(2.1)	5	(3.0)
CPK Increased	5	(2.1)	2	(1.2)
Fever	5	(2.1)	2	(1.2)
Insomnia	5	(2.1)	3	(1.8)
Dizziness	4	(1.7)	6	(3.6)
Epistaxis	4	(1.7)	0	
Fatigue	4	(1.7)	0	
Hypokalemia	4	(1.7)	0	
Leukopenia	4	(1.7)	0	
Rhinitis	4	(1.7)	5	(3.0)
Asthma	3	(1.3)	1	(0.6)
Bronchitis	3	(1.3)	2	(1.2)
Constipation	3	(1.3)	2	(1.2)
Flatulence	3	(1.3)	0	
Hematuria	3	(1.3)	1	(0.6)
Hypertension	3	(1.3)	3	(1.8)
Injury	3	(1.3)	3	(1.8)
Leukocytosis	3	(1.3)	1	(0.6)
Pain	3	(1.3)	2	(1.2)
Pleural Effusion	3	(1.3)	0	
Vomiting	3	(1.3)	5	(3.0)
Dyspepsia	2	(0.9)	2	(1.2)
Neuralgia	2	(0.9)	2	(1.2)
Pneumonia	2	(0.9)	2	(1.2)
Respiratory Disorder	2	(0.9)	4	(2.4)
Chronic Obstructive Airways Disease	1	(0.4)	3	(1.8)
Coughing	1	(0.4)	3	(1.8)
Dehydration	1	(0.4)	2	(1.2)
Gastritis	1	(0.4)	4	(2.4)
Mouth Dry	1	(0.4)	2	(1.2)
Sleep Disorder	1	(0.4)	2	(1.2)
Agitation	0	(0.0)	2	(1.2)
Asthenia	0	(0.0)	3	(1.8)
Depression	0	(0.0)	3	(1.8)
Edema Dependent	0	(0.0)	3	(1.8)
Infection Fungal	0	(0.0)	2	(1.2)
Moniliasis	0	(0.0)	4	(2.4)
Myocardial Infarction	0	(0.0)	2	(1.2)
Otitis Media	0	(0.0)	2	(1.2)

Source: Adapted from Applicant's Table 17.35 from NDA 21-158 18 month Safety Update

The next table provides a comparson of LFT values on therapy in patients with out of range LFTs at screening for the Combined Population. As shown in Table 85, 5.1% of gemifloxacin treated patients had ALT values of >4xULN with 0.9% >8xULN in comparison to 2.8% for comparator at >4xULN and none >8xULN. Also shown in this table is that 4.8% of gemifloxacin treated patients had AST values >4xULN with 1.2% >8xULN and comparator had 3.4% at >4xULN with none >8xULN. Similar percentages of patients in both arms had alkaline phosphatase levels>2xULN (10.4% for gemifloxacin and 10.2% for comparator with only 2 comparator patients>6xULN.) In the gemifloxacin arm 4.0% of patients had bilirubin elevations >2xULN in comparison to 2.3% for comparator but only gemifloxacin patients (3) had levels above 4xULN.

Table 85. Number (%) of Patients with Liver Function Tests Within Specified Ranges at the On-Therapy Visit - Patients Out of Range at Screening (Combined Population)

Functional Group/ Variable	Range	Treatment Group			
		Gemifloxacin 320mg qd N=1121*		All Comparators N=783*	
		n/Np+	(%)	n/Np+	(%)
ALT	<ULN	101/329	(30.7)	69/255	(27.1)
	ULN-<2xULN	144/329	(43.8)	135/255	(52.9)
	2-<4xULN	67/329	(20.4)	44/255	(17.3)
	4-<6xULN	11/329	(3.3)	6/255	(2.4)
	6-<8xULN	3/329	(0.9)	1/255	(0.4)
	≥8xULN	3/329	(0.9)	0/255	
AST	<ULN	108/328	(32.9)	84/210	(40.0)
	ULN-<2xULN	159/328	(48.5)	87/210	(41.4)
	2-<4xULN	45/328	(13.7)	34/210	(16.2)
	4-<6xULN	8/328	(2.4)	3/210	(1.4)
	6-<8xULN	4/328	(1.2)	2/210	(1.0)
	≥8xULN	4/328	(1.2)	0/210	
Alkaline Phosphatase	<ULN	73/289	(25.3)	46/207	(22.2)
	ULN-<2xULN	186/289	(64.4)	140/207	(67.6)
	2-<4xULN	28/289	(9.7)	19/207	(9.2)
	4-<6xULN	2/289	(0.7)	0/207	
	6-<8xULN	0/289		2/207	(1.0)
	≥8xULN	0/289		0/207	
Total Bilirubin	<ULN	197/272	(72.4)	169/219	(77.2)
	ULN-<2xULN	64/272	(23.5)	45/219	(20.5)
	2-<4xULN	8/272	(2.9)	5/219	(2.3)
	4-<6xULN	2/272	(0.7)	0/219	
	6-<8xULN	1/272	(0.4)	0/219	
	≥8xULN	0/272		0/219	

Data Source: Table 206b.

* N = total number of patients with out-of-range (≥ULN) values at screening.

+ n/Np = number of patients within the specified range/number of patients evaluated for the laboratory parameter.

Source Applicant's Table 17.28 from NDA 21-158, 18-month Safety Update

Specific Cases of Altered Hepatic Function

Study 185

Study 185 was a study to evaluate the treatment of CAP in hospitalized patients. Consequently these patients were older and sicker overall than most of the populations previously studied in this submission. Similar numbers of patients were in each arm. Four patients in the gemifloxacin 320mg qd from study 185 experienced AEs associated with abnormalities of hepatic function that led to withdrawal. Another patient experienced marked elevations in bilirubin but was not withdrawn. Two additional patients who were within the normal range at screening had elevations in ALT and/or AST >3xULN either on therapy or the end of therapy. There were no withdrawals from the comparator arm for hepatic enzyme elevations, but 3 patients who were in range at screening did experience elevations in at least one LFT of >3xULN.

The cases which required withdrawal from study 185 because of LFT elevations are described below.

