Factive® (gemifloxacin mesylate) Tablets

For the Treatment of Acute Bacterial Sinusitis

Briefing Document

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LIST OF ABBREVIATIONS

ABS	acute bacterial sinusitis
ADP_{90}	action potential duration at 90% repolarization
AE(s)	adverse experience(s)
ABECB	acute bacterial exacerbation of chronic bronchitis
Alk phos	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
$AUC_{(0-\infty)}$	area under the concentration-time curve extrapolated to infinity
AUC_{24}	area under the concentration-time curve to 24 hours
bid	twice daily
CAP	community acquired pneumonia
CAPD	continuous ambulatory peritoneal dialysis
CDC	Centers for Disease Control and Prevention
CFU	colony form unit
CI	confidence interval
CIP-R	ciprofloxacin resistant
Cip or Cipro	ciprofloxacin
C_{max}	maximum concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	electrocardiogram
E. coli	*Escherichia coli*
ELF	epithelial lining fluid
EMEA	European Agency for the Evaluation of Medicinal Products
EMM	erythema multiforme major
ERSP	erythromycin-resistant *S. pneumoniae*
FDA	Food and Drug Administration
FORCE	Factive Outpatient Respiratory Community Experience
Gati	gatifloxacin
Gemi	gemifloxacin
GGT	γ-glutamyl transpeptidase
GMT	geometric mean titer
g	gram

h	hour
H. influenzae	*Haemophilus influenzae*
HRT	hormone replacement therapy
HSP	hemophagocytic syndrome
INR	International Normalized Ratio
ITT	intent-to-treat
IU	international unit
IV	intravenous
K. pneumoniae	*Klebsiella pneumoniae*
kg	kilogram
Levo	levofloxacin
M. catarrhalis	*Moraxella catarrhalis*
MAC-R	macrolide resistant
MBC	minimum bactericidal concentration
MDRSP	multi-drug resistant *Streptococcus pneumoniae*
mg	milligram
MIC	minimum inhibitory concentration
MIC_{50}	minimum concentration of antibiotic needed to inhibit the growth of 50% of the bacteria strains tested in culture
MIC_{90}	minimum concentration of antibiotic needed to inhibit the growth of 90% of the bacteria strains tested in culture
min	minutes
mL	milliliters
Moxi	moxifloxacin
MPC	mutant prevention concentrations
msec	millisecond
N	number
NDA	New Drug Application
Nrash	no rash
NSAID	nonsteroidal anti-inflammatory drug
OC	oral contraceptive therapy
od	once daily
P. aeruginosa	*Pseudomonas aeruginosa*
PD	pharmacodynamic
PID	patient identification
PK	pharmacokinetic
Plc	placebo
PO	per os; orally
PP	per protocol
PT	prothrombin time
QRDR	quinolone resistance-determining region
RTI	respiratory tract infection

S. aureus	*Staphylococcus aureus*
S. pneumoniae	*Streptococcus pneumoniae*
S. pyogenes	*Streptococcus pyogenes*
SAE	serious adverse experience
SB	SmithKline Beecham
SD	standard deviation
sNDA	supplemental New Drug Application
SJS	Stevens-Johnson syndrome
$t_{1/2}$	half-life
TEN	toxic epidermal necrolysis
tid	three times daily
TOPO	topoisomerase
µg	micrograms
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cells
yr	year

1. EXECUTIVE SUMMARY

This supplemental New Drug Application (sNDA) seeks approval of gemifloxacin (Factive®) for the treatment of acute bacterial sinusitis (ABS). The proposed dosing regimen consists of 320 mg administered orally once daily for 5 days. Gemifloxacin was approved in April 2003 by the Food and Drug Administration (FDA) for the treatment of mild-to moderate community acquired pneumonia (CAP) (7-day dosing) due to: *Streptococcus pneumoniae* [including multidrug-resistant strains (MDRSP)], *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Klebsiella pneumoniae,* and acute bacterial exacerbations of chronic bronchitis (ABECB) (5-day dosing) due to *S. pneumoniae, H. influenzae, Haemophilus parainfluenzae,* and *M. catarrhalis*.

Based on epidemiologic studies, up to 1 billion cases of viral sinusitis occur annually in the United States (US). Assuming a 0.5% to 2% complication rate of acute bacterial infection of the sinus, these can be expected to be complicated by 5 to 20 million cases of ABS. This is a significant health issue because of the large number of patients involved and the significant morbidity associated with the condition. In rare cases, when untreated, ABS can lead to the development of orbital infections, brain abscess, meningitis, or possibly chronic sinus disease. Additionally, the same organisms that cause ABS may also cause more serious lower respiratory tract infections. When an antibiotic is needed, it is important for the clinician to use one that treats patients effectively. Considering the continuing increase in the prevalence of community-acquired respiratory pathogens with resistance to a variety of antimicrobial agents, antimicrobial agents with a spectrum of activity that can cover the common bacterial pathogens, particularly resistant *S. pneumoniae*, are needed.

Gemifloxacin is a synthetic, broad-spectrum, fluoroquinolone antibacterial agent. Gemifloxacin has excellent *in vitro* activity against both Gram-positive organisms and Gram-negative organisms, including enhanced potency against respiratory tract infection pathogens, particularly *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis.* Gemifloxacin is the most potent agent *in vitro,* compared with commercially available antimicrobials against *S. pneumoniae*, including isolates resistant to β-lactams and macrolides. Increasingly physicians are turning to the fluoroquinolones for the treatment of community-acquired respiratory infections. However resistance to this class is now growing. Gemifloxacin offers an important advance against the emerging problem of resistance. Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both deoxyribonucleic acid (DNA) gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. *S. pneumoniae* showing mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S. pneumoniae* (dual targeting) and has minimum inhibitory concentrations (MIC) that are still in the susceptible range for some of these double mutants.

The pharmacokinetic/pharmacodynamic (PK/PD) correlates for fluoroquinolones are well established; it is the AUC_{24}/MIC_{90} ratio that is the primary determinant of efficacy and the C_{max}/MIC ratio that correlates with a low potential for development of resistance. Gemifloxacin has the highest free drug AUC_{24}/MIC_{90} ratio compared to other fluoroquinolones and the highest free drug C_{max}/MIC ratio and is the only fluoroquinolone to achieve the target C_{max}/MIC of greater than 10.

The ABS program consisted of 5 clinical trials in 1846 subjects, 3 controlled (Studies 009, 010, and 186) and 2 uncontrolled studies (Studies 206 and 333). The 3 controlled studies (Studies 009, 010, and 186) evaluated the clinical and antibacterial efficacy of oral gemifloxacin 320 mg once daily in the treatment of patients with ABS. The gemifloxacin ABS clinical program began as a 7-day program in 1998. Two of the studies compared a 7-day regimen of gemifloxacin with either oral cefuroxime axetil 250 mg twice daily (bid) for 10 days (Study 009) or oral trovafloxacin 200 mg once daily (od) for 10 days (Study 010). During this period shorter courses of therapy for antibiotics for ABS were being studied with the advantages of increased patient compliance and less pressure for resistance. Therefore a third controlled study was initiated in 1999 (Study 186) that compared oral gemifloxacin 320 mg once daily for 5 days versus 7 days. Two supportive studies (Studies 206 and 333) to determine the bacteriologic efficacy of oral gemifloxacin 320 mg once daily for 5 days were also performed using sinus puncture to obtain specimens for bacterial culture.

In these clinical studies, clinical diagnosis of ABS was based on the presence of a purulent nasal discharge at the screening visit together with signs and symptoms of ABS. These same clinical signs and symptoms that do not improve or that worsen after 7 days are currently accepted criteria for diagnosis of ABS (Sande & Gwaltney 2004) and were more rigorous than those developed by the task force on rhinosinusitis sponsored by the American Academy of Otolaryngology Head and Neck Surgery for diagnosing rhinosinusitis (Lanza & Kennedy 1997).

The signs and symptoms of ABS were of 7 days' duration, but less than 28 days' duration. In Study 009, a study incorporating sinus punctures, a minimum of only 3 days' duration was allowed for severe cases. All studies required radiographic evidence of opacification or air fluid level and signs and symptoms to include purulent/mucoid nasal discharge or purulence in the nasal cavity on examination and at least one of the *major* or 2 of the *minor* criterion as follows:

Major criteria: facial pain/pressure/tightness over affected sinus(es), facial congestion/fullness, or nasal obstruction/blockage.

Minor criteria: tooth pain, earache, non-vascular headache, sore throat, cough, halitosis, fever, change in perception of smell, or periorbital swelling.

Clinical response (success or failure) at follow-up was the primary efficacy endpoint for the controlled studies (Studies 009, 010, and 186). Clinical success at follow-up was defined as

sufficient improvement or resolution of the signs and symptoms of ABS for patients who were clinical successes at the end of therapy visit such that no additional antibacterial therapy was required for ABS. The primary analysis population was the per-protocol (PP) population.

The combined results from the controlled studies of gemifloxacin demonstrated that the efficacy of 7 days of gemifloxacin was non-inferior to that of each of the approved comparators. Furthermore, the efficacy of 5 days of gemifloxacin was non-inferior to that of 7 days of gemifloxacin in this indication. In each study the lower limit of the 95% confidence interval (CI) for the treatment difference (gemifloxacin – comparator) was no less than the pre-defined non-inferiority limit of –15% for both the PP and intent-to-treat (ITT) population, in fact the lower limit of the 95% CI was no less than -10% except in the ITT population for Study 009 where the lower limit was just over -10% at -10.6%. Additionally, in all cases the confidence intervals included 0. Results across these studies provided consistent evidence of efficacy of gemifloxacin.

Bacteriological response at follow-up was the secondary efficacy endpoint for one controlled study (Study 009) and the primary efficacy endpoint for the uncontrolled studies (Studies 206 and 333), both of which evaluated gemifloxacin 320 mg once daily for 5 days. Bacteriological success was defined as all initial pathogens were eradicated or presumed eradicated at the follow-up assessment, without any new infections, but with or without colonization. In Study 009, which compared 7 days of gemifloxacin to 10 days of cefuroxime, gemifloxacin achieved a 93% bacteriological eradication versus 92.8% for cefuroxime. Additionally, gemifloxacin achieved 100% (14/14) bacteriological success in patients with MDRSP versus 80% for the cefuroxime group.

The two uncontrolled studies demonstrated high bacteriological success rates. Secondary endpoints demonstrated high rates of clinical success, supporting the findings of the controlled clinical trials.

Eradication rates of major ABS pathogens in patients treated with gemifloxacin for 7 days or 5 days were comparable. For both treatment regimens, eradication rates at follow-up were high for *S. pneumoniae* (54/55, 98.2%), *H. influenzae* (26/28, 92.9%), *M. catarrhalis* (7/7, 100.0%), and *Staphylococcus aureus* (13/14, 92.9%) in 7-day patients and for *S. pneumoniae* (97/103, 94.2%), *H. influenzae* (51/53, 96.2%), *M. catarrhalis* (17/17, 100.0%), and *S. aureus* (14/16, 87.5%) in 5-day patients.

Gemifloxacin 320 mg, administered once daily, was well tolerated in the large clinical program (N=8119) including 1846 subjects from the 5 ABS studies. Use of gemifloxacin was associated with small, measurable changes in the electrocardiographic (ECG) QTc interval. However, these prolongations were not clinically meaningful, and there were no cases of torsades de pointes. Because gemifloxacin has no drug interaction issues, specifically a lack of cytochrome P450, administration of co-medications that can potentiate QTc interval changes with other drugs

should not be problematic. Gemifloxacin treatment was not associated with any consistent liver clinical chemistry finding. Treatment-emergent changes of potential clinical concern related to hepatic laboratory values were very infrequent and never met Hy's rule. Gemifloxacin is generally associated with a similar or lower incidence of adverse events than in the all comparator group except for rash. Additionally, except for rash, the serious adverse events (SAEs), withdrawal, and death rates, although trending lower with gemifloxacin, were similar to the all-comparators group. Importantly, most cases of rash were of mild or moderate intensity, and there were no clinically significant dermatological complications; in particular, there were no cases of Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN).

At the request of the FDA, a landmark study (Study 344) was conducted among 1,011 young adult females. It was specifically designed to elicit rashes and to further evaluate and characterize the gemifloxacin-associated rash. The characteristics of rash observed in the study were consistent with those of rash observed in the clinical trial program. There were no reports of serious cutaneous reactions such as SJS or TEN or any other significant sequelae. The nature of the rash was consistent with a typical, exanthematous drug eruption. Typically, the pathology (routine histopathology, immunofluorescence, and immunohistochemistry) seen was a mild, superficial, perivascular lymphocytic reaction, i.e., the classic pathology of a delayed Type IV sensitivity mild drug rash. No pathology associated with more severe skin reactions to drugs was evident. The study also evaluated cross sensitization by treating subjects who developed a rash on gemifloxacin with ciprofloxacin or placebo; 5.9% developed rash when treated with ciprofloxacin and 2.0% developed rash when treated with placebo. This cross sensitization rate was low. The characteristics of rash in subjects receiving ciprofloxacin following gemifloxacin were similar to those described in subjects who only received ciprofloxacin (the cross sensitization rate to other fluoroquinolones was not evaluated in this study). Also, there was no evidence of subclinical sensitization to gemifloxacin.

Gemifloxacin has been on the market in the US for 2 years. The post-marketing data with an estimated exposure of nearly one million patients (approximately 205,000 ex-US and 760,000 US patients), the phase IV post marketing commitment study (Factive Outpatient Respiratory Community Experience or FORCE) (N=1,821), and the 5-day ABS subset of the clinical data (N=1,122) are all consistent with the safety profile of gemifloxacin reported in the clinical trial database which were reviewed previously by both the FDA and the Anti-Infective Drug Advisory Committee in 2003.

Overall, the results of the ABS clinical program have demonstrated that 5 days of gemifloxacin can provide appropriate antimicrobial coverage when used as an empirical therapy for the treatment of ABS in the prevailing environment of resistance to traditional antibacterial agents. Gemifloxacin, by virtue of its inherent *in vitro* potency, pharmacokinetics and pharmacodynamics, and proven clinical efficacy against both antibiotic sensitive and resistant strains of bacteria responsible for common respiratory diseases with short course therapy, offers clear benefits, while possessing a safety profile equivalent to that of currently marketed

antibiotics, including other fluoroquinolones. Gemifloxacin represents an important additional therapeutic option for treatment of ABS, particularly those cases where the risk of infection by resistant organisms is of concern.

2. INTRODUCTION

The product described in this document is a synthetic, broad-spectrum, fluoroquinolone antibacterial agent known as gemifloxacin (Factive®, SB-265805). Clinical testing of gemifloxacin began in 1997, and in December 1999 an NDA for use of gemifloxacin was submitted to the FDA for several indications including CAP, ABECB, and ABS. A non-approvable letter was issued in December 2000. In 2001, the sponsor conducted additional studies designed in conjunction with the FDA and also conducted additional analyses to address FDA questions. In June 2001, the sponsor submitted a new NDA for gemifloxacin for ABS with 5-day dosing, and a non-approvable letter was issued in April 2002 noting that the issues from the original NDA were pending resolution. In October 2002, the NDA was resubmitted for the use of gemifloxacin for two indications: the treatment of ABECB and CAP. The Anti-Infective Drugs Advisory Committee reviewed these indications on March 4, 2003, and the committee recommended approval (18 yes, 0 no, and 1 abstention for mild-to-moderate CAP and 15 yes, 3 no, and 1 abstention for ABECB). The FDA approved gemifloxacin on April 4, 2003 for mild-to-moderate CAP (7-day dosing) and ABECB (5-day dosing).

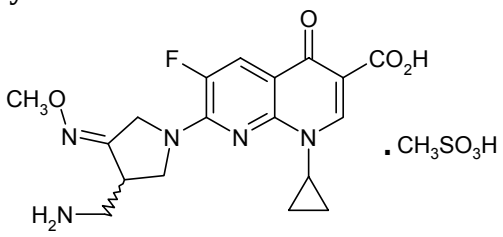
In 2004-2005 the sponsor launched gemifloxacin in the US and initiated a phase IV program, a commitment made to the FDA. Additionally, a phase III protocol comparing gemifloxacin for 5 days versus 7 days for the treatment of mild-to-moderate CAP was discussed with the FDA, initiated, and completed with the intent of moving all gemifloxacin usage to a 5-day treatment course for all indications. Also, several meetings were held with the FDA to discuss the 5-day ABS program. While the FDA indicated that gemifloxacin administered for 5 days was effective in the treatment of ABS, the FDA stated its view that gemifloxacin did not have a favorable risk/benefit profile in the treatment of ABS.

An sNDA was submitted in November 2005 for the use of gemifloxacin administered orally for 5 days for the treatment of both ABS and mild-to-moderate CAP. The FDA accepted the submission for the CAP indication, which has an action date of September 21, 2006. The FDA issued a refusal-to-file for the ABS indication. The sponsor submitted a request to file and over protest the FDA accepted the ABS application, which has an action date of December 15, 2006, and it is this indication that is presented below. This briefing document provides a short background on ABS and summarizes key chemistry and manufacturing, nonclinical, microbiological, and ABS clinical information as presented in the sNDA.

3. CHEMISTRY AND MANUFACTURING

Gemifloxacin is a synthetic fluoronaphthyridine antibiotic (Figure 1). The molecular formula of gemifloxacin mesylate is $C_{18}H_{20}FN_5O_4.CH_4O_3S$.

Figure 1: Gemifloxacin Mesylate



The final dosage form is a tablet containing 320 mg gemifloxacin as gemifloxacin mesylate sesquihydrate. The molecular weight of the free base is 76.0% of the gemifloxacin mesylate sesquihydrate. The dose strength and label claim are reported as the free base.

A 320 mg white to off-white film-coated oval debossed tablet with break lines on both faces is currently supplied in fixed dose packs of 5 and 7 tablets.

4. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

The primary pharmacology, safety pharmacology, general (oral and intravenous [IV]) toxicity, reproductive and genetic toxicity, phototoxicity, photomutagenicity, photocarcinogenicity, and antigenicity of gemifloxacin have been evaluated. Additional studies were conducted to establish the mechanism of hepatic findings and clastogenicity, and to characterize any risk of QTc prolongation.