1-Patient 185.202.30261, a 56-year-old (yo) male. The patient had no significant clinical history. Concomitant medications included acetaminophen and sotalol hydrochloride. The patient's baseline laboratory values at screening included ALT 44 IU/L (normal range 0-48 IU/L), AST 46 IU/L (normal range 0-42 IU/L), and alkaline phosphatase 41 IU/L (normal range 20-125 IU/L). On the fourth day of study medication relevant laboratory tests results showed ALT 157 IU/L, AST 141 IU/L, alkaline phosphatase 42 IU/L. The patient was asymptomatic and received no treatment for the event. Bilirubin values were normal at all times during the study. Study medication was stopped on the fifth day of treatment, and the patient was withdrawn from the study. Laboratory tests from samples taken 2 days after cessation showed ALT levels still high at 125 IU/L, while AST levels were returning to normal at 62 IU/L and alkaline phosphatase levels increased within the normal range to 51 IU/L. The event resolved between Day 7 and Day 24 (retest showed ALT 41 IU/L, AST 28 IU/L, and alkaline phosphatase increased to 69 IU/L but still normal). The investigator considered the increase in ALT and AST to be probably related to study medication.

2-Patient 185.310.29883, a 36-yo male. The patient's medical history included asthma and spinal meningitis. Concomitant or recent medications included albuterol, amoxicillin with clavulanate, azithromycin, ceftriaxone, detropropoxyphene, acetaminophen, diphenhydramine, docusate sodium, ibuprofen, ipratropium, morphine, oxycodone HCl, oxycodone terephthalate, PPD skin test, ranitidine, and cough syrup containing codeine, guaifenesin, sorbitol, and acetaminophen. Baseline laboratory values at screening included ALT 24 IU/L (normal range 0-48 IU/L), AST 12 IU/L (normal range 0-42 IU/L), and alkaline phosphatase 115 IU/L (normal range 20-125 IU/L). Elevated liver enzymes were noted on the fifth day of study medication, and relevant laboratory tests results showed ALT 233 IU/L, AST 117 IU/L, and alkaline phosphatase 368 IU/L. The patient also had an AE of pleural effusion beginning 7 days after the start of study medication; this AE was also recorded as leading to withdrawal. Bilirubin values were normal at all times during the study. Treatment with study medication was stopped after 8 doses (including an erroneous extra dose on 1 day), and the patient was withdrawn from the study. Laboratory results taken the day of the last dose of study medication showed that the liver enzymes were decreasing (ALT 186 IU/L, AST 43 IU/L, and alkaline phosphatase 352 IU/L). Both events resolved (the increased hepatic enzymes resolved within 23 days and the pleural effusion within 5 days). The investigator considered the increase in liver enzymes to be of a suspected relationship to treatment with study medication

3-Patient 185.357.29796, an 89-y.o. female. The patient's medical history included coronary artery disease, left ventricular diastolic dysfunction, pulmonary edema, chronic obstructive pulmonary disease, left bundle branch block, iron deficiency anemia, osteoarthritis, and dementia. She had a concurrent urinary tract infection at study start. Recent medications included acetylsalicylic acid, furosemide, acetaminophen, ferrous gluconate, potassium supplement, famotidine, cefuroxime, clarithromycin, salbutamol/ipratropium hydroxide, nitroglycerine, magnesium chloride, heparin, and dimenhydrinate (Gravol). Relevant baseline laboratory values included ALT 12 IU/L (normal reference range 0-48 IU/L), AST 13 IU/L (normal reference range 0-42 IU/L), and alkaline phosphatase 87 IU/L (normal reference range 20-125 IU/L). After 7 days of treatment with study medication, test results from a local laboratory showed that the patient's liver enzymes were elevated: ALT 91 IU/L, alkaline phosphatase 401 IU/L, and gamma-glutamyl transferase (GGT) 411 IU/L (normal reference range <35 IU/L). Treatment with study medication was then stopped, and the patient was withdrawn from the study. On Day 10 of the study, further test results from the local laboratory showed that the patient's ALT had decreased to 38 IU/L, alkaline phosphatase to 260 IU/L, and GGT to 284 IU/L). The investigator considered this event possibly related to treatment with study medication.

4-Patient 185.070.29584, a 60 yo Caucasian female without significant medical history. There were no concomitant medications noted. Her screening value for ALT was 56 IU/L (reference range 0-48), for AST was 60 IU/L (reference range 0-42), for alkaline phosphatase was 86 (reference range 20-125), and for bilirubin was 9 (reference range 0-22). Two days after taking the first dose of gemifloxacin 320 mg po qd she developed an increase in ALT to 153 and AST to 119. Alkaline phosphatase rose to 143 but bilirubin remained normal. The patient was asymptomatic and study medication was discontinued. Her LFT values returned to within reference range within 7 days. The investigator considered this as a probable relation to study medication.

Additional Cases with LFT Elevations of Interest

Combined ALT and Bilirubin Elevations

In the combined clinical studies population no patient in either group who was in range at screening for ALT and total bilirubin developed an ALT >3xULN with a concomitant bilirubin (BR) of 1.5 mg/dl at the on-therapy or end of therapy visit. One comparator patient who was tested after screening only at followup had an ALT of 1186 IU/L with a BR of 2.7 mg/dl. However, if the threshold is changed to an ALT of >2xULN with a BR of >1.5mg/dL there were no further patients in comparator but 3 patients in the gemifloxacin group achieving this level of abnormality. In addition there were 2 patients in the gemifloxacin group with borderline ALTs at screening (49 and 50 with an ULN of 48 IU/L) who had ALT increases to >2xULN and BR increases to >1.5 mg/dl. There were no similar borderline cases in comparator patients. Below are some examples of patients who received gemifloxacin with LFT changes of clinical concern.

1-185.305.29877 – This 35 yo Black male was treated for community acquired pneumonia (CAP) with 320 mg gemifloxacin for 14 days. He reportedly had a current history of anemia and elevated liver function tests. He was on no concomitant medications. His total eosinophil count was unremarkable. This patient's bilirubin rose to 68 µmol/L from 23.9 (0-22.2umol/L) while receiving gemifloxacin. However, the patient's ALT at this time was 172

IU/L, which was down from 225 IU/L at screening. The ALT rose to 271 at end therapy and the bilirubin fell to 15.4 umol/L at end therapy. The AST was 202 at screening, 128 at the on therapy visit, and 300 at end therapy.

2-009.086.09326 – This 42 yo Caucasian female was treated for ABS with 320 mg gemifloxacin po qd for 10 days. She experienced no treatment-emergent adverse events and was on no other medications. Her total eosinophil count was unremarkable. Bilirubin rose from 8 to 46 µmol/L at the end of therapy and the ALT peaked at 102 IU/L from 50 IU/L at screening.

3-012.061.17962 – This 70 yo Caucasian female was treated for an acute exacerbation of chronic bronchitis with 320 mg gemifloxacin for 4 days. Her past medical history was remarkable for a previous cholecystectomy. Concomitant and recent medications included atropine sulfate, metamizole sodium, metoclopramide, gentamicin, and cefuroxime. Other treatment-emergent adverse events included diarrhea, gastritis, and thrombocyopenia. These all resolved spontaneously. Her total eosinophil count was unremarkable. This patient's bilirubin rose from 11 to 33 µmol/L and the ALT was 123 IU/L while on therapy up from 36 IU/L at screening.

4-014.016.06936. This was a 38 yo Caucasian male with a complicated UTI treated for 10 days with gemifloxacin 320 mg. Concomitant and recent medications included acetaminophen and phenazopyridine. Other adverse events included headache and erythematous rash which led to early withdrawal. His bilirubin peaked at 46umol/L from 17.1 with an ALT of 162 IU/L from 137 at screening. The eosinophil count was normal.

ALT elevations only

No patients who received 320 mg doses of gemifloxacin and had normal LFT's at screening had an ALT elevation>8xULN. Three patients with out of range ALT at screening had ALT of >8xULN. One of these patients is described here.

Patient 061.043.13830 was a 32 y.o. Asian male treated for CAP with 320 mg of Gemifloxacin for 7 days. His past medical history was remarkable for an intracranial injury and seizures in 1998. Concomitant medications only included a combination prescription product that included loratadine and pseudoephedrine sulfate along with an over-the-counter cough syrup and cold remedy medication consisting of phenacetin, phenylpropanolamine, and phenyltoloxamine. He had no other adverse events. His total eosinophil count was unremarkable. This patient had a rise in ALT from 110 IU/L (~2.5X ULN) to 501 (~10 X ULN) on therapy, returning to 132 IU/L at end of therapy.

The higher level incidence of ALT elevations in patients receiving 480 and 640 mg doses of gemifloxacin was also noted. The following two patients experienced ALT elevations exceeding 8 X ULN:

Patient 067.011.17797 was a 55 y.o. Caucasian female treated for an uncomplicated UTI with a single oral 640 mg dose of

gemifloxacin. Concomitant medications consisted of metoprolol succinate, spironolactone, cyproterone, and estradiol. Her total eosinophil count was unremarkable. This patient experienced an ALT elevation to 8 X ULN (374 IU/L) two days after receiving the 640 mg dose. The ALT fell to roughly 2 X ULN (72 IU/L) 6 days later, with return to normal documented approximately one month later.

Patient 067.059.17989 was a 56 y.o. female treated for an uncomplicated UTI with a single oral 640 mg dose of gemifloxacin. There were no concomitant medications. Hyperglycemia was the only other treatment-emergent adverse event. Her total eosinophil count was unremarkable. This patient experienced an ALT elevation to 10 X ULN (432 IU/L) 3 days after receiving the 640 mg dose. The ALT had fallen to ~1.5 X ULN (69 IU/L) seven days later, and no follow up value was obtained.

Electrocardiographic Effects

The analyses provided by the sponsor were performed using the corrected QT (QTc) using Bazett's formula.

Preclinical

Gemifloxacin was compared with other fluoroquinlones in hERG and Purkinje fibre assay sytems. In dog Purknije fibres the following percentage increases in action potential duration at 90% repolarization (APD90) (1Hz) at 100um were caused by sparfloxacin (72%), grepafloxacin (37%), moxifloxacin (25%), gatifloxacin (19%), and gemifloxacin (15%). Levofloxacin only causes a 23% increase in APD90 at 1000 um.

IC50 values for inhibition of hERG expressed in a kidney cell line were: sparfloxacin (37um), grepafloxacin (93um), gemifloxacin (260um), gatfloxacin (329um), moxifloxacin (354) and levofloxacin (827 um).

Study SB-265805/RSD-100THH/1 was a single dose intravenous study in conscious beagle dogs. Dogs were dosed with 3, 10, and 30 mg/kg of gemifloxacin (as free base) or placebo.

With doses of 30 mg/kg, the QTc interval increased by about 16% (maximum increase of 44.8 msec over mean baseline of 281.3 msec). The peak increase occurred 5 minutes after the end of infusion and returned to baseline approximately 30 minutes after the end of infusion. An increase in QRS complex duration was observed in the 30 mg/kg group with a maximum increase of 24.7 msec over the mean baseline value of 58.4 msec. The increases in QRS duration occurred approximately 20 minutes after infusion and returned to baseline at 80 minutes after the end of infusion. A transient decrease in the PR interval was associated with an initial increase in heart rate observed during the first part of the infusion.

The no-effect dose for cardiovascular changes in the beagle dog in this study was 10 mg/kg, when gemifloxacin was given as an IV infusion over 30 minutes. For the 30 mg/kg dose, the Cmax for male and female dogs was 7.42 μg/ml and 9.55 μg/ml respectively. The AUC for the 30 mg/kg dose in male and female dogs was 22.4 μg-hr/ml and 34.7 μg-hr/ml, respectively.

Clinical Pharmacology Studies

In the combined clinical pharmacology population ECG data was obtained in over 1800 healthy subjects who received gemifloxacin, in over 400 subjects who received placebo and in 477 receiving other study drug. Manual measurements were obtained in close to 1400 gemifloxacin treated participants, the large majority (1011) of these participants were the female subjects under the age of 40 who were enrolled in rash study 344.

The following table presents the data of F3 transitions for the combined clinical pharmacology population.