4.1 Pharmacology: Mechanism of Action

Fluoroquinolones are antibacterial agents that act by inhibiting DNA synthesis through inhibition of the bacterial type II TOPO enzymes, DNA gyrase and TOPO IV, both of which are essential for bacterial growth (Wang 1996; Drlica and Zhao 1997). DNA gyrase, encoded by *gyrA* and *gyrB* genes, catalyzes adenosine triphosphate (ATP)-dependent DNA supercoiling during DNA replication (Wang 1996; Drlica & Zhao 1997). TOPO IV (specified by *parC* and *parE* genes) facilitates the separation of replicating DNA (Wang 1996; Drlica & Zhao 1997).

The enhanced Gram-positive activity of gemifloxacin, relative to other fluoroquinolones, is due to its greater binding affinity to both TOPO IV (Study No.SB-265805/RSD-1014CH/1 1999; Study No.SB-265805/RSD-1010MF/1 1999) and DNA gyrase. None of the commercially available quinolones bind to both sites at the plasma concentrations achieved at the therapeutic dose. This superior activity is retained even against many fluoroquinolone-resistant strains for gemifloxacin (Study No.SB-265805/RSD-1010MF/1 1999).

4.2 Toxicology

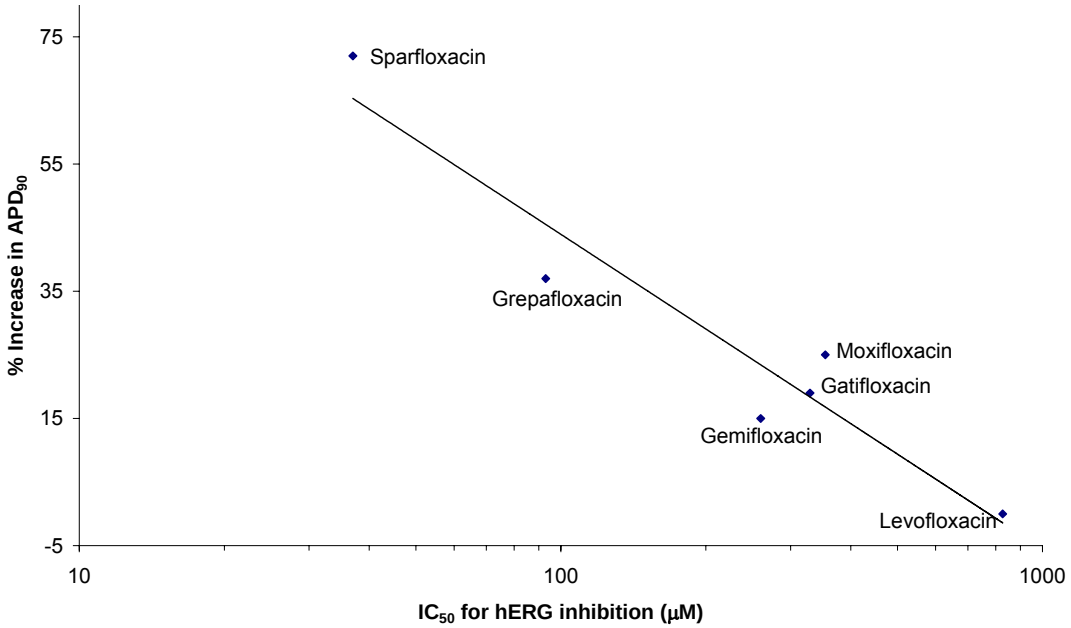
Gemifloxacin produces effects in nonclinical studies that are generally characteristic of the fluoroquinolone antibiotic class. In studies of class effects of potential clinical concern conducted against fluoroquinolone comparators, gemifloxacin's capacity to cause phototoxicity or adverse central nervous system (CNS) reactions, including its binding potency at GABA receptors, was shown to be very low.

Key findings include a weak potential to provoke QTc prolongation and hepatotoxicity in dogs.

In dogs, QTc was unaffected at approximately 5.5 times the mean human plasma maximum concentration (C_{max}) (320 mg) following oral administration of gemifloxacin, but QTc was mildly and reversibly prolonged following a 30-minute IV infusion (plasma C_{max} at the no-effect dose was approximately 3 times the human value).

Gemifloxacin was compared with other fluoroquinolones and macrolides in *in vitro* Purkinje fibre and hERG assay systems considered to reflect potential for prolongation of QTc. In dog Purkinje fibers, increases in action potential duration at 90% repolarization (APD_{90}) (1 Hz) at 100 μM were caused by sparfloxacin (72%;), grepafloxacin (37%), moxifloxacin (25%), gatifloxacin (19%), and gemifloxacin (15%). Levofloxacin increased the APD_{90} by 23% only at 1000 μM. There is evidence that greater magnitude of effect on action potential duration or potency of inhibition of key cardiac ion channels is alerting for increased likelihood of QTc prolongation. Prolongation of APD_{90} has been associated with inhibition of the rapidly activating delayed rectifier K^+ current, I_{Kr}, encoded by the human hERG gene. IC_{50} values for inhibition of hERG expressed in a kidney cell line were: sparfloxacin (37 μM), grepafloxacin (93 μM), gemifloxacin (260 μM), gatifloxacin (329 μM), moxifloxacin (354 μM), and levofloxacin (827 μM). Increases in APD_{90} correlated with inhibition of hERG (Figure 2). Gemifloxacin had only a minor effect in both *in vitro* systems even at a concentration (100 μM), approximately 30 times the mean C_{max} in humans after a 320 mg oral dose. Based on these nonclinical studies and the overall investigational package, gemifloxacin is concluded to have a low potential to cause clinically significant QTc prolongation in humans.

Figure 2: IC_{50} for hERG Inhibition versus Prolongation of APD_{90} (100 μM, 1 Hz) for Gemifloxacin and Comparator Quinolones



Hepatotoxicity in dogs showed the key characteristics of cholate stasis, with local deposition of gemifloxacin-related material in intrahepatic bile vessels (verified spectroscopically), reactive biliary cell changes, and subsequent bile-mediated hepatocellular involvement, predominantly periportally. These findings are distinct from the pattern of centrilobular necrosis produced by typical hepatocellular toxicants, including trovafloxacin. Reversibly altered activities of plasma alanine aminotransferase (ALT) and alkaline phosphatase (alk phos) acted as well-established markers of these effects. Further studies provided evidence of the critical solubility threshold dependency (pH solubility dependency) of gemifloxacin deposition in bile duct lumina. Therefore the most relevant determinant of cholate stasis will be the rate of presentation of drug to liver versus the rate of clearance, including into bile. Even a conservative comparative analysis of bioavailability and biliary excretion of gemifloxacin, bile flow, biliary pH, and solubility of gemifloxacin indicates that humans are relatively protected by a lesser biliary drug burden, and by bile pH, in contrast to the unfavorable pH of the bile in the animal models, favoring maintenance of gemifloxacin in solution.

It is concluded that when coupled with the overall profile in humans, the results of the nonclinical safety studies are consistent with gemifloxacin's clinical use.

5. HUMAN PHARMACOKINETICS

The absolute bioavailability of gemifloxacin following oral administration in healthy volunteers is on average 71% and is limited by the extent of absorption rather than by significant first-pass metabolism. Following a single dose oral administration of gemifloxacin to man, maximum serum concentrations were generally observed between 0.5 and 2.0 hours post-dose. Thereafter, concentrations generally declined in an apparently biexponential manner, with a terminal phase half-life ($t_{1/2}$) of approximately 8 hours. The pharmacokinetics of gemifloxacin were approximately linear over the dose range 20 to 800 mg. Following repeated administration of gemifloxacin, there was minimal accumulation of gemifloxacin at doses up to 640 mg once daily in young subjects and up to 480 mg once daily in the elderly. Urinary excretion of gemifloxacin generally accounted for 20% to 40% of the administered dose. The *in vitro* binding of gemifloxacin to plasma proteins was low in man (approximately 70%). A high fat breakfast had no clinically relevant effect on the bioavailability of gemifloxacin at doses of 320 and 640 mg and thus, gemifloxacin can be administered without regard to food.

Gemifloxacin has a low potential for cytochrome P450 enzyme-mediated drug-drug interactions. At steady state, gemifloxacin 320 mg once daily did not affect the repeat dose pharmacokinetics of oral theophylline, oral digoxin, or ethinylestradiol/levonorgestrel. Likewise, there was no pharmacodynamic effect on prothrombin time when gemifloxacin was co-administered with warfarin. Pharmacokinetic data indicated that either Maalox® or ferrous sulphate can be administered at least 3 hours prior to and 2 hours or more after administration of gemifloxacin and that sucralfate can be administered at least 2 hours after gemifloxacin administration. Simultaneous administration of calcium carbonate resulted in a modest reduction (on average 20%) in gemifloxacin area under the concentration-time curve (AUC) and C_{max}, whilst administration of calcium carbonate, either 2 hours before or 2 hours after gemifloxacin dosing, showed no notable reduction in systemic exposure. Co-administration of gemifloxacin with omeprazole at steady state resulted in increases in $AUC_{(0-\infty)}$ and C_{max} of gemifloxacin (on average 10% and 11%, respectively) that are not clinically significant. Co-administration of cimetidine reduced renal clearance of gemifloxacin by, on average, 28% compared to co-administration of gemifloxacin with placebo. However, this finding is unlikely to be of any clinical relevance, since only small increases in gemifloxacin AUC values (on average 10%) were seen following co-administration with cimetidine. Co-administration of probenecid reduced the renal clearance of gemifloxacin (on average 51%), but dose adaptation was not necessary. Results of population pharmacokinetic analysis of phase III data indicated that none of the classes of concomitant medications investigated (diuretics, calcium, estradiol/ethinylestradiol, estrogens, and progesterones) appear to alter the clearance of orally administered gemifloxacin.

Dosage adjustment of gemifloxacin is not considered necessary in patients with creatinine clearance >40 mL/min. However, for patients with creatinine clearance ≤40 mL/min, including hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) patients, it is recommended

that the clinical dose of gemifloxacin be halved (i.e., 160 mg once daily). Gemifloxacin was not notably cleared from patients during 4 hours of hemodialysis. Dosage adjustment is not required for elderly patients with good renal function (creatinine clearance >40 mL/min; see above). Dosage adjustment of gemifloxacin is also not considered necessary in patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C).

Gemifloxacin is extensively distributed into body tissues and fluids. Concentrations in bronchoalveolar macrophages, epithelial lining fluid, bronchial mucosa, and plasma after 5 daily doses of 320 mg gemifloxacin are summarized in Table 1.

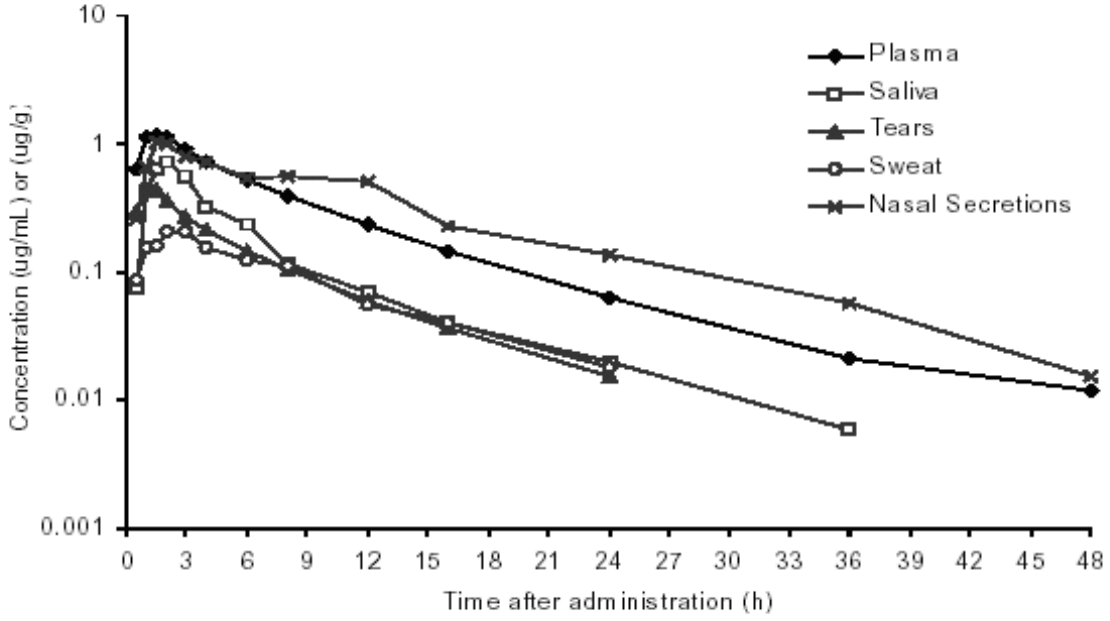
Table 1: Concentrations of Gemifloxacin after 5 Daily Doses of 320 mg

Tissue	Concentration (Mean ± SD)	Ratio Compared with Plasma
Plasma	1.40 (0.442) µg/mL	---
Bronchoalveolar macrophages	107 (77) µg/g	90.5 (106.3)
Epithelial lining fluid	2.69 (1.96) µg/mL	1.99 (1.32)
Bronchial mucosa	9.52 (5.15) µg/g	7.21 (4.03)

SD = standard deviation

Pharmacokinetics, pharmacodynamics, and tissue distribution data are all highly suggestive of the efficacy of gemifloxacin in ABS. The penetration of gemifloxacin into nasal secretion was determined in an open, randomized, two-way crossover single dose design in seventeen healthy male and female volunteers following a single oral dose of gemifloxacin (Study 026, NDA 21-158). Samples of nasal secretion were collected at times up to at least 24 hours post-dose. Gemifloxacin concentrations in nasal secretion exceeded those in plasma. The ratio of nasal secretion to plasma for AUC values was, on average, 1.30 (range: 0.59 to 2.6). The concentration time profiles and elimination half lives of gemifloxacin in nasal secretions were of similar shape to those for plasma (Figure 3).

Figure 3: Mean Plasma (μg/mL), Saliva (μg/mL), Tear (μg/mL), Sweat (μg/mL), and Nasal Secretion (μg/g) Concentrations of Gemifloxacin Following a Single Oral Administration of 320 mg Gemifloxacin



6. MICROBIOLOGY

6.1 Enhanced Potency Against Key Respiratory Pathogens

Gemifloxacin has broad-spectrum *in vitro* antibacterial activity, including excellent activity against the key respiratory pathogens, *S. pneumoniae, H. influenzae,* and *M. catarrhalis*. It has the lowest MICs against *S. pneumoniae* when compared with ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin (Table 2).

Table 2: *In Vitro* Activity of Gemifloxacin and Comparators Against *S. Pneumoniae* Isolates

# of Isolates	Gemifloxacin		Ciprofloxacin		Levofloxacin		Gatifloxacin		Moxifloxacin	
	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
6257	0.032	0.047	NT	NT	0.75	1	NT	NT	NT	NT
550	0.015	0.03	1	2	1	1	0.25	0.5	0.12	0.25
1450	≤0.015	0.06	1	1	1	1	0.25	0.25	NT	NT

NT = not tested

The MICs of gemifloxacin against *H. influenzae* and *M. catarrhalis* are comparable to or lower than those of other quinolones tested (Table 3 and Table 4, respectively).

Table 3: *In Vitro* Activity of Gemifloxacin and Comparators Against 290 *H. influenzae* Isolates Collected from 16 US 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

Table 4: *In Vitro* Activity of Gemifloxacin and Comparators Against 205 *M. catarrhalis* Isolates Collected from 16 US 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

It is also active against anaerobic isolates, with MICs ≤0.25 µg/mL against 78% of the isolates tested.

The minimum bactericidal concentrations (MBCs) of gemifloxacin are comparable to its MICs against a panel of 139 clinical isolates including *S. pneumoniae*, *H. influenzae*, and *Streptococcus pyogenes.* These data demonstrate that gemifloxacin is a cidal agent.

In time-kill viability studies, gemifloxacin exhibited bactericidal activity against a range of Gram-positive and Gram-negative organisms, including *S. pneumoniae, H. influenzae*, *S. aureus, Escherichia coli,* and *Pseudomonas aeruginosa.* Such activity, usually a 3-log reduction in viable cell numbers, was comparable to that of other quinolones.

6.2 Dual Enzyme Targeting

Quinolones act by inhibiting the bacterial enzymes that control the topological state of DNA: DNA gyrase, encoded by the *gyrA* and *gyrB* genes, and TOPO IV, encoded by the *parC* and *parE* genes. These enzymes catalyze DNA supercoiling, relaxing, knotting, and catenation by a double strand breaking and resealing mechanism, and are essential for prokaryotic cellular replication.

In *S. pneumoniae,* the principal target of fluoroquinolone action appears to vary with the specific antibacterial agent. TOPO IV seems to be the preferential target for ciprofloxacin and levofloxacin, whereas moxifloxacin and gatifloxacin primarily targets the *gyrA* subunit of DNA gyrase. Gemifloxacin is the only dual targeting quinolone with therapeutically relevant activity against both of these targets. The IC_{50} values for the binding of gemifloxacin to the *parC* and *gyrA* subunits of TOPO IV and DNA gyrase have been assessed in a number of studies, although there is no standardized methodology. A TOPO IV IC_{50} of 1.2 μg/mL and a DNA gyrase IC_{50} of 2 μg/mL for gemifloxacin has been reported (Study No.SB-265805/RSD-101MN5/1 2001). The dual activity of gemifloxacin is best demonstrated in studies of well-characterized resistant strains of *S. pneumoniae*. Gillespie et al. and Zhanel et al. have demonstrated that while mono targeting quinolones are rendered ineffective by single step mutations in their preferred target, gemifloxacin retains activity against mutants with mutations in either or both targets (MIC ≤0.25 μg/mL), as shown in Tables 5 and 6 (Gillespie et al. 2002; Zhanel et al. 2002).

Table 5: 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

*Selected by gemifloxacin
Data represents the mean of three E-test results.

Table 6: Susceptibility of Ciprofloxacin-Intermediate and -Resistant *S. Pneumoniae* to Fluoroquinolones and 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

Cip = ciprofloxacin; Gati = gaitfloxacin; Gemi =gemifloxacin; Levo = levofloxacin; Moxi = moxifloxacin

The high affinity of gemifloxacin for both of these targets accounts for its extremely high potency and, more critically, for its continued activity against quinolone-resistant *S. pneumoniae*. This is an important therapeutic advantage, given that quinolone resistance is emerging at an concerning rate in the US (Ferraro 2002).

6.3 Pharmacokinetic/Pharmacodynamic Parameters Correlate for Predicting Efficacy and Lack of Resistance Generation

PK/PD parameters predict the potential for efficacy, bacterial eradication, and development of resistance with antimicrobial therapy. Fluoroquinolones exhibit concentration-dependent killing and pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials have indicated that the primary determinant of efficacy is the AUC_{24}/MIC_{90} ratio. The target ratio necessary to achieve maximal bacteriological efficacy in *S. pneumoniae* infections for the existing quinolones is 25-30. The C_{max}/MIC_{90} ratio has also been shown to predict efficacy and is being increasingly accepted to also correlate with a low potential for development of resistance. A target C_{max}/MIC_{90} ratio of 10 predicts a high probability of efficacy and a low potential for development of resistance.

Gemifloxacin has the highest free drug AUC_{24}/MIC_{90} ratio (97 to 127) compared to other quinolones used to treat respiratory tract infections (levofloxacin and moxifloxacin) (Table 7). Gemifloxacin also has the highest free drug C_{max}/MIC_{90} ratio and is the only quinolone to achieve the target C_{max}/MIC_{90} ratio of greater than 10 (18.7 – 24).

Table 7: Comparative Free Drug Pharmacokinetic/Pharmacodynamic Parameters for *S. pneumoniae*

Antimicrobial (dose)	24 h AUC[a]/MIC_{90}[b]	C_{max}[a]/MIC_{90}[b]
Gemifloxacin (320 mg)	2.9-3.8/0.03 = 97-127	0.56-0.72/0.03 = 18.7-24
Moxifloxacin (400 mg)	24.0/0.25 = 96	2.3/0.25 = 9.2
Levofloxacin (500 mg)	29.5-36.1/1.0 = 30-36	3.5-4.3/1.0 = 3.5-4.3
Levofloxacin (750 mg)	50.4-74.7/1.0 = 50-74	4.6-7.2/1.0 = 4.6-7.2

[a] Data from product prescribing information for moxifloxacin and levofloxacin. Data from NDA 21-158 Item 6 for gemifloxacin 24 h AUC (Section B.6, Figure 8) and C_{max} (Section B.5.2, Table 6).
[b] MIC_{90}s from recent US surveillance study

Examination of these PK/PD parameters supports gemifloxacin's clinical efficacy and low potential for resistance generation.

6.3.1 Gemifloxacin Activity in the Face of Rising Antibiotic Resistance

The favorable characteristics of gemifloxacin mentioned above have a number of positive implications for its clinical use. One consequence is that gemifloxacin can be given for shorter courses of therapy relative to other antimicrobial agents. Indeed while gemifloxacin for 5 days was an effective therapy for ABS, moxifloxacin failed to show non-inferiority to comparator when administered for 7 days but is approved for a 10-day course (FDA 1999) thereby having the potential to reduce compliance and increase antibiotic resistance. A short course is more convenient for the patient and has the potential to increase compliance. Furthermore, decreased antibiotic use, in conjunction with shorter treatment regimens, may reduce the development of antibiotic resistance, as described more fully in Section 6.3.2.2.

Also of great impact is the ability of gemifloxacin to treat multi-drug resistant *S. pneumoniae* (MDRSP) infections, including those caused by penicillin-, macrolide-, and cephalosporin-resistant strains. Most importantly, gemifloxacin also shows activity against *S. pneumoniae* strains resistant to other quinolones, such as levofloxacin and moxifloxacin (Forrest et al. 1993; Preston et al. 1998; Craig 1998; Woodnutt 2000; Dagan et al. 2001). The activity of gemifloxacin against drug-resistant bacteria has been demonstrated *in vitro, in vivo,* and in clinical trials, where effective bacteriologic and clinical cures were demonstrated in patients with various resistance patterns, including patients with quinolone-resistant *S. pneumoniae* isolates.

6.3.2 *In Vitro* Data on Gemifloxacin Activity Against Resistant *S. Pneumoniae*

Several surveillance studies have demonstrated that gemifloxacin has the lowest MICs against *S. pneumoniae* non-susceptible to penicillin (Table 8) and macrolides (Table 9).

Table 8: *In Vitro* Activity of Gemifloxacin and Comparators Against Penicillin Non-Susceptible Isolates of *S. Pneumoniae*

# of Isolates	Penicillin MIC (µg/mL)	MIC_{90} (µg/mL)				
		Gemifloxacin	Ciprofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
1,050	0.12-1	0.047	NT	1	NT	NT
75	0.12-1	0.06	NT	1	0.5	0.125
67	0.12-1	0.03	2	1	0.5	0.25
1,016	≥2	0.047	NT	1	NT	NT
143	≥2	0.015	1	1	0.25	0.125

NT = not tested

Table 9: *In Vitro* Activity of Gemifloxacin and Comparators Against Isolates of Macrolide Resistant *S. Pneumoniae*

# of Isolates	Macrolide Resistance Criteria	MIC_{90} (µg/mL)			
		Gemifloxacin	Ciprofloxacin	Levofloxacin	Gatifloxacin
1,505	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

6.3.2.1 *In Vitro* Data on *S. Pneumoniae* Resistant to Quinolones

Decreased susceptibility of *S. pneumoniae* to fluoroquinolones primarily occurs through three mechanisms: mutations in the *gyrA* subunit of DNA gyrase, mutations in the *parC* subunit of TOPO IV, and/or active efflux of the drug from the cell (Janoir et al. 1996; Tankovic et al. 1996; Drlica & Zhao 1997; Jorgensen et al. 1999). Quinolone resistance in *S. pneumoniae* can be defined either phenotypically, as determined by an elevated MIC, or mechanistically, using molecular techniques to define sequence changes in the relevant genes. Studies on the gemifloxacin susceptibility of quinolone-resistant *S. pneumoniae*, as defined by both of these criteria, are described below.

6.3.2.1.1 Phenotypic Quinolone Resistance

For ciprofloxacin, non-susceptible *S. pneumoniae* are defined as organisms with an MIC ≥2 μg/mL, while resistant organisms have a ciprofloxacin MIC ≥4 μg/mL. For levofloxacin, the non-susceptible and resistant breakpoints are ≥4 μg/mL and ≥8 μg/mL, respectively.

In a study of 167 ciprofloxacin-resistant *S. pneumoniae* isolates from Canada, the MIC_{90} for gemifloxacin was 0.5 μg/mL, at least 8-fold lower and as much as 64-fold lower than that of any of the other quinolones tested (Table 10). In a separate Canadian study, 90 isolates with reduced susceptibility to ciprofloxacin were investigated. The MIC_{90} for gemifloxacin was 0.25 μg/mL compared with 2, 4, 16, and 32 μg/mL for moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin, respectively. Again, the MIC_{90} for gemifloxacin was at least 8-fold lower and as much as 128-fold lower than that of the other quinolones tested (Table 10).

Table 10: *In Vitro* Activity of Gemifloxacin and Comparators Against Isolates of Ciprofloxacin Non-Susceptible *S. Pneumoniae*

# of Isolates	Ciprofloxacin MIC (μg/mL)	MIC_{90} (μg/mL)				
		Gemifloxacin	Ciprofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
167	≥4	0.5	32	16	4	4
90	≥2	0.25	32	16	4	2

Table 11 shows the results of two additional studies of *S. pneumoniae* isolates with levofloxacin MICs ≥8 μg/mL as tested against moxifloxacin, gatifloxacin, and gemifloxacin. The gemifloxacin MIC_{90} was 1 μg/mL and 0.5 μg/mL, 4- to 16-fold lower than comparator quinolones.

Table 11: *In Vitro* Activity of Gemifloxacin and Comparators Against Isolates of Levofloxacin Non-Susceptible *S. Pneumoniae*

# of Isolates	Levofloxacin MIC (μg/mL)	MIC_{90} (μg/mL)			
		Gemifloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin
57	≥8	1	>16	8	NT
32	≥4	0.5	8	4	2

From January 2000 through February 2002, a large surveillance study was conducted on a cross sectional population in the US. This prospective study analyzed the *in vitro* activity of

gemifloxacin against *S. pneumoniae* presumed to have both first- and second-step mutations, using a levofloxacin marker (MICs >2 μg/mL). 7,553 isolates of *S. pneumoniae* were tested from 124 investigational centers; only one clinical isolate was taken per patient from a clearly identified respiratory, blood, or body fluid. 0.2% of isolates were intermediate, 0.8% were resistant, and 0.9% were non-susceptible to levofloxacin (MIC ≥3 μg/mL) (Table 12). Gemifloxacin had the lowest MIC_{90} (1 μg/mL) compared to moxifloxacin (12 μg/mL), gaitfloxacin, and levofloxacin (both >32 μg/mL).

Table 12: Phase II Results: *In Vitro* Activity of Gemifloxacin and Comparative Agents Against 77 *S. pneumoniae* Isolates Non-Susceptible to Levofloxacin (MIC >2 μg/mL)

Drug	%Sus	%Int	%Res	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Range
Gemifloxacin[a]	54.5	28.6	16.9	0.25	1	0.047 / 3
Gatifloxacin	23.4	11.7	64.9	4	>32	0.125 / >32
Levofloxacin	0.0	20.8	79.2	>32	>32	3 / >32
Moxifloxacin	27.3	16.9	55.8	3	12	0.047 / >32

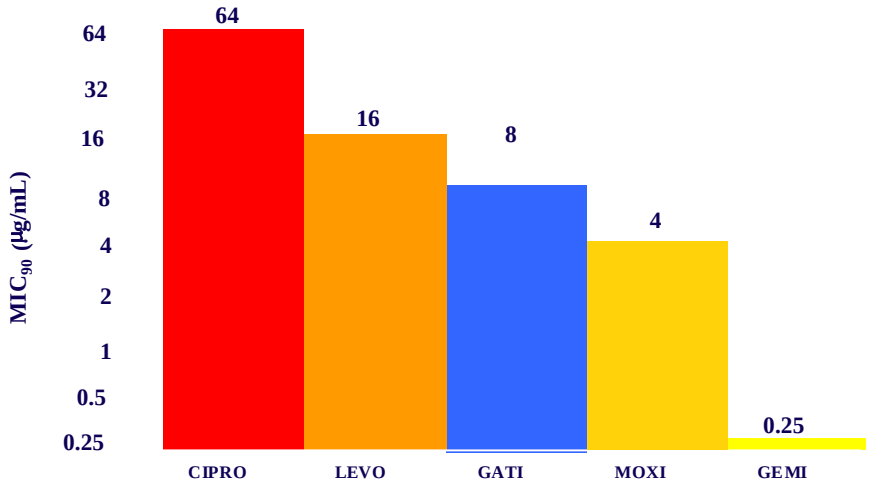
[a] Gemifloxacin susceptible *S. pneumoniae* is defined as a MIC ≤0.125 μg/mL; intermediate = 0.25 μg/mL; and resistant ≥0.5 μg/mL.

6.3.2.1.2 Molecularly Defined Quinolone Resistance

Recent studies have demonstrated that *gyrA/parC* double mutants are resistant to most fluoroquinolones in clinical use. The data provided within NDA 21-376 (Item 3A, Attachment 2) demonstrate that 98% of such isolates were resistant to ciprofloxacin (using a resistant breakpoint of ≥4 μg/mL) and ofloxacin, 95% were resistant to levofloxacin, 82% to gatifloxacin, and 25% to moxifloxacin. On the other hand, at the accepted resistant breakpoint of ≤0.5 μg/mL, gemifloxacin maintains activity against 41 of 44 *S. pneumoniae* isolates demonstrating second step mutations in the target binding sites. The gemifloxacin MIC_{90} against these double mutants was 16-fold lower than that of moxifloxacin, 32-fold lower than that of gatifloxacin, and 64-fold lower than that of levofloxacin (Figure 4).

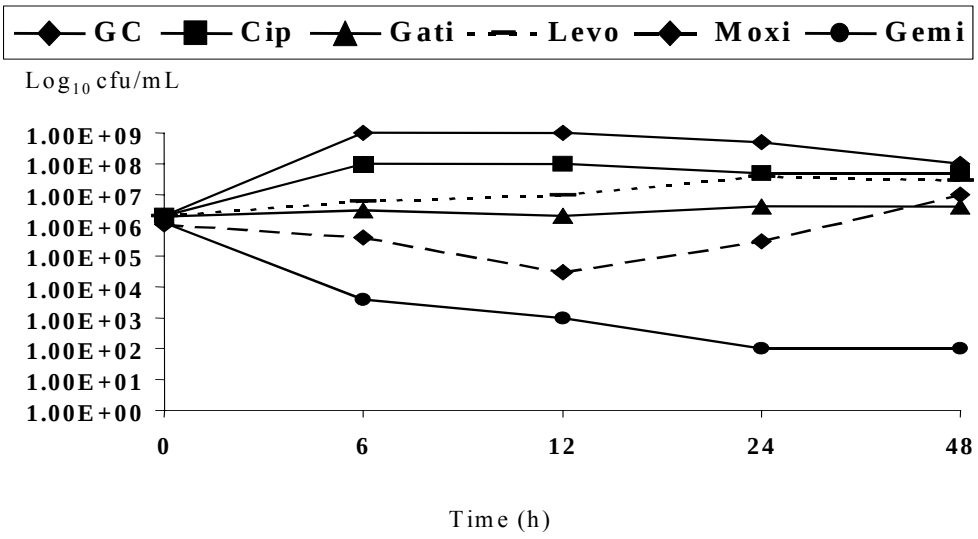
Two mutations in the quinolone resistance-determining regions (QRDR) are required for significant resistance to gemifloxacin to arise, in contrast to levofloxacin, for which resistance can arise from a single mutation.

Figure 4: Activity of Gemifloxacin and Comparator Quinolones Against *S. pneumoniae* Demonstrating Second Step Mutations in the QRDR



Zhanel et al. (2002) used an *in vitro* pharmacodynamic model to examine bacterial killing by gemifloxacin, moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin against a variety of first and second step quinolone-resistant *S pneumoniae* simulating free fluoroquinolone (protein unbound) C_{max} and AUCs achieved in human serum after standard oral doses (Zhanel et al. 2002). The data suggest that ciprofloxacin produces no inhibition in growth against low or high level ciprofloxacin-resistant *S. pneumoniae*, while gatifloxacin, levofloxacin, and moxifloxacin were bactericidal against low-level resistant strains but produced little to no inhibition of high-level resistant strains (Figure 5). Gemifloxacin was bactericidal against both low and high level resistant strains and was the only fluoroquinolone to eradicate the high-level ciprofloxacin-resistant *S. pneumoniae* from the model and maintain this effect over 48 hours. Gemifloxacin was bactericidal against both first and second step resistant strains.

Figure 5: Fluoroquinolone Killing of a Quinolone-Resistant *S. Pneumoniae* Isolate (17012) Simulating Free AUC_{24}/MIC Ratios



Strain	Cip	Levo	Gati	Moxi	Gemi	*ParC* Change	*GyrA* Change	Efflux
17012	16	8	4	2	0.12	Yes	Yes	No

6.3.2.2 *In Vivo* Models of *S. Pneumoniae* Respiratory Tract Infection

The efficacy of gemifloxacin has also been examined in experimental rat respiratory infections caused by strains of *S pneumoniae* with reduced susceptibility to quinolones (Table 13). These strains had gemifloxacin MICs ≥0.125 µg/mL and were highly resistant to ciprofloxacin and levofloxacin; 6 of them were genetically defined second step mutants. In these studies, gemifloxacin exhibited excellent efficacy against all strains of *S. pneumoniae* with gemifloxacin MICs of 0.125 to 0.25 µg/mL, and good efficacy against 2 of 5 strains of *S. pneumoniae* with MICs of 0.5 µg/mL. These data confirm the effectiveness of gemifloxacin for the treatment of infections caused by strains of *S pneumoniae* resistant to other fluoroquinolones. Importantly, gemifloxacin showed improved efficacy relative to levofloxacin against all ciprofloxacin-resistant *S. pneumoniae*, including isolates with second step mutations.

Table 13: Efficacy of Gemifloxacin against Respiratory Tract Infections in the Rat Caused by *S. Pneumoniae* with Differing *In Vitro* Susceptibilities

***S. pneumoniae* Strain**	**Resistance Profile**	**MIC (µg/mL)**		**CFU/Lungs**		
		Gemi	**Levo**	**NTC**	**Gemi**	**Levo**
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
PT9424123	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

CFU = colony forming units; CIP-R = ciprofloxacin resistant; MAC-R = macrolide resistant; NTC = non-treated control

[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

The efficacy of gemifloxacin in comparison with moxifloxacin and gatifloxacin in experimental models of respiratory tract infection (RTI) caused by *S. pneumoniae* was also examined. The susceptibility of the strains tested to the agents is shown in Table 14.

Table 14: MICs of Gemifloxacin, Moxifloxacin, and Gatifloxacin against *S. pneumoniae* Isolates Used in the Rat RTI Model

***S. pneumoniae* Strain**	**MIC (µg/mL)**		
	Gemifloxacin	**Moxifloxacin**	**Gatifloxacin**
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

With the exception of gatifloxacin against *S. pneumoniae* 509063, all therapies were significantly effective compared with untreated animals ($p \leq 0.01$) (Table 15). Gemifloxacin was highly effective against all strains tested and showed significant improvements ($p \leq 0.05$) in effect against some strains compared with moxifloxacin (*S. pneumoniae* 205118 and 622286) and gatifloxacin (*S. pneumoniae* 205118 and 509063). Moxifloxacin and gatifloxacin did not show better efficacy than gemifloxacin against any strain.