Table 86. Clinical Pharmacology Studies Combined Population (Healthy Volunteers Only): Number (%) of Subject Sessions with ECG Measurements of Potential Clinical Concern On-Therapy (F3 Transitions)

		Treatment		
Subject Session Counts**		Gemifloxacin Only n (%)	Placebo only n (%)	Other only* n (%)
M_QTc† *>470msec (females) >450msec(males)*	High	16/1395 (1.1)	7/415 (1.6)	8/477 (1.6)
PR interval *>300msec*	High	0/1706 (0.0)	1/414 (0.2)	0/553 (0.0)
QRS interval *>200msec*	High	0/1873 (0.0)	1/453 (0.2)	0/638 (0.0)
QTc interval *>500msec*	High	2/1853 (0.1)	0/453 (0.0)	0/606 (0.0)

Data Source: Table DST22
† M_ Manually read ECG Parameter
*only subjects from the post-NDA population receiving ciprofloxacin alone had F3 transitions
**an additional 20 gemifloxacin, 10 placebo and 10 other only subject sessions from NDA Study 021 were reanalyzed manually and this information is included in this table
Source: Applicant's Table 11.5 from NDA 21-158 18 month Safety Update

Two gemifloxacin treated subjects had electronic QTc values of greater than 500 msec. One of them was a participant in study 344.

Overall the incidence of F3 transitions is similar for gemifloxacin, placebo and other treated groups. In addition the percentage of healthy volunteer subject sessions with manually measured QTc values flagged as F1, F2, and F3 transitions were again similar in gemifloxacin treated subjects and placebo: 6.8%, 3.0%, and 1.1% for gemifloxacin subjects and 10.6%, 4.0%, and 1.6% for placebo.

Mean Manual QTc changes

Study 344 subjects were evaluated in Parts A and B for changes in baseline in Manual QTc. The table below illustrates that the administration of either gemifloxacin or ciprofloxacin resulting in on average a 4.9 msec increase in manual QTc from baseline.

Table 87. Summary of Change From Baseline in Manual QTc from Part A of Study 344

Regimen	Comparison	n	Mean	s.d.	Median	Min	Max
Gemifloxacin	Single-Pre	831	1.9	23.07	2	-121	76
	Repeat-Pre	788	4.9	25.10	4	-88	105
Ciprofloxacin	Single-Pre	169	3.8	21.71	6	-57	69
	Repeat-Pre	160	4.9	23.85	5	-78	63

Source: Appendix C of report for Study 344
Source:Applicant's Table 11.8 from NDA 21-158 18 month Safety Update

Clinical Studies

Paired ECG recordings were performed in seven Phase III studies (CAP Studies 011, 049 and 185, complicated UTI Study 013, and ABECB Studies 105, 207, and 212). In the Combined Population paired ECG recordings were obtained in 436 of 6775 patients in the gemifloxacin group and 400 of 5248 patients in the all comparators group.

Demographics and Comorbid Conditions

In the combined population the distribution of age and gender were similar in the gemifloxacin and all comparators groups (Table 88).

Table 88. Frequency Distribution for Gender and Age in Patients with Paired QTc (Combined Population)

		Treatment Group			
		Gemifloxacin 320mg qd N=407		All Comparators N=380	
Demographics		**n**	**(%)**	**n**	**(%)**
Gender	Male	228	(56.0)	224	(58.9)
	Female	179	(44.0)	156	(41.1)
Age Group	≥18 to <40 yrs	64	(15.7)	57	(15.0)
	≥40 to <65 yrs	185	(45.5)	167	(43.9)
	≥65 to <75 yrs	89	(21.9)	97	(25.5)
	≥75 yrs	69	(17.0)	59	(15.5)

Data source: Table 252a.
Source: Applicant's Table 11.16 from the NDA 21-158 Safety Update

There are several conditions which are known to have the potential to cause QT prolongation. These include clinically significant bradycardia, idiopathic long QT syndrome, myocardial infarction/ischemia, mitral valve prolapse, hypocalcemia, hypokalemia, hypothyroidism, hypertension, cardiomyopathy, heart failure, alcohol abuse, and head injury. In the combined population about 45% of the patients in each group had at least one comorbid condition associated with prolongation of the QT interval.

Table 89. Percentage of Patients with Paired QTc with Comorbid Conditions Known to Predispose to QT Prolongation (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=407		All Comparators N=380	
Conditions	**n**	**(%)**	**n**	**(%)**
Patients with at least 1 comorbid condition known to predispose to QTc prolongation	187	(45.9)	168	(44.2)
Hypertension	130	(31.9)	103	(27.1)
Ischemic Heart Disease/Angina Pectoris	60	(14.7)	54	(14.2)
Heart Failure	31	(7.6)	21	(5.5)
Myocardial Infarction	25	(6.1)	11	(2.9)
Hypothyroidism	19	(4.7)	20	(5.3)
Atrial Flutter/Fibrillation	11	(2.7)	10	(2.6)
Alcohol Abuse/Dependence	9	(2.2)	9	(2.4)
Serum Potassium Decreased	5	(1.2)	2	(0.5)
Injury, Intracranial	4	(1.0)	0	
Mitral Valve Disorder	4	(1.0)	1	(0.3)
Tachycardia	3	(0.7)	5	(1.3)
Hypertensive Heart Disease	2	(0.5)	1	(0.3)
Extrasystoles, Ventricular	1	(0.2)	1	(0.3)

Source: Applicant's Table 11.18 from NDA 21-158 18 month Safety Update

Certain baseline ECG abnormalities are also associated with risk factors for QT prolongation. In the combined population 38.8% of patients in the gemifloxacin group and 35.8% of the all comparator group have such ECG abnormalities.