Table 15: Efficacy of Gemifloxacin, Moxifloxacin, and Gatifloxacin Against *S. pneumoniae* in the Rat RTI Model

***S. pneumoniae* Strain**	**Log_{10} CFU/lungs**			
	Gemifloxacin	**Moxifloxacin**	**Gatifloxacin**	**Non-Treated Controls**
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 gatifloxacin $p<0.05$
** Significantly different to moxifloxacin $p<0.05$
[c] Not significantly different to non-treated controls ($p>0.05$)
+Genetically-defined second step mutants

6.3.2.2.1 Efficacy of Short Course Gemifloxacin

Bast et al (2006 in press) used an *in vivo* experimental pneumococcal pneumonia model in mice to evaluate the clinical bacteriological success of gemifloxacin and levofloxacin after 2 and 5 days dosing. The A66 *S. pneumoniae* strain was used for all experiments. A66 is fully susceptible *in vitro* to all the fluoroquinolones, including gemifloxacin (MIC, 0.03 mg/L) and levofloxacin (MIC, 0.5 mg/L), and shows no efflux or mutations in the any of the four QRDR. As shown in Tables 16 and 17, gemifloxacin-treated mice demonstrated better clinical success than those treated with levofloxacin, independent of both the clinical condition of the mouse prior to the start of treatment and the duration of therapy. Gemifloxacin remained effective for both the 2- and 5-day treatment periods, with survival rates of 100% and 83-94%, respectively. By contrast levofloxacin showed less protection, with clinical success rates of 40% and 40-58% for the 2- and the 5-day treatment periods, respectively. Bacteriological success rates at the end

of therapy paralleled the clinical success rates for both treatment periods. Isolates recovered from 7 of 37 (19%) levofloxacin-treated mice had a levofloxacin MIC 4 times that of the infecting parent strain (MIC 0.5 mg/L). Of these 2 (29%) had a QRDR mutation in *parC*. Most interesting was the rapidity by which the mutants were selected (8 hours following the first dose). By contrast none of the isolates recovered from mice treated with gemifloxacin showed reduced susceptibility.

Table 16: Clinical and Microbiological Outcomes for Mice Infected with A66 and Treated with Gemifloxacin and Levofloxacin for 2 Days

Disease Severity[a]	Gemifloxacin				Levofloxacin			
	Sample Size	Temp[b] (°C)	No. Survived (% Survival)	No. Eradicated (% Eradication)	Sample Size	Temp[b] (°C)	No. Survived (% Survival)	No. Eradicated (% Eradication)
Moderate	18	33.2 ± 0.6	18 (100)	16 (89)	15	32.6 ± 0.4	6 (40)[c]	1 (7)[d]

Table 17: Clinical and Microbiological Outcomes for Mice Infected with A66 and treated with Gemifloxacin and Levofloxacin for 5 Days

Disease Severity[a]	Gemifloxacin				Levofloxacin			
	Sample Size	Temp[b] (°C)	No. Survived (% Survival)	No. Eradicated (% Eradication)	Sample Size	Temp[b] (°C)	No. Survived (% Survival)	No. Eradicated (% Eradication)
Moderate	18	33.2 ± 0.7	15 (83)	18 (100)	12	32.7 ± 0.4	7 (58)[e]	0 (0)[d]
Severe	17	31.3 ± 0.6	16 (94)	16 (94)	10	31.4 ± 0.6	4 (40)[f]	2 (20)[c]

[a] Moderate, surface-temperature of ≥ 32°C; Severe, surface-temperature of > 30 °C but < 32°C.
[b] Temperature immediately prior to treatment. Values are means ± SD.
[c] P = 0.0001 compared with the value for the gemifloxacin group.
[d] P < 0.0001 compared with the value for the gemifloxacin group.
[e] P = 0.2 compared with the value for the gemifloxacin group.
[f] P = 0.004 compared with the value for the gemifloxacin group.

In summary, gemifloxacin had an excellent effect against all strains of *S. pneumoniae* tested and importantly afforded good protection against ciprofloxacin-resistant strains of *S. pneumoniae*, including isolates demonstrating second step mutations in the QRDR. Overall, gemifloxacin was the most effective agent tested in experimental RTI caused by strains of *S. pneumoniae* having

varying susceptibility to standard antimicrobial agents and was significantly faster and more effective than levofloxacin in an experimental pneumococcal pneumonia model caused by a strain of *S. pneumoniae* having full susceptibility to all fluoroquinolones. The excellent effect obtained confirms the impressive *in vitro* activity of gemifloxacin against this organism and indicates a high potential benefit for the use of gemifloxacin in the treatment of RTIs caused by *S. pneumoniae.*

6.4 Summary of Microbiology

Gemifloxacin is a novel fourth-generation fluoroquinolone with excellent activity against *S. pneumoniae* and demonstrates excellent *in vitro* activity versus penicillin-, macrolide-, cephalosporin-, and quinolone-resistant strains. Gemifloxacin retains good activity against Gram-negative organisms which have been identified as occasional pathogens in prior ABS studies. In addition, the pharmacokinetic and pharmacodynamic properties of gemifloxacin, including oral bioavailability, a $t_{1/2}$ of approximately 8 hours, and a long post antibiotic effect (from 1 to >6 hours), indicate that it is appropriate for once daily oral dosing.

Key microbiological features of gemifloxacin include:

1. Enhanced activity against key respiratory pathogens

2. Dual targeting of DNA gyrase and TOPO IV enzymes

3. Excellent pharmacokinetic/pharmacodynamic correlates for predicting efficacy and lack of resistance generation

These attributes translate into demonstrable advantages for the physician in the treatment of ABS, CAP, and ABECB, particularly in the setting of *S. pneumoniae*, including antibiotic-resistant strains, the principal pathogen in these indications. Uniquely among the current quinolones, gemifloxacin offers an important advance for the emerging problem of quinolone-resistant *S. pneumoniae*.

7. REVIEW OF GEMIFLOXACIN EFFICACY IN ACUTE BACTERIAL SINUSITIS

7.1 Background and Rationale

Based on epidemiologic studies, up to 1 billion cases of viral sinusitis occur annually in the US (Gwaltney, Jr. 2004). Acute viral sinusitis, an infection or inflammatory condition of one or more of the paranasal sinuses, is one of the common causes of respiratory tract infections and in most cases resolves spontaneously without treatment. However, published estimates indicate that 0.5% to 2% of cases of acute viral sinusitis in adults are complicated by bacterial sinusitis (Gwaltney, Jr. 1996). The term acute bacterial sinusitis (ABS) has been used to identify what is considered a bacterial infection of the sinus. In the US, which has an average incidence of four acute respiratory illnesses per person per year (Gwaltney, Jr. et al. 2004) this represents 5 to 20 million cases of ABS per year.

If left untreated or if inadequately treated, ABS can lead to irreversible changes and possibly the development of chronic sinusitis. The incidence of chronic sinusitis is approximately 10% in the US (Collins 1997). Other complications such as brain abscess, cellulitis, epidural or subepidural empyema, osteomyelitis, meningitis, and cavernous sinus thrombosis may also develop, albeit rarely.

The primary etiology of acute sinusitis is rhinogenic infection, followed by allergies, exposure to toxins, anatomic abnormalities, odontogenic infections, and congenital disorders such as cystic fibrosis (International Rhinosinusitis Advisory Board 1997; Krouse 2004). Typically, sinusitis begins with a common viral cold. In addition to rhinoviruses, some 200 other strains of viruses produce infections of the upper respiratory tract (International Rhinosinusitis Advisory Board 1997). Initiation of infection stimulates several inflammatory pathways and activates the parasympathetic nervous system, resulting in engorgement of the vessels of the venous tissue of the turbinates, extracellular plasma leakage, discharge of seromucous glands and goblet cells, and neural stimulation leading to pain, sneezing, and cough reflexes. The excessive mucus discharges from the goblet cells, which are plentiful in the sinus cavity, together with transudation of plasma into the sinus cavity contribute to the increase in volume and viscosity of the intranasal fluid. Swelling of the nasal mucosa may lead to occlusion of the infundibulum or ostiomeatal complex, the most important and complex anatomic region of the sinuses. This region is the drainage area for the maxillary and frontal sinuses, and for the anterior ethmoid cells. Its occlusion, together with the increase in the amount and viscosity of intranasal fluid, can severely limit mucociliary clearance and cause fluid retention in the sinuses. The resultant viscous fluid provides an excellent medium for bacteria to grow and subsequently cause infection.

Because the nasal passages and nasopharynx are colonized with the same bacterial species that cause bacterial sinusitis, it is these areas that serve as a reservoir for the bacterial infection that

ensues. Nose blowing creates pressure differentials that, in turn, lead to bacteria-containing nasal secretions being deposited in the sinuses, initiating bacterial sinusitis (Gwaltney, Jr. et al. 2000). In addition, sinus obstruction is believed to lead to reduced oxygen tension and increase lactic acid levels, thereby providing favorable conditions for bacterial growth (Johansson et al. 1988).

The recommendation for treating ABS with appropriate and judicious antimicrobial therapy is based on published evidence of bacteriologic and clinical improvement. Studies using pre- and post- treatment sinus aspirate cultures have shown that antimicrobials with appropriate spectra given in adequate doses and duration are effective in eradicating or substantially reducing bacterial titers in the sinus cavity compared with treatment in which the drug spectrum or dose is inadequate (Table 18) (Gwaltney, Jr. 2004).

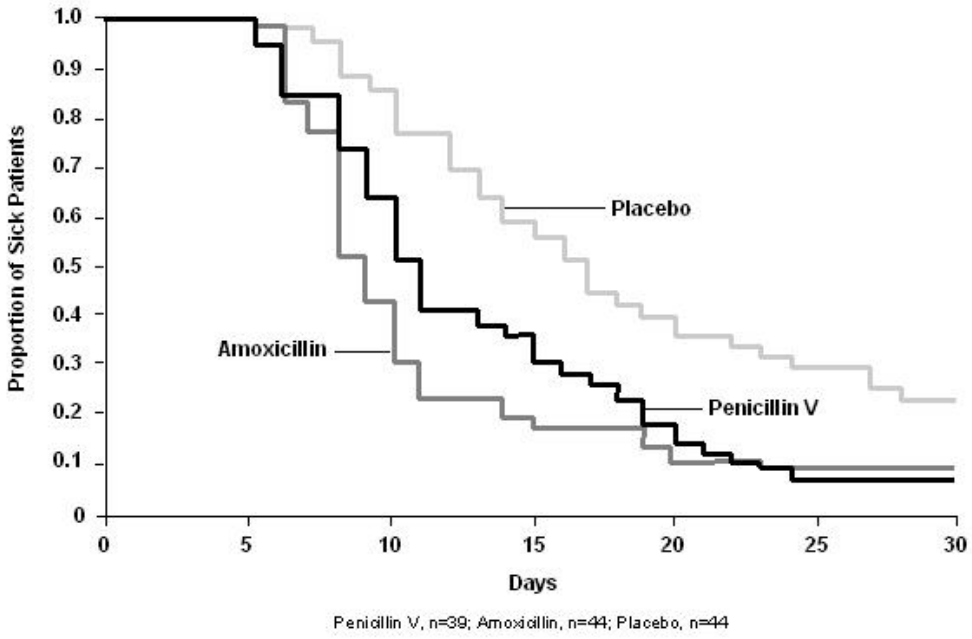
Table 18: Comparative Bacteriological Cure Rates (Determined by Sinus Puncture) in Patients with Acute Community-Acquired Bacterial Sinusitis

Reference	No. Bacteriologic Cures/No. Cases
(Carenfelt et al. 1975)	
Antibiotic concentration ≥ MIC of causative bacteria[1]	19/21 (90%)
Antibiotic concentration < MIC of causative bacteria	15/33 (45%)
(Hamory et al. 1979)	
Appropriate antimicrobial and dose	47/49 (96%)
Inappropriate antimicrobial[2]	0/6 (0%)
(Carenfelt et al. 1990)	
Appropriate antimicrobial and dose	105/115 (91%)
Suboptimal dose[3]	37/50 (74%)
(Gwaltney, Jr. et al. 1992)	
Appropriate antimicrobial and dose	126/136 (93%)
Suboptimal dose[3]	1/5 (20%)
Suboptimal dose[4]	15/21 (71%)

(Gwaltney, Jr. 2004)
[1] Antibiotic concentration in sinus aspirate after 2 to 3 days of treatment; [2] Clindamycin for *H. influenzae*; [3] Cefaclor 500 mg bid; [4] Cefaclor 500 mg three times daily (tid)

Evidence of clinical improvement after antimicrobial therapy in ABS was reported in a double-blind controlled trial of antimicrobial therapy in adults (Lindbaek et al. 1996). A significant difference in the duration of illness favoring antimicrobial therapy appeared by the third day of treatment and continued throughout the 30-day observation period (Figure 6)

Figure 6: Duration of Illness in Adults with Acute Community-Acquired Sinusitis in a Randomized Double-Blind Clinical Trial of Antimicrobial Treatment



Penicillin V, n=39; Amoxicillin, n=44; Placebo, n=44

From Lindbaek M, Hjortdahl P, Johnsen U, Randomised, double-blind, placebo-controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. BMJ. 1996;313:325-329

By day 10, 86% of antimicrobial-treated patients recovered or were much better compared with 57% of those on placebo. By day 10, 86% of patients on treatment also showed sinus CT scan improvement compared with 66% on placebo. After 30 days, 25% of patients receiving placebo judged themselves to be still sick compared with 10% of those on antimicrobial treatment.

The role of antimicrobial agents in therapy of ABS was assessed in the landmark diagnosis and treatment guidelines published by the Agency for Health Care Policy and Research in 1999 (Lau et al. 1999). This analysis demonstrated by means of meta-analysis of six clinical studies that treatment of ABS with antibacterials is significantly more effective than treatment without antibacterials, clinically curing one-third more cases and reducing treatment failures by one-half, compared with placebo. In an update of the original evidence report, a total of 39 studies conducted from 1997 to 2004 and enrolling 15,739 patients qualified for inclusion in the meta-analysis (Ip et al. 2005). The results demonstrated that overall, antibiotics were more effective than placebo, reducing the risk of clinical failure by approximately 25 to 35% within 7 to 14 days after treatment initiation ($p<0.01$).

More than half of all ABS infections are caused by 2 well-known respiratory tract pathogens: *S. pneumoniae* (30%) and *H. influenzae* (25%). Pathogens such as *M. catarrhalis*, *S. aureu*s, and non-pneumococcal streptococcal species such as *S. pyogene*s, though also important, are less frequent causative pathogens. Anaerobic organisms and certain Gram-negative bacilli are infrequently involved in ABS (Anon et al. 2004).

The antimicrobial resistance patterns among the most common pathogens are constantly changing. Although the relative importance of the different bacterial species causing bacterial sinusitis has not changed substantially in recent years, importantly there have been clinically significant changes in their antimicrobial susceptibilities.

Of particular concern with respect to ABS is the fact that the rate of penicillin resistance among *S. pneumoniae* tends to be greater among upper respiratory isolates (45%) than among lower respiratory isolates (35%) or invasive infections such as bacteremia and meningitis (26%) (Doern et al. 2001). Moreover, penicillin resistance is greater among specimens obtained from out-patient sources than among those obtained from in-patient sources, leading many physicians to anticipate a greater likelihood of resistance when treating ABS in the out-patient setting (Brown & Rybak 2004). Additionally, data from the Respiratory Surveillance Program suggest that more resistant bacteria colonize the nasopharynx of individuals with sinusitis who have recently used antimicrobials relative to their counterparts who have not recently used antimicrobials (Sokol 2001).

As discussed in Section 6, surveillance data concerning antibacterial treatment for a wide range of medical conditions including ABS have accurately documented the increasing prevalence of drug-resistant *S. pneumoniae*. Recent data from the Alexander Project (a worldwide surveillance study of respiratory tract pathogens and resistance trends) have revealed that 12% of all US isolates collected between 1998 and 2000 demonstrated intermediate resistant to penicillin (MIC 0.12 to 1 μg/mL), and that 25% were fully resistant (MIC ≥ 2 μg/mL) (Jacobs et al. 2003). Of note, the US had the greatest rate of β-lactamase production, the principal mechanism of resistance to penicillins among *H. influenzae*, at 30%.

Similarly, the PROTEKT US (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the United States) surveillance study, which was initiated in 2000 to chart the emergence and spread of antimicrobial resistance among isolates of *S. pneumoniae* and *H. influenzae* across the US, recently reported data on 2001–2002 isolates (Brown & Rybak 2004). Of 10,012 *S. pneumoniae* isolates, 35.4% were non-susceptible to penicillin (14.2% demonstrated only intermediate resistance, MIC 0.12–1 μg/mL; 21.2% were resistant, MIC ≥2 μg/mL); 27.9% were resistant to erythromycin (MIC ≥1 μg/mL), and 0.2% were intermediate, (MIC 0.5 μg/mL). A total of 27.5% of *H. influenzae* isolates were β-lactamase producers and 28.9% were considered resistant to ampicillin (MIC ≥4 μg/mL). In addition, the PROTEKT study showed that 46.2% of *S. pneumoniae* sinus sample isolates (n=390) were

resistant to penicillin and 40.8% were resistant to a macrolide. Moreover, approximately 30% of these isolates were MDRSP, defined as resistant to 2 or more drug classes, including penicillin, second generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole. The authors also found 26.4% of *H. influenzae* (n=121) isolates to be β-lactamase positive from sinus sources. Co-resistance between β-lactam and macrolides is common; yet, currently it does not seem to affect susceptibility to the fluoroquinolone class. In addition, a total of 105 (1.0%) isolates were resistant to levofloxacin (MIC ≥8 μg/mL).

The continued increase in MDRSP rates prompted a recent study by the sponsor to evaluate resistance rates in selected geographical communities in the US (FAST Study 2004; Jones 2005a; Jones 2005b). Jones et al. studied recent clinical isolates of *S. pneumoniae* from 17 US cities/regions; the overall MDRSP rate was 24.4%, with a range of 17.5% to 40.3%. The overall fluoroquinolone resistance rate was <3.6%, with gemifloxacin showing the lowest MIC values compared with the other respiratory fluoroquinolones; the MIC_{90}s for both MDRSP and non-MDRSP isolates were 0.03 μg/mL for gemifloxacin, 0.12 μg/mL for moxifloxacin, and 1.0 μg/mL for levofloxacin. Among the fluoroquinolones tested, gemifloxacin (0.8% resistant) and moxifloxacin (0.6% resistant) were more active than levofloxacin (1.3% resistant). MIC distributions showed gemifloxacin to have lower MICs than comparator fluoroquinolones (Table 19).