Table 90. Percentage of Patients with Selected ECG Abnormalities at Off-Therapy in Patients with Paired ECG Recordings (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=436		All Comparators N=400	
ECG Abnormality*	**n**	**(%)**	**n**	**(%)**
Patients with at least 1 selected ECG abnormality	169	(38.8)	143	(35.8)
S-T Changes Nonspecific	57	(13.1)	42	(10.5)
T Wave Inversion	38	(8.7)	37	(9.3)
Right Bundle Branch Block	24	(5.5)	25	(6.3)
Q Wave >0.04 Seconds	17	(3.9)	8	(2.0)
U Wave	14	(3.2)	7	(1.8)
PVCs Nonspecific	12	(2.8)	11	(2.8)
Left Ventricular Hypertrophy	12	(2.8)	4	(1.0)
S-T Segment Depression	9	(2.1)	7	(1.8)
Left Bundle Branch Block Nonspecific	7	(1.6)	8	(2.0)
QT Interval Increased	5	(1.1)	5	(1.3)
S-T Changes Segment Elevation	4	(0.9)	7	(1.8)
Myocardial Infarction Anterior Old	5	(1.1)	2	(0.5)
T Wave Peaked	5	(1.1)	4	(1.0)
Digitalis Effect	4	(0.9)	2	(0.5)
PVCs Unifocal	6	(1.4)	5	(1.3)
Myocardial Infarction Inferior Old	4	(0.9)	6	(1.5)

Source: Applicant's Table 11.20 from the NDA 21-158 18 month Safety Update

It is also known that some medications are known to prolong QT interval. In the combined population 12.5% of patients in the gemifloxacin group with paired ECG recordings and 16.1% of

patients in the all comparator group with paired ECG recordings received concomitant medications known to cause QT prolongation.

Mean Changes in QTc

The mean changes in QTc for the combined population are depicted below. Treatment differences between the groups were not significant in any of the populations evaluated.

Table 91. Mean Changes in the QTc Interval from the Off-Therapy Value in Patients with Paired QTc Measurements

Population	Treatment Group		Treatment Difference	P value
	Gemifloxacin	Comparator		
Combined	2.56	-0.39	2.95	0.08
Combined subset with QT prolonging conditions	1.52	-1.68	3.20	0.21

Source: Adapted from pp. 316-318 from NDA 21-158 18 month Safety Update

The range of on-therapy changes in QTc is presented in the table below. Of note is for changes of QTc greater than 50msec there were 10 patients in the gemifloxacin group in comparison to 2 in the all comparator group. For those same mean QTc changes in the subset of patients in the combined population who had comorbid conditions known to predispose to QT prolongation there are 6 patients in the gemifloxacin group and 1 in the all comparator group.

Table 92. Number of Patients With Changes in QTc (Combined Population)

Change from Off-Therapy in QTc (msec)	Treatment Group: Gemifloxacin 320mg qd N=407		All-Comparators N=380	
	n	(%)	n	(%)
< -60	2	(0.5)	1	(0.3)
≥ -60 to < -50	4	(1.0)	7	(1.8)
≥ -50 to < -40	7	(1.7)	6	(1.6)
≥ -40 to < -30	24	(5.9)	20	(5.3)
≥ -30 to < 0	145	(35.6)	155	(40.8)
≥ 0 to < 30	175	(43.0)	159	(41.8)
≥ 30 to < 40	23	(5.7)	19	(5.0)
≥ 41 to < 50	17	(4.2)	11	(2.9)
≥ 51 to < 60	5	(1.2)	0	
≥ 60	5	(1.2)	2	(0.5)

Source: Applicant's Table 11.24 from NDA 21-158 18 month Safety Update

Absolute QTc Values

The number and percentage of patients in the combined population who received gemifloxacin who had absolute QTc values outside of the reference range (>450 msec,male, or >470 msec, female) was higher in the gemifloxacin group than for the all comparator group but the gemifloxacin group also had a larger percentage of patients who had off therapy QTc values that were out of range. There were 3 patients in each group who had QTc values of >500 msec off-

therapy but there were 5 in the gemifloxacin group who had a QTc of >500 msec on therapy in comparson to 2 in the comparator group.

Table 93. Number of Patients with Absolute QTc Greater than Reference Range (>450 msec male, >470msec female) Combined Population

		Gemifloxacin 320mg qd N=407		All Comparators N=380	
ECG Measurement	**Range**	**n**	**(%)**	**n**	**(%)**
QTc Off-Therapy	Outside	29	(7.1)	14	(3.7)
QTc On-Therapy	Outside	34	(8.4)	21	(5.5)

Source: Applicant's Table 11.28 from NDA 21-158 18 month Safety Update

Table 94. Number of Patients with QTc >500 msec Combined Population

		Gemifloxacin 320mg qd		All-Comparators	
ECG Measurement	**Range**	**N=407 n**	**(%)**	**n**	**N=380 (%)**
QTc Off-Therapy	Outside	3	(0.7)	3	(0.8)
QTc On-Therapy	Outside	5	(1.2)	2	(0.5)

Source: Applicant's Table 11.30 from NDA 21-158 18 month Safety Update

The table below lists and describes all the patients in the combined populations for both groups who had treatment emergent QT prolongation of >60 msec or >500 msec. Those patients whose off therapy value was >500msec but whose value changed minimally or decreased were not included.

Table 95. Patients with Treatment Emergent QTc prolongation (to >500 msec from <500 msec or increase in QTc by>60 msec) Combined Population (all measurements in msec)

Medication	Patient Number	QTc off therapy	QTc on therapy	Change in QTC	Comments
Gemifloxacin	185.357.29796	489	501	12	LBB, CAD, Withdrawn for increased hepatic enzymes
Gemifloxacin	185.364.29739	450	505	55	Hypertension, LVH, CAD
Gemifloxacin	212.018.52689	378	474	96	Hypertension on a thiazide(lowest K 3.8), cardiomegaly
Gemifloxacin	011.158.05533	Out of range	>500 and/or	>60	On mianserin
Gemifloxacin	011.182.25945	In range	>500		Low K
Amoxicillin-clavulanic acid	011.182.25943	In range	>500 and/or	>60	
levofloxacin	212.048.53882	393	457	64	Hypertension, Ischemic heart disease

Source: Adapted from pp. 322-325 NDA 21-158 18 month Safety Update

Qualitative ECG Changes

On-therapy qualitative changes were also evaluated as these may be related to a drug effect. The incidence of any qualitative changes was very small. The total percentage of patients who had paired ECG recordings in the combined population who experienced qualitative ECG changes

was 4.4% in the gemifloxacin group and 6.5% in the all comparator group. The most common finding in either group was the new presence of a U wave (1.4% for gemifloxacin and 1.0% for comparator.)