Table 19: MIC Distributions of Gemifloxacin, Moxifloxacin, and Levofloxacin Against All *S. Pneumoniae* Tested

Gemifloxacin	**MIC (μg/mL)**										
	≤0.004	**0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.50**	**1**	**2**	**4**
Total_n	4	135	1053	256	10	2	7	11			1
%	0.3	9.1	71.2	17.3	0.7	0.1	0.5	0.7			0.1
Cumulative	0.3	9.4	80.6	97.9	98.6	98.7	99.2	99.9			100.0
Moxifloxacin	**MIC (μg/mL)**									
	≤0.03	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**
Total_n	6	327	1077	48	2	2	8	8		1
%	0.4	22.1	73.0	3.2	0.1	0.1	0.5	0.5		0.1
Cumulative	0.4	22.5	95.5	98.7	98.8	98.9	99.4	99.9		100.0
Levofloxacin	**MIC (μg/mL)**									
	≤0.12	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**>32**
Total_n	2	5	641	804	8		1	15	2	1
%	0.1	0.3	43.3	54.4	0.5		0.1	1.0	0.1	0.1
Cumulative	0.1	0.4	43.8	98.2	98.7		98.8	99.8	99.9	100.0

For the MDRSP isolates (361 of 1479 isolates), 11.9% were resistant to ceftriaxone, 87.5% to penicillin, 54.6% to tetracycline, 80.1% to cefuroxime, 80.1% to trimethoprim/sulfamethoxazole, and 82.8% to erythromycin. When the *in vitro* activity of commonly prescribed fluoroquinolones was tested against these MDRSP isolates, gemifloxacin showed the greatest degree of *in vitro* activity (MIC range: $\leq$ 0.004 to 4.0 μg/mL, 2.2% resistant) followed by moxifloxacin (MIC range: 0.03 to 16.0 μg/mL, 1.7% resistant) and levofloxacin (MIC range: 0.25 to $\geq$32 μg/mL, 3.6% resistant) (FAST Study 2004; Jones 2005a; Jones 2005b).

In addition to the well-known resistance to penicillin, between 32% and 35% of pneumococcal isolates also exhibited high-level resistance to macrolides, with approximately 70% being co-resistant to both penicillin and macrolides (Jacobs et al. 2003). *S. pneumoniae* resistance to fluoroquinolones has been documented, but less frequently. Presently, fluoroquinolone (levofloxacin) resistance among sinus isolates of *S. pneumoniae* is 1 to 1.5% in the US, although the rate of clinical failures in respiratory tract infections is on the increase (Doern et al. 2005; Fuller & Low 2005). Resistance to the newer fluoroquinolones with enhanced potency remains relatively low in the US (Doern et al. 1998). Of recent concern is the emergence of pneumococcal strains that possess first-step mutations following exposure to less active first/second-generation fluoroquinolones (e.g., ciprofloxacin and levofloxacin), which can readily develop a second mutation, thus reducing their susceptibility to the newer fluoroquinolones with enhanced activity (e.g., moxifloxacin), so called cross-resistance within the fluoroquinolone class (Doern et al. 2005; Fuller & Low 2005). Fluoroquinolone resistance to *S. pneumoniae* is primarily conferred by mutations in the bacterial enzymes TOPO II and IV. The different fluoroquinolones have different affinities for these two enzymes: ciprofloxacin, levofloxacin, and trovafloxacin favor TOPO IV, while moxifloxacin primarily targets the *gyrA* subunit of TOPO II (DNA gyrase) (Heaton et al. 2000; Yague et al. 2002). *S. pneumoniae* having mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. In comparison, gemifloxacin exhibits bactericidal activity against both DNA gyrase and TOPO IV in *S. pneumoniae* at therapeutically relevant drug levels (Yague et al. 2002; Leo et al. 2005), MIC values are still in the susceptible range for some of these double mutants. Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some *S. pneumoniae* resistant to other fluoroquinolones are susceptible to gemifloxacin (Appelbaum et al. 2004).

Other commonly used antimicrobials are also compromised by emerging resistance in *S. pneumoniae*, with resistance to tetracycline, trimethoprim/sulfamethoxazole, and occasionally chloramphenicol being observed (Doern et al. 2005).

Thus, the increasing rates of antimicrobial resistance in the two most common pathogens of ABS, *S. pneumoniae* and *H. influenzae*, are cause for concern and present a considerable challenge to physicians attempting to successfully treat infections caused by these organisms.

There are many antibiotics indicated for ABS, but the emergence of resistant bacteria has rendered many of these drugs less effective. Antibiotics with acceptable *in vitro* antimicrobial activity against the two most common pathogens that cause ABS, *S. pneumoniae* and *H. influenzae*, are listed in Table 20. In highly resistant *S. pneumoniae*, only high-dose amoxicillin, telithromycin, and the fluoroquinolone class remain effective. Additional options that offer short course treatments and that can maintain effectiveness in the setting of an increasing rate of antimicrobial resistance amongst clinical strains of *S. pneumoniae* and *H. influenzae* are needed.

Table 20: Antimicrobial Treatment of ABS in Adults

Drug	Dose	Frequency	Duration
Amoxicillin-clavulate*	125 mg to 2 g	2X	10 days
Cefdinir*	600 mg	1X	10 days
Cefpodoxime proxetil	200 mg	2X	10 days
Cefuroxime axetil*	250 mg	2X	10 days
Levofloxacin	750 mg	1X	5 days
Moxifloxacin	400 mg	1X	10 days
Telithromycin	800 mg	1X	5 days

Modified from (Gwaltney, Jr. 2004)
* Found effective in pre- and post-treatment sinus aspirate and culture studies

7.2 Overview of Gemifloxacin Clinical Program in ABS

The clinical program to evaluate the efficacy of gemifloxacin (320 mg PO for 5 days) in the treatment of ABS consisted of 3 double-blind, randomized, actively-controlled clinical studies (Studies 009, 010, and 186), and 2 uncontrolled studies (Studies 206 and 333) (Table 21). The design of all gemifloxacin ABS studies followed the guidelines on antimicrobials and ABS recommended by the FDA (FDA/CDER 1998).

The three controlled studies (Studies 009, 010, and 186) were randomized, double-blind, double-dummy, parallel-group studies designed to evaluate the clinical and antibacterial efficacy of oral gemifloxacin 320 mg once daily in the treatment of patients with ABS. The gemifloxacin ABS clinical program began as a 7-day program in 1998. Two of the studies compared a 7-day regimen of gemifloxacin with either oral cefuroxime axetil 250 mg twice daily for 10 days (Study 009), or oral trovafloxacin 200 mg once daily for 10 days (Study 010). When Study 009 and Study 010 were performed both cefuroxime and trovafloxacin were considered the best in class oral antibiotics for the indication of ABS. During this period shorter courses of therapy for antibiotics for ABS were being studied with the advantages of increased patient compliance and

less pressure for resistance. Therefore a third controlled study was initiated in 1999 (Study 186) which compared oral gemifloxacin 320 mg once daily for 5 days versus 7 days.

The two uncontrolled studies (Studies 206 and 333) were open, single-group studies designed to assess the bacteriological eradication, clinical efficacy, and safety of oral gemifloxacin 320 mg once daily for 5 days in the treatment of patients with ABS.

Studies 009, 206, and 333 had an endpoint of bacteriological response evaluated in samples collected by the most accurate, FDA recommended method (sinus puncture rather than endoscopy) and thus form the basis for bacteriological eradication evaluations in the sections that follow.

Table 21: Acute Bacterial Sinusitis Controlled and Uncontrolled Studies

Protocol No.	Completion Status start/end date	Location (No. of Centers)	Study Design	Treatment Dose	Treatment Duration	Number Enrolled/ITT/ Completed	Gender (M/F) [ITT] Mean Age (range in yrs)
Controlled Studies							
Study 009*	Completed Oct 98/May 99	61 Centers: Canada, Hungary, Mexico, Poland, USA	Randomized, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od PO or Cefuroxime axetil 250 mg bid PO	Gemifloxacin 7 days Cefuroxime axetil 10 days	Gemifloxacin 331/331/299 Cefuroxime axetil 331/329/306	Gemifloxacin 144/187; 38.7 yrs (16-79) Cefuroxime axetil 133/196; 39.3 yrs (17-79)
Study 010**	Completed Oct 98/Feb 99	73 Centers: Belgium, Estonia, France, Germany, Ireland, Netherlands, UK	Randomized, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od PO or Trovafloxacin 200 mg od PO	Gemifloxacin 7 days Trovafloxacin 10 days	Gemifloxacin 195/195/176 Trovafloxacin 193/192/168	Gemifloxacin 79/116; 41.0 yrs (18-79) Trovafloxacin 78/114; 40.2 yrs (18-84)
Study 186+	Completed Nov 99/Mar 00	58 Centers: Belgium, Canada, Estonia, Finland, Germany, Ireland, Italy, Lithuania, Netherlands	Randomized, double-blind, parallel-group	Gemifloxacin 320 mg od PO	Gemifloxacin 5 days Gemifloxacin 7 days	Gemifloxacin 5 days 214/212/203 Gemifloxacin 7 days 198/198/190	Gemifloxacin 5 days 89/123; 41.3 yrs (18-78) Gemifloxacin 7 days 84/114; 39.3 yrs (18-80)
Uncontrolled Studies							
Study 206++	Completed Nov 99/Apr 00	39 Centers: Costa Rica, Hungary, Poland, USA	Open-label, multicenter, single-group	Gemifloxacin 320 mg od PO	Gemifloxacin 5 days	Gemifloxacin 461/461/445	Gemifloxacin 182/279; 37.6 yrs (16-81)
Study 333	Completed Feb 01/Mar 02	49 Centers: Hungary, USA	Multicenter, open-label	Gemifloxacin 320 mg od PO	Gemifloxacin 5 days	Gemifloxacin 451/451/431	Gemifloxacin 175/276; 42.3 yrs (18-82)

Abbreviations: ITT=intent-to-treat; od=once daily; PO=*per os*, by mouth; UK=United Kingdom; USA=United States of America; yr=year.
Source: Statistical Tables 52, 53, 54, and 55; and Study Reports.

* The patient data listed for this study exclude data from a total of 15 patients (7 gemifloxacin, 8 cefuroxime) enrolled by a disqualified investigator (Dr. DeAbate).

** The patient data listed for this study exclude data from a total of 14 patients (7 gemifloxacin, 7 trovafloxacin) enrolled by an investigator (Dr. Passage) excluded at the discretion of the Sponsor based on the findings of a failed GCP audit.

\+ The patient data listed for this study exclude data from a total of 11 patients (5 gemifloxacin 7-day, 6 gemifloxacin 5-day) enrolled by an investigator (Dr. Passage) excluded at the discretion of the Sponsor based on the findings of a failed GCP audit.

++ The patient data listed for this study exclude data from a total of 8 patients enrolled by a disqualified investigator (Dr. DeAbate).

7.3 Demography and Patient Characteristics

In the gemifloxacin phase III studies in ABS, a total of 1,846 patients received treatment with gemifloxacin 320 mg PO once daily (1,122 for 5 days and 724 for 7 days) and 521 patients received treatment with active comparator (2 patients who were randomized in the gemifloxacin group and 3 patients who were randomized in the active comparator group were not treated).

The following clinical and bacteriologic efficacy analysis populations were defined for all five studies:

> **Intent-to-treat (ITT):** All randomized/enrolled patients who took at least one dose of study drug (to which they were randomized for controlled studies).
>
> **Clinical Per Protocol (PP):** A subset of the ITT population that excludes patients who violated the protocol to an extent that could bias efficacy results.
>
> **Bacteriology ITT:** All randomized/enrolled patients who took at least one dose of study drug (to which they were randomized for controlled studies) and had evidence of infection with at least one pathogen identified at screening.*
>
> **Bacteriology PP:** Those clinical PP patients who had evidence of infection with at least one pathogen identified at screening. The bacteriology PP population is a subset of the bacteriology ITT population.*
>
> *In Study 333, pre-therapy pathogens were identified from specimens obtained by both sinus endoscopy and by sinus puncture (sinus aspirates). The bacteriology populations were originally based on the culture results of specimens obtained by sinus endoscopy. Since results obtained by sinus puncture are generally considered more accurate than those obtained by sinus endoscopy, microbiology results are based only on sinus puncture culture results.

Clinical response (success or failure) at follow-up was the primary efficacy endpoint for the controlled studies (Studies 009, 010, and 186). Clinical success at follow-up was defined as sufficient improvement or resolution of the signs and symptoms of ABS for patients who were clinical successes at the end of therapy visit such that no additional antibacterial therapy was required for ABS.

Bacteriological response (success or failure) at follow-up was the primary efficacy endpoint for the uncontrolled studies (Studies 206 and 333). Bacteriological response (success or failure) at follow-up was a secondary efficacy endpoint for the controlled studies (Studies 009, 010, and 186). Bacteriological success was defined as all initial pathogens were eradicated or presumed

eradicated at the follow-up assessment, without any new infections, but with or without colonization.

The follow-up visit was 7-14 days (Day 17-24) after the last dose of study medication in Studies 009 and 010 and 11-20 days (Day 18-25) after the last dose of study medication in Studies 186, 206, and 333.

The percent of patients withdrawn from the studies ranged from 3.5% for the gemifloxacin group in Study 206 to 13.0% in the trovafloxacin group in Study 010. The most common reasons for patients to withdraw from the study were adverse events and lost to follow.

The populations selected were representative of patients with ABS without serious complications. Patients were male or female, aged ≥ 16 years (Study 009) or ≥ 18 years (Studies 010, 186, 206, and 333), with a clinical diagnosis of ABS based on the presence of a purulent nasal discharge at the screening visit together with signs and symptoms of ABS. The signs and symptoms of ABS were to be of 7 days' duration (for mild to moderate cases), but less than 28 days' duration. In Studies 009, 206 and 333, a minimum of only 3 days' duration was allowed for severe cases. All studies required that signs and symptoms also include purulent/mucoid nasal discharge or purulence in the nasal cavity on examination and at least one *major* or 2 *minor* criterion as follows:

> *Major* criteria: facial pain/pressure/tightness over affected sinus(es), facial congestion/fullness, or nasal obstruction/blockage.
>
> *Minor* criteria: tooth pain, earache, non-vascular headache, sore throat, cough, halitosis, fever, change in perception of smell, or periorbital swelling.

Furthermore, patients were required to have a Water's view X-ray (Studies 009, 010, and 186) or computed axial tomography (CAT) scan (Study 186 only) of the affected sinus(es) within 48 hours (Studies 009 and 010) or within 72 hours (Study 186, 206, and 333) prior to randomization/enrollment that was consistent with a diagnosis of ABS (i.e., sinus opacification and/or an air-fluid level).

In the controlled ABS studies treatment groups were generally well matched with respect to demographic and baseline characteristics (Table 22). There were more females than males in each treatment group in each study, and mean age was approximately 40 years. Most patients were Caucasian, and all patients had an abnormality on X-ray/CAT scan, as was required by the entry criteria. No major differences between the clinical PP and ITT populations were noted.

Samples for culture were obtained by sinus puncture in Studies 009, 206, and at some sites in Study 333. Samples were obtained by sinus endoscopy in Studies 010 (only at centers in

France), 186 (only at centers in Lithuania and selected centers in Germany), and 333. For purposes of assessment and analysis of the bacteriologic outcomes, microbiology results are based only on specimens obtained by sinus puncture.

Table 22: Demographic and Baseline Characteristics: ABS Studies 009, 010, 186, 206, and 333 (Clinical PP)

	Study 009		Study 010		Study 186		Study 206	Study 333
	Gemifloxacin 320 mg od 7 days	Cefuroxime 250 mg bid 10 days	Gemifloxacin 320 mg od 7 days	Trovafloxacin 200 mg od 10 days	Gemifloxacin 320 mg od 5 days	Gemifloxacin 320 mg od 7 days	Gemifloxacin 320 mg od 5 days	Gemifloxacin 320 mg od 5 days
	N=277	N=290	N=152	N=155	N=178	N=171	N=426	N=373
Gender, n (%)								
Male	121 (43.7)	114 (39.3)	65 (42.8)	62 (40.0)	74 (41.6)	69 (40.4)	169 (39.7)	142 (38.1)
Female	156 (56.3)	176 (60.7)	87 (57.2)	93 (60.0)	104 (58.4)	102 (59.6)	257 (60.3)	231 (61.9)
Age (years)								
Mean (SD)	39.0 (13.9)	39.4 (12.8)	41.2 (13.4)	40.0 (15.0)	40.8 (14.4)	39.1 (13.6)	37.7 (14.0)	42.3 (13.8)
Range	16 – 79	17 – 79	18 - 78	18 - 84	18 - 78	18 – 80	16 - 81	18 – 82
Race, n (%)								
Caucasian	265 (95.7)	271 (93.4)	148 (97.4)	151 (97.4)	173 (97.2)	168 (98.2)	400 (93.9)	286 (76.7)
Black	3 (1.1)	6 (2.1)	1 (0.7)	1 (0.6)	1 (0.6)	2 (1.2)	11 (2.6)	59 (15.8)
Asian	3 (1.1)	1 (0.3)	2 (1.3)	3 (1.9)	1 (0.6)	0	0	2 (0.5)
Other*	6 (2.2)	12 (4.1)	1 (0.7)	0	3 (1.7)	1 (0.6)	15 (3.5)	26 (7.0)
X-ray/CAT scan, n (%)								
Abnormalities	277 (100.0)	290 (100.0)	152 (100.0)	155 (100.0)	178 (100.0)	171 (100.0)	426 (100.0)	373 (100.0)
Air-fluid level**	115 (41.5)	119 (41.0)	48 (31.6)	36 (23.2)	75 (42.1)	65 (38.0)	179 (42.0)	176 (47.2)
Opacification**	190 (68.6)	201 (69.3)	125 (82.2)	136 (87.7)	135 (75.8)	134 (78.4)	289 (67.8)	248 (66.5)
History of allergic rhinitis, n (%)	71 (25.6)	71 (24.5)	24 (15.8)	19 (12.3)	21 (11.8)	29 (17.0)	56 (13.1)	183 (49.1)

Abbreviations: bid=twice daily; CAT=computed axial tomography; n=number of patients; od=once daily; PP=per protocol; SD=standard deviation.
* Other includes Eurasian, Hispanic American, and Hispanic in Study 009; Caucasian/Philippine in Study 010; Asian, East Indian, and Peruvian in Study 186; Hispanic and Multiracial in Study 206; and Hispanic, Middle East, Middle East/Syrian, Multiracial, Portuguese, and Spanish in Study 333.
** Patients may have both an air–fluid level and sinus opacification.