Table 96. Percentage of Patients with Paired ECGs Who had Treatment Emergent Qualitative ECG Changes (Combined Population)

	Treatment Group			
	Gemifloxacin 320mg qd N=436		All-Comparators N=400	
ECG Abnormality	**n**	**(%)**	**n**	**(%)**
U Wave	6	(1.4)	4	(1.0)
S-T Changes Nonspecific	5	(1.1)	11	(2.8)
T Wave Inversion	4	(0.9)	5	(1.3)
T Wave Peaked	2	(0.5)	5	(1.3)
S-T Changes Segment Elevation	1	(0.2)	0	
S-T Segment Depression	1	(0.2)	1	(0.3)
Total Patients	**19**	**(4.4)**	**26**	**(6.5)**

Source Table 11.34 Safety Update

Clinical Conditions Associated with Arrhythmias

Syncope, cardiac arrest, sudden death, and convulsions are clinical conditions that could be surrogates for drug-induced arrhythmias. These events were slighly more common in the gemifloxacin arm as demonstrated below.

One of the sudden deaths in the gemifloxacin arm was a 62 yo man with ABECB with "arteriosclerosis obliterans," and a history of AF and an MI in the past. Three days after completing therapy he experienced an unexpected cardiac arrest. Review of this case by investigators drew the conclusion that his death was due to his underlying medical condtions. The gemifloxacin treated patient whose diagnosis at death was listed as "Malignant Arrhythmia" was a 75 yo man with COPD, CAD, and possibly CHF on multiple medications who on the last day of therapy (which he appeared to be failing) was described as having a malignant arrhythmia and failure.

No cases of torsades de pointes were reported for either treatment group.

Table 97. Number of Patients in the All-Exposed population with Syncope, Convulsions, Sudden Death, Malignant Arrhythmia, and Cardiac Arrest

		Treatment Group		
		Gemifloxacin N=7659	All Comparators N=5549	
Preferred Term	**n**	**%**	**n**	**%**
Syncope	10	(0.1)	5	(0.1)
Convulsions	1	(<0.1)	4*	(0.1)
Sudden death	3	(<0.1)	0	
Cardiac arrest	7	(0.1)	5	(0.1)
Malignant Arrhythmias	1	(<0.1)	0	

Source Adapted from Applicant's Table 11.36 from NDA 21-158, 18-month Safety Update

Laboratory Abnormalities

The effects of gemifloxacin therapy on liver function test have been covered in a separate section. This section will concentrate on abnormalities seen in hematologic parameters, renal function lab values, hypo- and hyperglycemia, and CPK abnormalities.

Hematology Values

Very few treatment emergent hematology lab parameters were seen other than what would be expected in patients with bacterial infections such as elevated white blood cell counts and increased platelet counts. There were no notable differences in the occurrence of other treatment emergent hematology lab abnormalities such as anemia, thrombocytopenia, or neutropenia. There were 3 patients treated with gemifloxacin and 2 treated with comparator who developed on-therapy neutropenia to approximately 1.0 x 10-9/L or less.

Renal Chemistry Values

Changes in renal function values were infrequent and similar in both groups in the combined population. Only 0.2% of patients in either group had a serum creatinine outside the F2F3 range at both the on-therapy and end of therapy visit.

Other Metabolic Parameters (Glucose, CPK)

The percentage of out of range glucose values were almost identical in both groups in the combined clinical population. Similar proportions of patients by treatment group, 5.9% of the gemifloxacin group and 5.8% of the all comparator group, had levels of glucose higher than the F3 range at the on–therapy visit. Levels of glucose lower than the F3 range were present in 0.1% of both groups at the on-therapy visit.

There were 21 patients in the gemifloxacin group of the combined clinical population with CPK values outside the F2F3 range on-therapy with 10 of those values greater than 1000. Only 6 of the all comparator patients had values outside of the F2F3 range at on-therapy and only 1 of these was >1000.

Appendix A

Rash Tables by gender, duration of therapy, and indication.

Table A-1. Rates of Rash in Females < 40 years old by "Indication"

Dosage regimen →	**320 mg** gemifloxacin (daily dose for specified number of days)					**640 mg**		CONTROL
	3 days	5 days	7 days	10 days	14 days	1 day		
Indication ↓								
A B Sinusitis		7/240 (2.9%)	29/224 (12.9%)					3/164 (1.8%)
ABECB		0/3	2/2	0/2				0/11
CAP			7/96 (7.3%)		5/21 (23.8 %) 1/1*			1/94 (1.1%)
UUTI	10/270 (3.7%)					7/391 (1.8%)		1/453 (0.2%)
CUTI				5/43 (11.6%)				1/43 (2/3%)
GU (male only)								
Pyelonephritis				12/78 (15.4%)				1/75 (1.3%)
Skin				3/8 (37.5%)				1/17 (5.9%)
Totals Female < 40	10/270 (3.7%)	7/243 (2.9%)	38/322 (11.8%)	20/131 (15.3%)	6/22 (27.3%)	7/391 (1.8%)		8/857 (0.9%)

Source: Applicant's April 10, 2001 submission to NDA 21-158

*dosage regimen listed as "7 to 14 days"

Table A-2. Rates of Rash in Females > 40 years old by "Indication"

Dosage regimen →	**320 mg** gemifloxacin (daily dose for specified number of days)					**640 mg**		CONTROL
	3 days	5 days	7 days	10 days	14 days	1 day		
Indication ↓								
A B Sinusitis		2/160 (1.3%)	14/203 (6.9%)					0/153 (0%)
ABECB		8/446 (1.8%)	7/224 (3.1%)	1/23 (4.3%)				8/581 (1.4%)
CAP			9/267 (3.4%)		8/74 (10.8%) 0/14*			7/246 (2.8%)
UUTI	4/169 (2.4%)					7/247 (2.8%)		5/313 (1.6%)
CUTI				17/229 (7.4%)				5/216 (2.3%)
GU (male only)								
Pyelonephritis				0/44				1/53 (1.9%)
Skin				1/12 (8.3%)				0/6
Totals Female > 40	4/169 (2.4%)	10/606 (1.6%)	30/694 (4.3%)	19/308 (6.2%)	8/88 (9.1%)	7/247 (2.8%)		26/1568 (1.7%)

Source: Applicant's April 10, 2001 submission to NDA 21-158

*dosage regimen listed as "7 to 14 days"