The bacterial pathogens isolated were typical of those seen in patients with ABS and were evenly distributed between the gemifloxacin and comparator treated patients (Table 23). Notably, 22% to 24% of the *S. pneumoniae* isolates obtained by sinus puncture were MDRSP.

Table 23: Number (%) of Patients with Key Pathogens Associated with ABS at Screening

Pre-Therapy Pathogen*	Gemifloxacin 320 mg od 7 day Study 009		Gemifloxacin 320 mg od 5 days Studies 206 and 333		Cefuroxime 250 mg bid 10 days Study 009	
	Bacteriology PP Follow-Up Population N=133	Bacteriology ITT Population N=160	Bacteriology PP Follow-Up Population N=267	Bacteriology ITT Population N=297	Bacteriology PP Follow-Up Population N=138	Bacteriology ITT Population N=151
S. pneumoniae	55 (41.4)	66 (41.3)	103 (38.6)	113 (38.0)	58 (42.0)	63 (41.7)
MDRSP	14 (10.5)	16 (10.0)	24 (9.0)	25 (8.4)	15 (10.9)	15 (9.9)
H. influenzae	28 (21.1)	36 (22.5)	16 (6.0)	22 (7.4)	31 (22.5)	35 (23.2)
S. aureus	14 (10.5)	16 (10.0)	53 (19.9)	58 (19.5)	9 (6.5)	11 (7.3)
K. pneumoniae	14 (10.5)	17 (10.6)	8 (3.0)	12 (4.0)	18 (13.0)	19 (12.6)
M. catarrhalis	7 (5.3)	9 (5.6)	17 (6.4)	18 (6.1)	5 (3.6)	5 (3.3)
E. coli	3 (2.3)	4 (2.5)	12 (4.5)	13 (4.4)	3 (2.2)	4 (2.6)

Abbreviations: ABS=acute bacterial sinusitis; bid=twice daily; ITT=intent-to-treat; MDRSP=multi-drug resistant *S. pneumoniae*; n=number of patients; od=once daily; PP=per protocol.
* Note: Percentages are based on the total number of patients; some patients may have more than one pathogen.

7.4 Results of ABS Clinical Studies

7.4.1 Overall Success Rates

Overall clinical, bacteriological, and radiological success rates for the ABS clinical studies are summarized in Table 24, 25, and 26, respectively. Clinical response (success or failure) at follow-up (test of cure) was the primary efficacy parameter in the controlled studies (Studies 009, 010, and 186) and a secondary efficacy parameter in the uncontrolled studies (Studies 206 and 333).

At follow-up in the 3 controlled clinical studies, treatment with gemifloxacin 320 mg once daily resulted in high clinical response rates. The proportion of gemifloxacin treated patients with a clinical response of success ranged between 87.1 and 90.1% and for the comparator groups between 89.3% and 91.0% (clinical PP populations).

The clinical success rates at follow-up in Studies 009, 010 and 186 clearly demonstrate that gemifloxacin 320 mg PO once daily for 7 days was at least as good as the response for the

comparators (i.e., cefuroxime 250 mg twice daily (bid) PO for 10 days and trovafloxacin 200 mg PO once daily for 10 days) and that gemifloxacin 320 mg PO once daily for 5 days was at least as good as the response for gemifloxacin 320 mg PO for 7 days (Table 24 and Figure 7). In each study the lower limit of the 95% confidence interval (CI) for the treatment difference (gemifloxacin – comparator) was no less than the FDA agreed upon pre-defined non-inferiority limit of –15%, in fact the lower limit of the 95% CI was no less than -10% except in the ITT population for Study 009 where the lower limit was just over -10% at -10.6%. Additionally, in all cases the confidence intervals included 0. Results across these studies provided consistent evidence of efficacy of gemifloxacin.

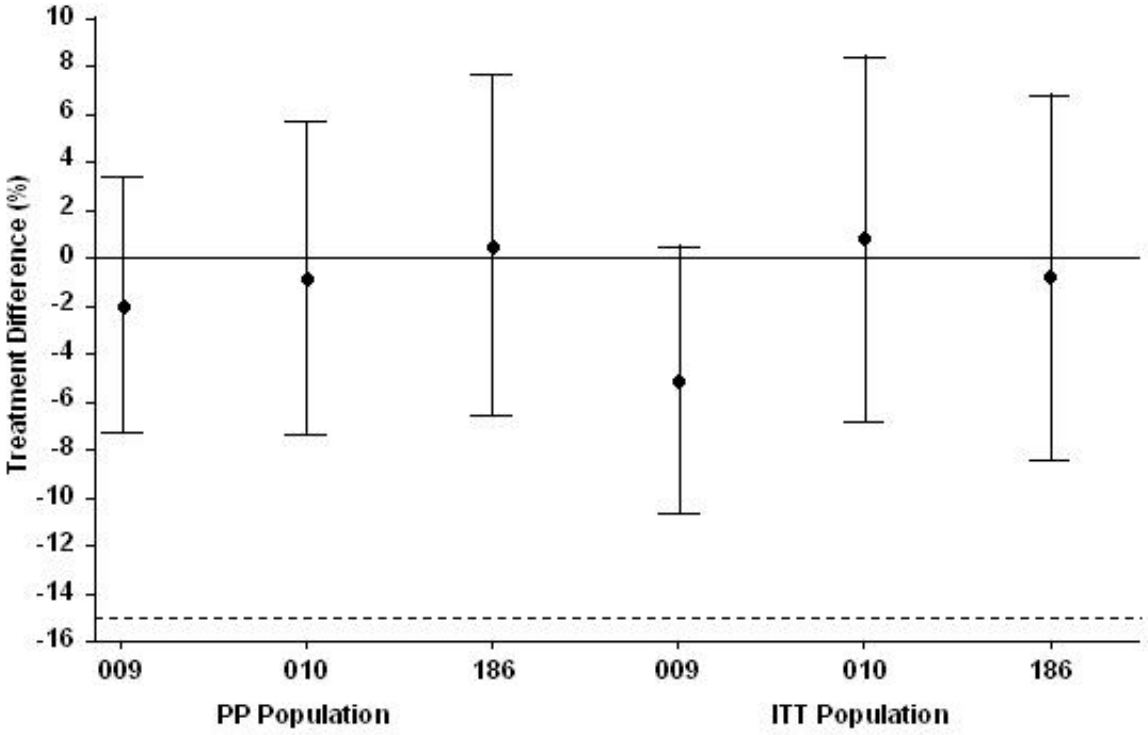
The results of the ITT population analysis were consistent with the conclusions from the clinical PP population analyses.

Table 24: Summary of Clinical Success Rates at Follow-Up: ABS Studies

	Success Rate		
	Gemifloxacin	**Comparator**	**Treatment Difference**
	% (n/N)	**% (n/N)**	**% (95% CI)***
CLINICAL PP			
Controlled Studies			
009	87.4 (242/277)**	89.3 (259/290	-1.95 (-7.23, 3.34)
010	90.1 (137/152)**	91.0 (141/155)	-0.84 (-7.38, 5.71)
186	87.1 (155/178)***	86.5 (148/171)**	0.53 (-6.57, 7.63)
Uncontrolled Studies			
206	90.4 (385/426)***		(85.75, 93.18)
333	87.1 (325/373)***		(83.73, 90.53)
ITT			
Controlled Studies			
009	81.9 (271/331)	86.9(286/329)	-5.06 (-10.58, 0.46)
010	83.1(162/195)	82.3 (158/192)	0.79 (-6.75, 8.33)
186	83.0 (176/212)	83.8 (166/198)	-0.82 (-8.02, 6.38)
Uncontrolled Studies			
206	87.9 (405/461)		(84.87, 90.83)
333	84.0 (379/451)		(80.66, 87.42)

* For uncontrolled studies, the 95% CI around the success rate is shown
** 7 days gemifloxacin
*** 5 days gemifloxacin

Figure 7: ABS Clinical Response at Follow-Up: Treatment Differences and 95% Confidence Intervals Clinical PP and ITT Population



Data Source: Table 62
Treatment difference is Gemi 320mg OD Success rate
(for study 186: Gemi 320mg OD 5 days success rate minus Gemi 320mg OD 7 days success rate)

The success rate in the bacteriology PP follow-up population in was high (93.2% [124/133] in the gemifloxacin group and 94.2% [130/138] in the cefuroxime group; 95% CI for the treatment difference: –6.75, 4.81) (Table 25). The success rate was slightly lower for the bacteriology ITT population (84.4% [135/160] in the gemifloxacin group and 90.1% [136/151] in the cefuroxime group), with a 95% CI for the treatment difference of -13.07, 1.69. Although Study 009 was not designed to demonstrate non-inferiority for the secondary endpoints, the lower limit of the 95% CI for the treatment difference (gemifloxacin – cefuroxime axetil) was not less than the protocol-specified lower limit of -15% (for the primary endpoint) for both the bacteriology PP and bacteriology ITT populations at follow-up.

Table 25: Summary of Bacteriological Response at Follow-Up: ABS Studies

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	Success Rate+		
	Gemifloxacin	**Comparator**	**Treatment Difference**
	% (n/N)	**% (n/N)**	**% (95% CI)***
CLINICAL PP			
Controlled Studies			
009	93.2 (124/133)**	94.2 (130/138)	-0.97 (-6.75, 4.81)
Uncontrolled Studies			
206	91.0 (192/211)***		(87.1, 94.9)
333	94.6 (53/56)***		(88.7, 100.0)
ITT			
Controlled Studies			
009	84.4 (135/160)	90.1 (136/151)	-5.69 (-13.07, 1.69)
Uncontrolled Studies			
206	87.0 (200/230)		(82.6, 91.3)
333	86.6 (58/67)		(78.4, 94.7)

* For uncontrolled studies, the 95% CI around the success rate is shown
** 7 days gemifloxacin
*** 5 days gemifloxacin
+Success is either bacteriological eradication or presumed bacteriological eradication.

The treatment differences and 95% CI for the combined clinical/radiological response rates for the PP and ITT populations at follow-up were no less than the pre-defined non-inferiority limits of -15% for Studies 009, 010, and 186. Again the results indicate that the lower limit of the 95% CI was no less than -10% except in the ITT population for Study 009 where the lower limit was just over -10% at -10.5% (Table 26).

Table 26: Summary of Combined Clinical/Radiological Success Rates at Follow-Up: ABS Studies

	Success Rate		
	Gemifloxacin	**Comparator**	**Treatment Difference**
	% (n/N)	**% (n/N)**	**% (95% CI)***
CLINICAL PP			
Controlled Studies			
009	239/277 (86.3)**	255/290 (87.9)	-1.65 (-7.17, 3.87)
010	135/152 (88.8)**	138/155 (89.0)	-0.22 (-7.24, 6.81)
186	149/178 (83.7)***	137/171 (80.1)**	3.59 (-4.48, 11.67)
Uncontrolled Studies			
206	376/426 (88.3)***		(85.21, 91.32)
333	307/373 (84.3)***		(80.61, 88.07)
ITT			
Controlled Studies			
009	265/331 (80.1)	279/329 (84.8)	-4.74 (-10.54, 1.05)
010	160/195 (82.1)	153/192 (79.7)	2.36 (-5.47, 10.20)
186	169/212 (79.7)	154/198 (77.8)	1.94 (-5.99, 9.87)
Uncontrolled Studies			
206	395/461 (85.7)		(82.49, 88.88)
333	361/451 (82.6)		(79.05, 86.16)

* For uncontrolled studies, the 95% CI around the success rate is shown.
** 7 days gemifloxacin
*** 5 days gemifloxacin

7.4.2 Clinical and Bacteriological Efficacy against Primary Pathogens Associated with ABS

Table 27 summarizes clinical success rates and bacteriological eradication rates at follow-up for all initial pathogens in Study 009. At follow-up, 93.1% (149/160) of initial pathogens in the gemifloxacin group and 92.8% (154/166) in the cefuroxime group were eradicated or presumed eradicated. The eradication rates were as follows: *S. pneumoniae* (98.2% for gemifloxacin and 93.1% for cefuroxime), MDRSP (100.0% vs. 80.0%), *H. influenzae* (92.9% vs. 100.0%), *S. aureus* (92.9% vs. 88.9%), *K. pneumoniae* (85.7% vs. 94.4%), *M. catarrhalis* (100.0% in both groups), and *E. coli* (66.7% vs. 100%).

Table 27: Clinical and Bacteriological Efficacy by Pre-Therapy Pathogens at Follow-Up: Study 009 (Bacteriology PP Population)

	Gemifloxacin 320 mg od 7 days		Cefuroxime 250 mg bid 10 days	
Pre-Therapy Pathogen	**Clinical Success**	**Bacteriological Eradication***	**Clinical Success**	**Bacteriological Eradication***
Outcome at Follow-Up	**N+=133 n/N** (%)**	**N+=133 n/N** (%)**	**N+=138 n/N** (%)**	**N+=138 n/N** (%)**
All pathogens	147/160 (91.9)	149/160 (93.1)	149/166 (89.8)	154/166 (92.8)
S. pneumoniae	54/55 (98.2)	54/55 (98.2)	54/58 (93.1)	54/58 (93.1)
MDRSP***	14/14 (100.0)	14/14 (100.0)	12/15 (80.0)	12/15 (80.0)
H. influenzae	26/28 (92.9)	26/28 (92.9)	30/31 (96.8)	31/31 (100.0)
S. aureus	12/14 (85.7)	13/14 (92.9)	8/9 (88.9)	8/9 (88.9)
K. pneumoniae	12/14 (85.7)	12/14 (85.7)	17/18 (94.4)	17/18 (94.4)
M. catarrhalis	7/7 (100.0)	7/7 (100.0)	5/5 (100.0)	5/5 (100.0)
E. coli	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	3/3 (100.0)

Abbreviations: bid=twice daily; od=once daily; PP=per protocol.
Patients can have more than one pathogen.
*Success is either bacteriological eradication or presumed bacteriological eradication.
+ N is the number of patients in the bacteriology PP populations at end of therapy or follow-up.
** n/N=number of successes/number of patients with a specific pathogen.
***MDRSP strains were resistant to 2 or more of the following antibiotics or classes of antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Table 28 summarizes clinical success rates and bacteriological eradication rates for gemifloxacin 7-day patients and gemifloxacin 5-day patients at follow-up, based on bacteriology PP populations: At follow-up, 93.1% (149/160) of initial pathogens in the gemifloxacin 7-day group and 93.7% (312/333) in the gemifloxacin 5-day group were eradicated or presumed eradicated. The eradication rates were as follows: *S. pneumoniae* (98.2% for gemifloxacin 7-day and 94.2% for gemifloxacin 5-day), MDRSP (100.0% for both groups), *H. influenzae* (92.9% vs. 96.2%), *S. aureus* (92.9% vs. 87.5%), *K. pneumoniae* (85.7% vs. 87.5%), *M. catarrhalis* (100.0% in both groups), and *E. coli* (66.7% vs. 91.7%).

Clinical success corresponded closely with bacteriological eradication in both treatment groups.

Table 28: Clinical and Bacteriological Efficacy by Pre-Therapy Pathogens at Follow-Up: Study 009 and Studies 206 and 333 Combined (Bacteriology PP Population)

	Study 009 Gemifloxacin 320 mg od 7 days		Studies 206 and 333 Gemifloxacin 320 mg od 5 days	
Pre-Therapy Pathogen	**Clinical Success**	**Bacteriological Eradication***	**Clinical Success**	**Bacteriological Eradication***
Outcome at Follow-Up	**N+=133 n/N** (%)**	**N+=133 n/N** (%)**	**N+=267 n/N** (%)**	**N+=267 n/N** (%)**
All pathogens	147/160 (91.9)	149/160 (93.1)	309/333 (92.8)	312/333 (93.7)
S. pneumoniae	54/55 (98.2)	54/55 (98.2)	96/103 (93.2)	97/103 (94.2)
MDRSP***	14/14 (100.0)	14/14 (100.0)	24/24 (100.0)	24/24 (100.0)
H. influenzae	26/28 (92.9)	26/28 (92.9)	51/53 (96.2)	51/53 (96.2)
S. aureus	12/14 (85.7)	13/14 (92.9)	13/16 (81.3)	14/16 (87.5)
K. pneumoniae	12/14 (85.7)	12/14 (85.7)	7/8 (87.5)	7/8 (87.5)
M. catarrhalis	7/7 (100.0)	7/7 (100.0)	17/17 (100.0)	17/17 (100.0)
E. coli	2/3 (66.7)	2/3 (66.7)	11/12 (91.7)	11/12 (91.7)

Abbreviations: bid=twice daily; od=once daily; PP=per protocol.
Patients can have more than one pathogen.
*Success is either bacteriological eradication or presumed bacteriological eradication.
+N is the number of patients in the bacteriology PP populations at end of therapy or follow-up.
** n/N=number of successes/number of patients with a specific pathogen.
***MDRSP strains were resistant to 2 or more of the following antibiotics or classes of antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

7.4.3 Clinical and Bacteriological Efficacy against Drug-Resistant Pathogens

The clinical and bacteriological efficacy of gemifloxacin was evaluated for patients with infection from drug-resistant strains of *S. pneumoniae* and *H. influenzae*.

Multi-Drug Resistant *S. pneumoniae*

Multi-drug resistant *S. pneumoniae* (MDRSP) is defined as resistance to 2 of more of the following classes of drugs: penicillin, second-generation cephalosporins, macrolides, trimethoprim/sulfamethoxazole, and tetracyclines.

Among patients from Study 009, 29 strains of *S. pneumoniae* isolated from patients (14 from gemifloxacin patients and 15 from cefuroxime patients) in the bacteriology PP follow-up population were classified as multi-drug resistant. In both groups, most of the MDRSP strains were resistant to 2 (15 strains) or 3 (12 strains) antibiotics, but there was one strain in the gemifloxacin group resistant to 5 antibiotics. There was a 100% (14/14) clinical success rate and bacteriological eradication rate at follow-up for these strains in gemifloxacin patients and an

80% (12/15) clinical success rate and bacteriological eradication rate in cefuroxime patients. Notably for the cefuroxime-treated patients with MDRSP who demonstrated clinical failure at follow-up, 100% (3/3) of these MDRSP strains were resistant to cefuroxime *in vitro*, suggesting that both clinical and bacteriological outcomes were related to the *in vitro* susceptibility of the isolates from the sinus. All gemifloxacin-treated patients with MDRSP strains demonstrating *in vitro* cefuroxime resistance were considered to have responded successfully to treatment.

Among the gemifloxacin-treated patients with MDRSP from Studies 009, 206, and 333 (bacteriology PP follow-up population), 38 strains of *S. pneumoniae* isolated from patients (14 from gemifloxacin 7-day patients and 24 from gemifloxacin 5-day patients) in the bacteriology PP follow-up population were classified as multi-drug resistant. In both groups, most of the MDRSP strains were resistant to 2 (13 strains) or 3 (16 strains) antibiotics, but there were 5 strains resistant to 5 antibiotics. In all of these strains, there was a 100% clinical success rate and bacteriological eradication rate at follow-up in both the gemifloxacin 7-day patients and gemifloxacin 5-day patients.

Multi-drug Resistant *H. influenzae*

Susceptibility testing results were analyzed for isolates of *H. influenzae* according to their susceptibility to ampicillin, clarithromycin, or gemifloxacin. This summary only includes data for patients who took gemifloxacin and for specimens obtained by sinus puncture.

In Study 009, there was a 100% (2/2) clinical success rate at follow-up for ampicillin-resistant (MIC $\geq$ 4 μg/mL) *H. influenzae* isolates in gemifloxacin-treated patients, and a 75.0% (3/4) clinical success rate in cefuroxime-treated patients (bacteriology PP population).

Among gemifloxacin-treated patients from Studies 009, 206, and 333, there was a 100% (2/2 for gemifloxacin 7-day patients and 3/3 for gemifloxacin 5-day patients) clinical success rate at follow-up for ampicillin-resistant (MIC $\geq$ 4 μg/mL) *H. influenzae* isolates (bacteriology PP population).

7.4.4 Subgroup Analyses

The clinical success rates at follow-up in the various demographic subgroups (age, gender, and race) were in general accordance with the response rates observed in the total patient population. No clinically important differences were noted between treatment groups.

7.5 Conclusions from ABS studies

Gemifloxacin administered for 5 days or 7 days has excellent clinical and bacteriological efficacy for the treatment of ABS, including infections due to MDRSP.

The combined results from the controlled studies of gemifloxacin demonstrated that the efficacy of 7 days of gemifloxacin was at least as good as that of each of the approved comparators. Furthermore, the efficacy of 5 days of gemifloxacin was at least as good as that of 7 days of gemifloxacin in this indication, as noted below:

- In Study 009, the clinical, bacteriological, and combined clinical and radiological efficacy rates of gemifloxacin 320 mg once daily for 7 days were at least as good as those of cefuroxime axetil 250 mg twice daily for 10 days.

- In Study 010, the clinical efficacy of gemifloxacin 320 mg once daily for 7 days at follow-up was at least as good as that of trovafloxacin 200 mg once daily for 10 days. The combined clinical and radiological efficacy of gemifloxacin at follow-up was at least as good as to that of trovafloxacin.

- In Study 186, the clinical, and combined clinical and radiological efficacy rates of gemifloxacin 320 mg once daily for 5 days at end of therapy were at least as good as those of gemifloxacin 320 mg once daily for 7 days.

The two uncontrolled studies of oral gemifloxacin 320 mg once daily for 5 days, designed to assess bacteriologic efficacy, demonstrated high bacteriological success rates. Secondary endpoints demonstrated high rates of clinical success, supporting the findings of the controlled clinical trials.

Eradication rates of major ABS pathogens in patients treated with gemifloxacin for 7 days or 5 days were comparable. For both treatment regimens, eradication rates at follow-up were high for *S. pneumoniae* (54/55, 98.2%), *H. influenzae* (26/28, 92.9%), *M. catarrhalis* (7/7, 100.0%), and *S. aureus* (13/14, 92.9%) in 7-day patients and for *S. pneumoniae* (97/103, 94.2%), *H. influenzae* (51/53, 96.2%), *M. catarrhalis* (17/17, 100.0%), and *S. aureus* (14/16, 87.5%) in 5-day patients.

22% to 24% of the *S. pneumoniae* isolates obtained by sinus puncture were MDRSP. In the bacteriology PP population, the clinical and bacteriological success rates were 100% for MDRSP-related infections.

Overall, the results demonstrate that gemifloxacin administered orally for 5 days is an effective antibacterial treatment for ABS. The data support the indication of gemifloxacin at a dose of

320 mg PO for 5 days for the treatment of ABS caused by *S. pneumoniae, H. influenzae, M. catarrhalis*, *S. aureus* (methicillin-susceptible strains only), *K. pneumoniae*, or *E. coli*.

8. REVIEW OF SAFETY

8.1 Demographics

The safety profile of gemifloxacin is based on clinical, phase IV, and post marketing data. The clinical data comprise 8119 patients in phase II and phase III studies who received gemifloxacin 320 mg PO orally and 5248 patients who received comparators. A subset of the clinical data, 1122 patients who were in the gemifloxacin 5-day ABS program, is also presented. The phase IV data are based on results available from a planned interim report on 1,821 patients (see Section 8.8) and the post marketing experience is from the first two years of marketing in the US on approximately 760,000 patients (see Section 8.9).

The demographic characteristics of the safety populations are summarized in Table 29.

Table 29: Demographic Characteristics in Clinical Studies (Gemifloxacin 320 mg Versus All Comparators)

Demographic Characteristics	Treatment Group					
	Gemifloxacin 320 mg PO		5 Day ABS Gemifloxacin 320 mg PO		All Comparators	
	N=8119		N=1122		N=5248	
	n	(%)	N	(%)	N	(%)
Age (years)						
≥16 - <18	22	(0.3)	13	(1.2)	8	(0.2)
≥18 - <40	2207	(27.2)	562	(50.1)	1029	(19.6)
≥40 - <65	3576	(44.0)	474	42.2)	2398	(45.7)
≥65 - <75	1449	(17.8)	56	(5.0)	1126	(21.5)
≥75	865	(10.7)	17	(1.5)	687	(13.1)
Mean (SD)	51.7	18.04	40.2 (14.25)		55.1 (17.19)	
Median	53		39		57	
Range	16-98		16-82		16-99	
Gender						
Male	3948	(48.6)	445	39.7	2511	(47.8)
Female	4170	(51.4)	677	60.3	2737	(52.2)
Race						
Caucasian	6792	(83.7)	985	87.8	4825	(91.9)
Black	380	(4.7)	79	7.1	192	(3.7)
Asian	463	(5.7)	3	0.3	43	(0.8)
Other	484	(6.0)	55	4.9	188	(3.6)

8.2 Patient Adverse Event Profile

8.2.1 Overall

The overall adverse event (AE) rate and the rates of specific AEs were similar or lower in the overall gemifloxacin 320 mg PO group 5-day group and 5-day ABS group versus the all-comparators group, except that the gemifloxacin group had a higher incidence of rash (Table 30).

The uncommon adverse event, hypoglycemia, deserves special notice due to reports of these events causing potentially significant safety concerns in patients receiving other quinolones. Adverse events of hypoglycemia were rarely reported in patients receiving gemifloxacin with only 3 events reported (<0.1%) and none in association with the concomitant administration of insulin or oral hypoglycemic agents. In comparison 13 events of hypoglycemia (0.2%) were reported in the patients receiving the pooled comparators, and 9 of these events occurred in association with the concomitant administration of insulin or oral hypoglycemic agents. Using laboratory-defined parameters, serum glucose reduced by 25% of the lower end of the normal range, to identify patients with hypoglycemic episodes, a very small number of patients (≤0.2% out of 8,119 gemifloxacin-treated patients, ≤0.2% of 1,122 5-day ABS gemifloxacin-treated patients, and 0.3% of 5,248 comparator treated patients) were noted to present with hypoglycemia at screening. Although infrequently observed at screening, a comparable percentage of gemifloxacin 320 mg treated and comparator treated patients were hypoglycemic by these laboratory criteria at either the on therapy (0.3% versus 0.5%) or at the end of therapy visit (0.3% versus 0.3%). Hypoglycemia as defined above was reported for one patient receiving insulin, but was not reported for any patient receiving oral hypoglycemic agents concomitant with gemifloxacin 320 mg, whereas in the comparator group, hypoglycemia was reported for 2 patients receiving insulin and 2 patients receiving oral hypoglycemic agents concomitant with the oral comparator.

Table 30: Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences in Either Treatment Group During the Interval On-Therapy Plus 30 Days Post-Therapy

Preferred Term	Treatment Group					
	Gemifloxacin 320 mg PO		5 Day ABS Gemifloxacin 320 mg PO		All Comparators	
	N=8119		N=1122		N=5248	
	N	(%)	N	(%)	N	(%)
Patients with at least one AE	3543	(43.6)	353	(31.5)	2492	(47.5)
Diarrhea	402	(5.0)	45	(4.0)	325	(6.2)
Headache	345	(4.2)	30	(2.7)	273	(5.2)
Nausea	303	(3.7)	41	(3.7)	237	(4.5)
Rash*	283	(3.5)	29	(2.6)	59	(1.1)
Abdominal Pain	177	(2.2)	8	(0.7)	116	(2.2)
Dizziness	140	(1.7)	17	(1.5)	134	(2.6)
Vomiting	132	(1.6)	7	(0.6)	106	(2.0)
Insomnia	110	(1.4)	9	(0.8)	92	(1.8)
Rhinitis	116	(1.4)	7	(0.6)	74	(1.4)
Hyperglycemia	115	(1.4)	6	(0.5)	70	(1.3)
Back pain	102	(1.3)	9	(0.8)	75	(1.4)
Taste perversion	30	(0.4)	9	(0.8)	108	(2.1)
Creatinine phosphokinase increased	112	(1.4)	7	(0.6)	64	(1.2)
SGPT increased	119	(1.5)	6	(0.5)	49	(0.9)
Injury	104	(1.3)	10	(0.9)	60	(1.1)
Hypertension	52	(0.6)	12	(1.1)	35	(0.7)
Sinusitis	89	(1.1)	8	(0.7)	69	(1.3)
Pharyngitis	76	(0.9)	8	(0.7)	73	(1.4)
Dyspepsia	74	(0.9)	8	(0.7)	74	(1.4)
Bronchitis	69	(0.8)	3	(0.3)	75	(1.4)
Constipation	91	(1.1)	1	(0.1)	62	(1.2)
Upper resp tract infection	63	(0.8)	4	(0.4)	67	(1.3)
Fatigue	71	(0.9)	5	(0.4)	57	(1.1)
Flatulence	79	(1.0)	13	(1.2)	40	(0.8)
SGOT increased	83	(1.0)	5	(0.4)	36	(0.7)
Moniliasis genital	52	(0.6)	8	(0.7)	57	(1.1)
Somnolence	47	(0.6)	13	(1.2)	43	(0.8)
Mouth dry	38	(0.5)	9	(0.8)	51	(1.0)
Pruritus	55	(0.7)	11	(1.0)	23	(0.4)
Otitis media	22	(0.3)	11	(1.0)	14	(0.3)

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

Proportionally, slightly fewer patients in the gemifloxacin 320 mg PO group (17.3%) than in the all-comparators group (20.3%) had at least one AE of suspected or probable relationship to study medication. Unlike other members of the quinolone class, gemifloxacin has a low potential for CNS side effects.

8.2.2 Serious Adverse Events (SAEs)

The overall incidence of SAEs was low in both treatment groups: 3.6% among patients treated with gemifloxacin 320 mg PO and 4.3% among patients in the all-comparators group. The proportion of patients having SAEs with a suspected or probable relationship to study medication was less than 1% in the gemifloxacin 320 mg PO group (N=8119), the 5-day ABS gemifloxacin-320 mg PO group (N=1122), and the all-comparators group (N=5248).

8.2.3 Withdrawals Due to AEs

The overall incidence of adverse events leading to withdrawal in the gemifloxacin 320 mg treatment group was equal to or lower than the incidence in the all-comparators treatment group, 3.6% (290/8119) in the overall 320 mg PO group and 0.6% (7/1122) in the 5-day ABS group versus 4.3% (226/5248) in the all-comparators group, respectively. Similarly, low percentages of patients in the gemifloxacin 320 mg PO and all-comparators groups were withdrawn for AEs of suspected or probable relationship to study medication during the interval on-therapy plus 30 days post-therapy, 2.0% (165/8119) in the overall 320 mg group and 0.4% (5/1122) in the 5-day ABS group versus 2.1% (109/5248) in the all-comparators group, respectively.

8.2.4 Deaths

The death rate in the gemifloxacin 320 mg PO treatment group was very low and similar to that in the all-comparators group, 0.5% (40/8119) versus 0.6% (30/5248), respectively. There were no deaths, 0% (0/1122) in the 5-day ABS treatment group.

8.3 Rash

Reports of photosensitivity reaction with gemifloxacin were rare. A total of 6/9003 patients in the all exposed gemifloxacin group and 2/5549 in the all-comparators group reported photosensitivity reactions in clinical studies. All reports were considered by the investigator to be of mild or moderate intensity, and no patients were withdrawn due to a photosensitivity reaction.

Patients taking gemifloxacin 320 mg PO had greater incidences of rash and rash leading to withdrawal than those taking comparators. A significant difference in the incidence of rash was observed between the gemifloxacin 320 mg PO group and the all-comparators group, 3.5% (283/8119) overall and 1.1% (59/5248) patients, respectively ($p<0.001$). The incidence of rash observed was less in the 5-day ABS treatment group 2.6% (29/1122) compared to the overall gemifloxacin 320 mg PO group (Table 31).

Table 31: Incidence of Adverse Experiences of Rash for Both Treatment Groups

Type of AE	Treatment Group					
	Gemifloxacin 320 mg PO N=8119		5 Day ABS Gemifloxacin 320 mg PO N=1122		All Comparators N=5248	
	N	(%)	N	(%)	n	(%)
Rash*	283	(3.5)	29	(2.6)	59	(1.1)
SAE of rash*	7	(0.1)	0	(0)	1	(<0.1)
Rash* leading to withdrawal	66	(0.8)	3	(0.3)	15	(0.3)

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

SAEs of rash were rare in both treatment groups, occurring in 7/8119 (0.1%) patients in the gemifloxacin 320 mg PO group and 1/5248 (<0.1%) patient in the all-comparators group. In the 5-day ABS gemifloxacin group, there were no SAEs of rash. The specific reasons for the rash SAEs reported on gemifloxacin are presented in Table 32. The first four were classified as SAEs because the patients were hospitalized. This represents the different standard of care in Eastern Europe. These patients would have been treated for rash as outpatients in North American or Western Europe. In the Canadian case the patient was afebrile and the rash cleared in 2 days. The Dutch case had a rash that began quickly and was of long duration, but the patient was not admitted to hospital. The US case was more complex and may have represented a cutaneous reaction to mycoplasma infection. It does not fit either a serum sickness vasculitis or a serum sickness-like reaction. However, with rash, fever and joint involvement it can be considered a possible serum sickness-like reaction. Of the 7 patients with SAEs of rash only two are of possible concern (<0.03%); however, both cases had multiple possible etiologies.

Table 32: Reason for Gemifloxacin Rash SAEs

Patient Description	Center Location	Reason for SAE	Comments/Outcome
18 yr old male, 7 days dosing, ABS	Hungary	Hospitalization	Paul-Bunnell test positive "Rash probably associated with underlying mononucleosis and drug"
24 yr old female, 8 days dosing, ABS	Poland	Hospitalization	Hospitalization for treatment with steroid and anti-histamine. Recovered by day three.
52 yr old female, 9 days dosing, ABS	Poland	Hospitalization	Mild rash. No medical reason for hospitalization but patient required reassurance.
60 yr old female, 8 days after 1st dose, UTI	Poland	Hospitalization	Rxed with steroid, antihistamine and calcium. Recovered within 7 days.
87 yr old male, 7 days dosing, CAP	Canada	Investigator judgment	Patient noted to have rash 48 hours post therapy. Asymptomatic, afebrile, reported to be fading in 2 days without intervention.
72 yr old male, 2 days dosing, ABECB	Netherlands	Investigator judgment	Allergic to gold and penicillin. Receiving 8 co- medications. Maculopapular, maculoconfluent rash on body and limbs with severe itching. "Treated with antihistamine. Resolving at day 18".
42 yr old female, 4 days dosing, ABS	US	Investigator judgment	Serum sickness onset 13 days after last dose, generalized maculopapular rash with few vesicles, fever, chills, joint pains, cough, CXR infiltrate in RLL serological diagnosis of acute mycoplasma pneumoniae infection. Largely resolved after 15 days

Rash as a cause of withdrawal was very low in both treatment groups, occurring in 66/8119 (0.8%) patients in the gemifloxacin 320 mg PO group and 15/5248 (0.3%) patients in the all-comparators group, respectively.

There were 7 reported cases of facial edema in the gemifloxacin 320 mg PO treatment group (N=8119) (Table 33). None appeared to represent angioedema and did not represent even urticaria. Two used pharmacologic interventions (oral corticosteroids for one patient and antihistamines for both). It should be noted that oral corticosteroids were prescribed for the concomitant rash and not specifically for the 'facial edema'. Of the three patients who reported facial edema on therapy, two completed their course of gemifloxacin while one discontinued gemifloxacin after the first dose. All the reactions were either mild or moderate. None of the episodes of facial edema were associated with fever or eosinophilia, and none were considered by the investigator to be serious.

Table 33: Episodes of Facial Edema in Clinical Trials

PID	Verbatim Text	Gender	Age	Maximum Intensity	Onset	Rash	Fever	Eosinophilia	Treatment	Outcome
013.028.02115	Eyelid edema	F	34	Mild	On-therapy	No	No	Elevated at baseline (990)-declined (410) on therapy	None	Resolved in 2 days
053.037.37001	Facial edema	F	21	Moderate	3 weeks post-therapy	No	No	No	None	Resolved in 2 days
053.037.37005	Facial edema	F	52	Moderate	On therapy	Yes	No	No	Drug Stopped / Allegra Rx	Resolved in 5 days
053.037.52009	Facial swelling	F	40	Moderate	3 weeks post-therapy	No	No	Elevated at Baseline (620)-declined (210) on therapy	None	Resolved in 1 day
186.272.32353	Submandibular swelling	F	59	Mild	12 days post-therapy	No	No	No	None	No resolution date provided
212.164.55322	Swelling of the eyelids	F	42	Moderate	On therapy	No	No	No	None	Resolved in 5 days
634.561.00001	Facial edema	F	44	Moderate	2 days post-therapy	Yes	No	No	Prednisone Loratadine	Resolved in 7 days

Having observed that the rash rate was increased in patients taking gemifloxacin, multivariate analysis was conducted to determine risk factors for rash. Relevant risk factors identified for rash included patients with longer treatment duration, patients <40 years of age, and female patients. In female patients ≥40 years or age, the use of hormone replacement therapy (HRT) was also associated with the occurrence of rash but not for drug-related rash. In female patients <40 years or age, the use of oral contraceptives (OCs) was not associated with rash.