Table A-3. Rates of Rash in Males < 40 years old by "Indication"

Dosage regimen →	**320 mg** gemifloxacin (daily dose for specified number of days)					**640 mg**		CONTROL
	3 days	5 days	7 days	10 days	14 days	1 day		
Indication ↓								
A B Sinusitis		2/147 (1.4%)	13/184 (7.1%)					1/126 (0.8%)
ABECB		0/5	1 /2	0/1				0/9
CAP			5/133 (3.8%)		2/27 (7.4%) 1 / 4*			3/133 (2.3%)
UUTI (female only)								
CUTI				6/52 (11.5%)				1/44 (2.3%)
GU (male only)	0/69	2/69 (2.9%)						
Pyelonephritis				0/12				0/10
Skin				1/10 (10%)				0/6
Totals Male < 40	0/69 (0%)	4/221 (1.8%)	19/319 (6.0%)	7/75 (9.3%)	3/31 (9.7%)			5/328 (1.5%)

Source: Applicant's April 10, 2001 submission to NDA 21-158

*dosage regimen listed as "7 to 14 days"

Table A-4. Rates of Rash in Males > 40 years old by "Indication"

Dosage regimen →	**320 mg** gemifloxacin (daily dose for specified number of days)					**640 mg**		CONTROL
	3 days	5 days	7 days	10 days	14 days	1 day		
Indication ↓								
A B Sinusitis		1/132 (0.8%)	6/132 (4.5%)					1/93 (1.1%)
ABECB		2/532 (0.4%)	8/326 (2.5%)	1/38 (2.6%)				4/ 757 (0.5%)
CAP			8/311 (2.6%)		0/63 (0%) 2/15 (13.3%)			4/327 (1.2%)
UUTI (female only)								
CUTI				6/280 (2.1%)				2/281 (0.7%)
GU (male only)	0/2	0/4						
Pyelonephritis				2/21 (9.5%)				0/8
Skin				0/9				0/8
Totals Male > 40	0/2	3/668 (0.4%)	22/769 (2.9%)	9/348 (2.6%)	2/78 (2.6%)			11/1474 (0.7%)

Source: Applicant's April 10, 2001 submission to NDA 21-158
*dosage regimen listed as "7 to 14 days"

Table A-5. Rates of Rash by Age, Gender, and duration of treatment

Category	**320 x 3 days**	**320 mg x 5 days**	**320 mg x 7 days**	**320 x 10 days**	**320 x 14 days**	**640 mg x 1 day**		**CONTROL**
Totals Female < 40	10/270 (3.7%)	7/243 (2.9%)	38/322 (11.8%)	20/131 (15.3%)	6/22 (27.3%)	7/391 (1.8%)		8/857 (0.9%)
Totals Female > 40	4/169 (2.4%)	10/606 (1.6%)	30/694 (4.3%)	19/308 (6.2%)	8/88 (9.1%)	7/247 (2.8%)		26/1568 (1.7%)
Totals Male < 40	0/69 (0%)	4/221 (1.8%)	19/319 (6.0%)	7/75 (9.3%)	3/31 (9.7%)			5/328 (1.5%)
Totals Male > 40	0/2	3/668 (0.4%)	22/769 (2.9%)	9/348 (2.6%)	2/78 (2.6%)			11/1474 (0.7%)
TOTALS	14/510	24/1738	109/2104	55/862	19/219	14/638		50/4227
	Sum of 3, 5, 7, 10 and 14 days 221 / 5433 (4.1%)					(2.2%)		(1.2%)
	Total patients 5433 (gemi 320 mg) plus 638 (gemi 640 mg) plus 4227 control = 10.298							

Source: Compiled from the Applicant's April 10, 2001 submission to NDA 21-158

Appendix B

Definition of F2 and F3 Flagging Criteria for Laboratory Values

The Sponsor developed multiple flagging criteria and applied them to clinical laboratory data collected at screening, on-therapy, and at the end of therapy These flags are defined as follows:

Out of Laboratory Normal Range (F1): This flag denotes a value above or below the normal range supplied by the specified laboratory.

Change From Baseline (F2): This flag denotes a value that increased or decreased from baseline by more than a specified amount defined by the sponsor and is referred to as the F2 flag. The associated range is referred to as the F2 range. F2 flags are applied solely on the basis of the amount of the change from a patient's baseline value, without respect to the ending value. If a patient had an abnormally high or low baseline value, they may have an *improved* on-therapy or end-of-therapy value that is F2-flagged.

Extended Normal Range (F3): This flag denotes a value that falls outside an extended normal range defined by the sponsor. This range is independent of direction of change or other values, and is outside the normal range. This flag is referred to as the F3 flag, and the associated range is referred to as the F3 range.

Combined Flagging Criteria (F2F3): This flag denotes a value that changed (increased or decreased) from baseline by more than a specified amount and also falls outside an extended normal range. It denotes values that are both F2 and F3 flagged and is referred to as the F2F3 flag.

Table B-1 and Table B-2 list the specifications for the F2 and F3 flags that identify sponsor-defined values of potential clinical concern for hematology and clinical chemistry, respectively.

Table B-1 Hematology F2 and F3 Flagging Criteria for Phase II and Post-NDA Clinical Studies

Laboratory Test	F2 Lower Limit F2 Higher Limit*	F3 Lower Limit F3 Higher Limit*	F2 Lower Limit F2 Higher Limit*	F3 Lower Limit F3 Higher Limit*	Normal Range**	Standard Units
Hematology		***Phase II Limits***	***Post-NDA Limits***			
Hemoglobin	<80% of Baseline	<80% NRL	<85% of Baseline	<85% NRL	Original	g/L
	None	>105% NRH	>115% of Baseline	>105% NRH		
Hematocrit	<80% of Baseline	<80% NRL	<85% of Baseline	<85% NRL	Original	Ratio L/L
	None	>105% NRH	>115% of Baseline	>105% NRH		
Red Blood Cells	None	<75% NRL	<80% of Baseline	<75% NRL	Original	$x10^{12}$/L
	None	>110% NRH	>120% of Baseline	>110% NRH		
Reticulocytes	None	None	None	None	Original	x1A/L
	None	None	None	None***		
White Blood Cells	<75% of Baseline	<75% NRL	None	<75% NRL	Original	$x10^{9}$/L
	>150% of Baseline	>150% NRH	None	>150% NRH		
Basophils	None	None	None	None	0 – 0.093	$x10^{9}$/L
	>200% of Baseline	>200% NRH	None	>200% NRH		
Eosinophils	None	None	None	None	0 – 0.287	$x10^{9}$/L
	>200% of Baseline	>200% NRH	>200% of Baseline	>200% NRH		
	<50% of Baseline	<50% NRL	None	<50% NRL	1.3 – 3.75	$x10^{9}$/L

Table B-1 Continued

Lymphocytes						
	>200% of Baseline	>150% NRH	None	>125% NRH		
	None	None	None	None	0 – 0.34	$x10^9$/L
Monocytes						
	>200% of Baseline	>200% NRH	None	>150% NRH		
	<75% of Baseline	<80% NRL	<50% of Baseline	<80% NRL	1.7 – 5.75	$x10^9$/L
Neutrophils						
	>150% of Baseline	>150% NRH	>150% of Baseline	>150% NRH		
	<75% of Baseline	<100	<75% of Baseline	<100	100 - 500	$x10^9$/L
Platelets						
	None	>500	>125% of Baseline	>500		

* NRL = Normal Range Low; NRH = Normal Range High.
** Original = The reference range was supplied by the central laboratories.
*** Reticulocyte values were F2-flagged in error for patients in study 186.

Source: Applicant's Table 10.5 from the NDA 21-058 18-Month Safety Update

Table B-2 Clinical Chemistry F2 and F3 Flagging Criteria for Phase II and Post-NDA Clinical Studies

Laboratory Test	F2 Lower Limit F2 Higher Limit*	F3 Lower Limit F3 Higher Limit*	F2 Lower Limit F2 Higher Limit*	F3 Lower Limit F3 Higher Limit*	Normal Range**	Standard Units
Clinical Chemistry *Phase II Limits*			***Post-NDA Limits***			
	None	None	None	None	Original	IU/L
ALT (SGPT)						
	>Baseline +75% NRS	>200% NRH	>Baseline +75% NRS	>200% NRH		
	None	None	None	None	Original	IU/L
AST (SGOT)						
	>Baseline +75% NRS	>200% NRH	>Baseline +75% NRS	>200% NRH		
	None	None	None	None	Original	IU/L
Alkaline Phosphatase						
	>Baseline +50% NRS	>150% NRH	>Baseline +75% NRS	>200% NRH		
	None	<50% NRL	None	None	Original	umol/L
Serum creatinine						
	>125% of Baseline	>150% NRH	>125% of Baseline	>150% NRH		
	None	None	None	None	Original	IU/L
Creatine Phosphokinase						
	>Baseline +100% NRS	>250% NRH	>Baseline +100% NRS	>250% NRH		
	None	None	None	None	Original	mmol/L
Blood Urea Nitrogen						
	>150% of Baseline	>150% NRH	>150% of Baseline	>150% NRH		
	<Baseline –50% NRS	<90% NRL	<Baseline –50% NRS	<90% NRL	Original	mmol/L
Calcium						
	>Baseline +50% NRS	>110% NRH	>Baseline +50% NRS	>110% NRH		
	None	<90% NRL	Baseline – 50% NRS	<80% NRL	Original	g/L
Total Protein						
	None	>110% NRH	None	None		
	<Baseline –50% NRS	<80% NRL	<Baseline –50% NRS	<85% NRL	35 – 50	g/L
Albumin						
	None	None	None	None		

Note: ALT (SGPT) = Alanine Aminotransferase; AST (SGOT) = Aspartate Aminotransferase.
* NRS = Normal Range Span; NRL = Normal Range Low; NRH = Normal Range High.
** Original = The reference range was supplied by the central laboratories.

- continued -

Table B-2 (continued) Clinical Chemistry F2 and F3 Flagging Criteria for Phase II and Post-NDA Clinical Studies

Laboratory Test	F2 Lower Limit F2 Higher Limit*	F3 Lower Limit F3 Higher Limit*	F2 Lower Limit F2 Higher Limit*	F3 Lower Limit F3 Higher Limit*	Normal Range**	Standard Units
Clinical Chemistry	***Phase II Limits***		***Post-NDA Limits***			
Total Bilirubin	None	None	None	None	Original	umol/L
	>Baseline +50% NRS	>150% NRH	>Baseline +50% NRS	>150% NRH		
Random Glucose	None	<2	None	<50% NRL	2 – 8	mmol/L
	None	>8	None	>150% NRH		
GGT+	None	None	None	None	Original	U/L
	>Baseline + 100% NRS	>250% NRH	>Baseline + 100% NRS	>250% NRS		
LDH++	None	None	None	None***	Original	U/L
	>Baseline + 50% NRS	>150% NRH	>Baseline + 50% NRS	None		
Potassium++	<Baseline – 50% NRS	<3	<Baseline – 50% NRS	<3	Original	mmol/L
	>Baseline + 75% NRS	>6	>Baseline + 75% NRS	>6		
Sodium++	<Baseline – 50% NRS	<95% NRL	<Baseline – 50% NRS	<95% NRL	Original	mmol/L
	>Baseline + 50% NRS	>105% NRH	>Baseline + 50% NRS	>105% NRH		

Note: ALT (SGPT) = Alanine Aminotransferase; AST (SGOT) = Aspartate Aminotransferase; GGT = Gamma-Glutamyl Transferase; LDH = Lactate Dehydrogenase.
* NRS = Normal Range Span; NRL = Normal Range Low; NRH = Normal Range High.
** Original = The reference range was supplied by the central laboratories.
*** LDH values were F2-flagged in error for patients in study 186.
+ Test performed in only studies 001, 002 and 003.
++ Test performed in only studies 001, 002 and 003 and Post-NDA studies.

Source: Applicant's Table 10.6 from the NDA 21-058 18 Month Safety Update

Appendix C

Selected References

1. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243-50.
2. Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol 2001 Jun;137(6):765-70
3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994 Nov 10;331(19):1272-85.
4. Hooper DC. Emerging Mechanisms of Fluoroquinolone Resistance. Emerging Infect Dis 2001;7:337-431.