8.3.1 Rash by Duration of Treatment

The incidence of rash increased with longer gemifloxacin treatment durations, the lowest incidence being the 5-day subgroup (1.5%) (Table 34). This trend was also observed in the all-comparators group, although it was less marked.

Table 34: Number (%) of Patients with Rash by Duration of Treatment (5, 7, or 10 days)

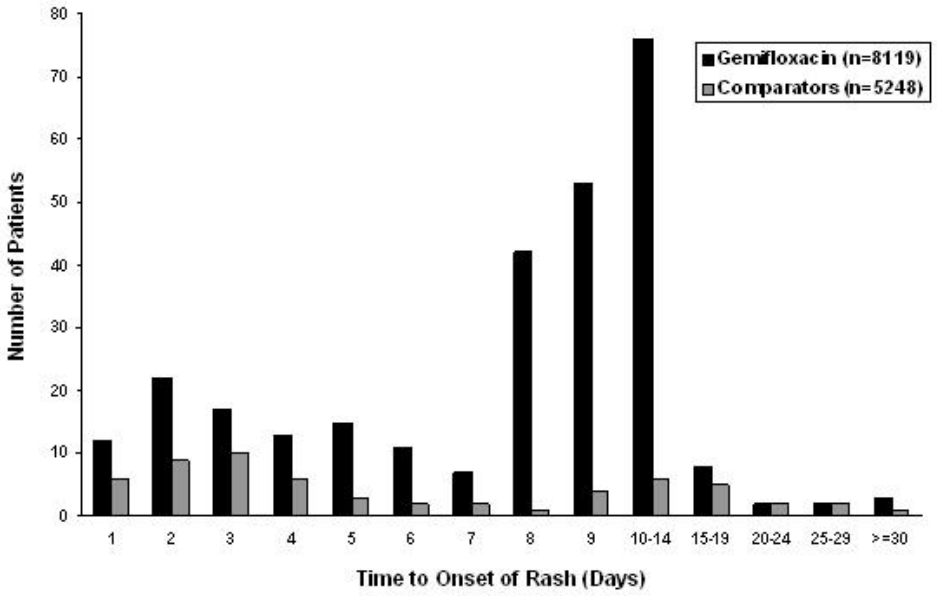
Day	Treatment Group			
	Gemifloxacin 320 mg PO		All Comparators	
	N=7286		N=4487	
	N	(%)	n	(%)
5	56/3696	(1.5)	3/334	(0.9)
7	135/2732	(4.9)	24/2234	(1.1)
10	55/858	(6.4)	21/1919	(1.1)

8.3.2 Time to Onset of Rash

The median time to onset of the rash from the start of study medication was 9.0 days for the gemifloxacin group and 4.0 days for the all-comparators group (Figure 8).

The distribution of values for time to onset of rash showed clustering of values around the medians, but otherwise no clear patterns were evident.

Figure 8: Time to Onset of Rash from Start of Study Medication

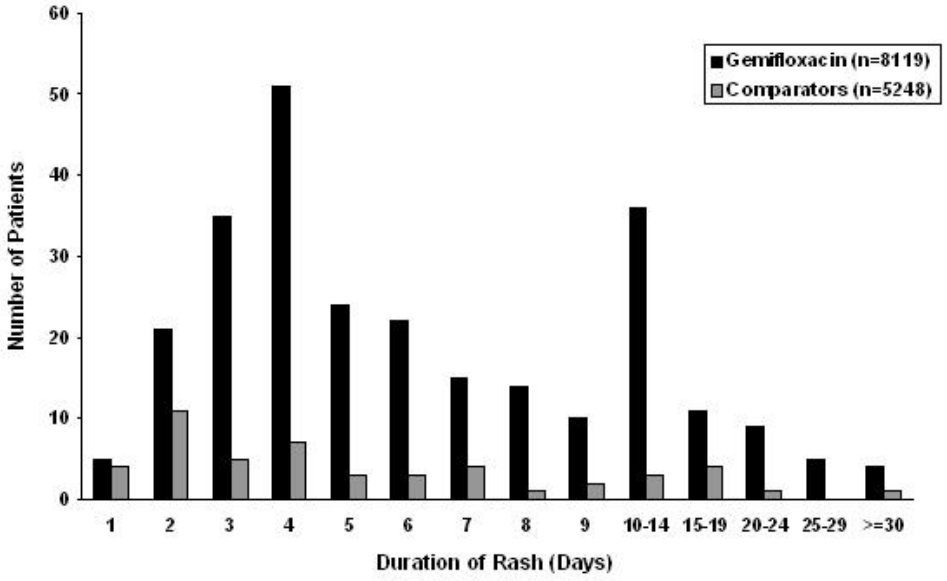


8.3.3 Duration of Rash

The median duration of the rash for the gemifloxacin group was 5.0 days, compared with 4.0 days for the all-comparators group.

The overall distribution of values for duration of rash was similar in the 2 treatment groups (Figure 9).

Figure 9: Duration of Rash



8.3.4 Severity of Rash

In both the gemifloxacin group and the all-comparators group, most rashes were of mild or moderate intensity, 86.6% and 93.4%, respectively. Among patients with rashes, the frequency of rashes classified as severe was low in both treatment groups, 13.4% of patients in the gemifloxacin group and 6.6% of patients in the all-comparators group.

The percentage of patients with severe rash did not increase with increasing duration of exposure to gemifloxacin (Table 35).

Table 35: Maximum Severity of Rash By Duration of Exposure with Gemifloxacin 320 mg PO

Severity	Extent of Exposure - Time Interval*											
	Unknown		0-3 days		4-5 days		6-7 days		8-10 days		>=11 days	
	n	%	n	%	n	%	n	%	n	%	n	%
Mild	1	(100.0)	18	(60.0)	18	(50.0)	49	(43.8)	44	(47.3)	8	(72.7)
Moderate	0		8	(26.7)	14	(38.9)	50	(44.6)	33	(35.5)	2	(18.2)
Severe	0		4	(13.3)	4	(11.1)	13	(11.6)	16	(17.2)	1	(9.1)
Total+	1	(100.0)	30	(100.0)	36	(100.0)	112	(100.0)	93	(100.0)	11	(100.0)

*Includes rash AEs occurring on-therapy plus 30 days post-therapy
+Total number of patients with rash during specified interval
Note: Day 0 is Day 1 of study medication

8.3.5 Rash by Gender

The frequency of rash was higher for both males and females in the gemifloxacin group than in the all-comparators group. The frequency of rash was higher in females than in males in both the gemifloxacin and the all-comparators treatment groups.

8.3.6 Rash by Age, Gender, and Planned Treatment Duration

Table 36 presents the occurrence of rash according to age and gender, by planned 5-, 7-, and 10-day treatment duration for the overall population. The occurrence of rash by the planned 5-day treatment duration for the overall population was 2.5% or less for either males or females and for those both < 40 and ≥ 40 years of age for the gemifloxacin overall population.

Table 36: Number (%) of Patients with Rash by Age and Gender According to Planned Treatment Duration

	Gemifloxacin 320 mg PO			All Comparators		
	N=7286			N=4487		
Duration of Treatment	**5 Days**	**7 Days**	**10 Days**	**5 Days**	**7 Days**	**10 Days**
Gender/ Age (yrs)	**N (%)**	**n (%)**	**n (%)**	**N (%)**	**n (%)**	**N (%)**
Both, <40	16//755 (2.1)	75/860 (8.7)	27/205 (13.2)	0/1	3/156 (1.9)	9/523 (1.7)
Both, ≥40	40/2941 (1.4)	60/1871 (3.2)	28/653 (4.3)	3/333 (0.9)	21/2078 (1.0)	12/1396 (0.9)
All Males	16/1859 (0.9)	52/1437 (3.6)	16/419 (3.8)	2/202 (1.0)	8/1157 (0.7)	6/967 (0.6)
Males <40	6/356 (1.7)	26/453 (5.7)	7/74 (9.5)	0/1	2/82 (2.4)	3/211 (1.4)
Males ≥40	10/1503 (0.7)	26/984 (2.6)	9/345 (2.6)	2/201 (1.0)	6/1075 (0.6)	3/756 (0.4)
All Females	40/1837 (2.2)	83/1294 (6.4)	39/439 (8.9)	1/132 (0.8)	16/1077 (1.5)	15/952 (1.6)
Females <40	10/399 (2.5)	49/407 (12.0)	20/131 (15.3)	0/0	1/74 (1.4)	6/312 (1.9)
Females ≥40	30/1438 (2.1)	34/887 (3.8)	19/308 (6.2)	1/132 (0.8)	15/1003 (1.5)	9/640 (1.4)

8.3.7 Rash by Oral Contraceptive Use or Hormone Replacement Therapy

The incidence of rash by OC use or HRT for each treatment group was assessed in female patients (Table 37 and 38, respectively). The frequency of rash was consistently higher in the gemifloxacin 320 mg PO group compared with the all-comparators group for both the OC use, 8.4% (42/498) versus 1.3% (4/307) subgroups, respectively, and HRT, 5.4% (27/497) versus 1.2% (5/408) subgroups, respectively.

For female patients in the gemifloxacin group, the incidence of rash was higher in the OC use subgroup, 8.4% (42/498), versus the non-OC use subgroup, 4.1% (151/3672), but this difference was predominantly noted in the women over 40 years of age. The incidence of rash was also higher in the HRT subgroup, 5.4% (27/497), versus the non-HRT subgroup, 4.5% (166/3673) with the difference between the two groups again more predominantly noted in the women over 40 years of age. This trend was not noted in the all-comparators group.

Table 37: Number (%) of Female Patients with Rash by Oral Contraceptive Use

	Treatment Group							
	Gemifloxacin 320 mg PO N=4170				All Comparators N=2737			
	OC Use				OC Use			
	YES		NO		YES		NO	
	n	%	n	%	n	%	N	%
Female Patients <40 yrs	n=438		n=799		n=271		n=426	
Rash	37	(8.4)	59	(7.4)	4	(1.5)	4	(0.9)
Female Patients ≥40 yrs	n=60		n=2873		n=36		n=2004	
Rash	5	(8.3)	92	(3.2)	0		31	(1.5)
All Female Patients	n=498		n=3672		n=307		n=2430	
Rash	42	(8.4)	151	(4.1)	4	(1.3)	35	(1.4)

Table 38: Number (%) of Female Patients with Rash by HRT Use

	Treatment Group							
	Gemifloxacin 320 mg PO N=4170				All Comparators N=2737			
	HRT Use				HRT Use			
	YES		NO		YES		NO	
	n	%	n	%	N	%	n	%
Female Patients <40yrs	n=9		n=1228		n=7		n=690	
Rash	0	(0)	96	(7.8)	1	(14.3)	7	(1.0)
Female Patients ≥40yrs	n=488		n=2445		n=401		n=1639	
Rash	27	(5.5)	70	(2.9)	4	(1.0)	27	(1.6)
All Female Patients	n=497		n=3673		n=408		n=2329	
Rash	27	(5.4)	166	(4.5)	5	(1.2)	34	(1.5)

8.3.8 Rash by Indication

The incidence of rash for the ABS indication was assessed (Table 39). The frequency of rash was higher in the gemifloxacin 320 mg PO 7-day group (8.6%) compared to the 5-day group (2.6%). In the combined 5-day and 7-day ABS populations, the rash rate was 4.9%, overall. The rash rate was 4.4% in the $\geq$ 40 female and 2.5% in the < 40 year female 5-day ABS population.

Table 39: Patients with ABS with Rash On Therapy Plus 30 Days Post Therapy

Population	Gemifloxacin			
	5 Days		7 Days	
	Total Pts.	n (%)	Total Pts.	n (%)
Both, all ages	1122	29 (2.6)	724	62 (8.6)
Both, < 40 years	575	13 (2.3)	402	42 (10.4)
Both, ≥ 40 years	547	16 (2.9)	322	20 (6.2)
All Females	677	23 (3.4)	417	43 (10.3)
Females, < 40 years	358	9 (2.5)	224	29 (12.9)
Females, ≥ 40 years	319	14 (4.4)	193	14 (7.3)
All Males	445	6 (1.3)	307	19 (6.2)
Males, < 40 years	217	4 (1.8)	178	13 (7.3)
Males, ≥ 40 years	228	2 (0.9)	129	6 (4.7)

8.3.9 Previous Gemifloxacin Exposure

In the full safety population (all patients who received at least one dose of gemifloxacin 320 mg PO), the total number of patients who were known to be exposed to gemifloxacin prior to re-exposure with gemifloxacin was 41/8119 (0.5%). The cross-tabulation showed that of these patients who were previously exposed to gemifloxacin, no patient reported a rash AE at either the first exposure or upon re-exposure. These findings suggest that previous exposure to gemifloxacin does not appear to be a risk factor for the development of rash although the patient number is small.

8.3.10 Previous Quinolone Exposure

The total number of patients who were known to be exposed to another fluoroquinolone at any time prior to starting treatment with gemifloxacin was 270/8119 (3.3%). The quinolones of prior exposure included ciprofloxacin (124 patients) levofloxacin (89 patients), norfloxacin (20 patients), gatifloxacin (18 patients), ofloxacin (16 patients), trovafloxacin (10 patients), moxifloxacin (9 patients) cinoxacin (5 patients), pipemidic acid (7 patients), grepafloxacin (3 patients), sparfloxacin (2 patients), and pefloxacin (1 patient). There were 28 patients that reported previous exposure to more than one quinolone, resulting in 308 previous quinolone exposures. A total of 101/270 (37.4%) of the patients with prior quinolone exposure had received another quinolone during the two weeks immediately prior to gemifloxacin treatment.

Of the 270 patients that were known to be previously exposed to a quinolone antibiotic, 10 (3.7%) patients developed a rash (6 mild, 3 moderate, 1 severe) during gemifloxacin administration. For four of the ten patients, the medical history was notable for allergies to other

medications. This rash rate is similar to that described for the overall oral 320 mg group. These findings suggest that previous exposure to quinolone antibiotics does not sensitize patients to develop a rash upon subsequent exposure to gemifloxacin treatment.

8.3.11 Subsequent Exposure to Another Quinolone

Patients receiving gemifloxacin who developed a rash AE during the on-therapy plus 30 day post-therapy and were known to be subsequently exposed to another quinolone antibiotic were identified. Of fourteen patients identified, twelve had subsequent exposures shortly prior to or after the reported rash had developed and two patients had concurrent quinolone exposure (day 3 for both) during treatment with gemifloxacin therapy. For the patients with concurrent exposure to another quinolone and gemifloxacin the rash AE occurred on day 3 and day 12 after the first dose of gemifloxacin for the two patients, respectively. Of the twelve with actual subsequent exposure to another quinolone, two patients developed rash only after exposure to another quinolone but still within the 30 days post-therapy with gemifloxacin. For one of these patients the rash was observed during the subsequent quinolone exposure (and 15 days after completion of gemifloxacin) and for the other patient the rash was observed two days after completion of the subsequent quinolone exposure (and 11 days after completion of gemifloxacin). This particular patient then had a subsequent exposure to yet another quinolone and had an uneventful course with no rash events being reported.

Of the final ten patients who developed a rash AE associated with gemifloxacin treatment (with the rash event observed prior to any exposure to another quinolone), none developed a rash upon subsequent exposure to another quinolone antibiotic.

Overall, fifteen subsequent exposures occurred, as follows: exposure occurred at 6 days, 10 days, 13 days, 15 days, 16 days, 17 days (2), 18 days, 25 days, 30 days, 35 days (2), 74 days, 114 days, and 130 days (1) after the first dose of gemifloxacin. Three patients had two subsequent exposures.

The two patients who completed a course of gemifloxacin and then upon exposure to another quinolone developed rash may represent sub-sensitization or just delayed response to gemifloxacin itself. Whereas, the ten patients who developed a rash AE associated with gemifloxacin treatment, none developed a rash upon subsequent exposure to another quinolone antibiotic. These findings suggest that patients who developed a rash associated with gemifloxacin treatment are at low risk for cross-sensitization when subsequently exposed to other quinolone antibiotics.

8.3.12 Systemic Signs in Association with Rash

The number of patients in the combined population that met the definition of systemic involvement and also developed a rash AE was determined. Systemic signs were defined in terms of the laboratory values assessment, as follows:

Eosinophils: one high F2-flag (laboratory value increased by >200% of baseline, where the baseline value is not 0), AND

Liver function tests: at least one high F2F3-flag at any visit (laboratory value increased from baseline by more than the pre-specified amount and is outside the extended normal range high) for at least one of the following:

Alkaline phosphatase, ALT, and aspartate aminotransferase (AST): value increased from baseline by 75% and is >200% of normal range high.

Total bilirubin: value increased from baseline by 50% and is >150% of normal range high.

Patients not meeting the above criteria were categorized as not having systemic involvement.

Thirty-nine of 8119 (0.48%) of patients treated with gemifloxacin met the above criteria; although a small sample size, only 2 of the 39 (5.1%) patients developed a rash. Both patients who developed a rash had a history of allergic disease, which was likely to be a predisposing factor for the development of rash and systemic signs. In comparison, 281 of 7799 (3.5%) patients who did not meet the above laboratory criteria also developed a rash. These findings suggested that gemifloxacin use in patients developing rash did not appear to be associated with an increased risk for systemic involvement.

The 2 patients who met the laboratory criteria summarized above and also had a rash AE are summarized as follows:

PID 013.059.02417: This 35-year-old Caucasian female (country Sweden) had a history of rhinoconjunctivitis (due to pollen) and presented with increased white blood cell level at baseline. The patient took gemifloxacin for 10 days. The patient developed a rash on Day 8 lasting for 5 days described as mild and probably related to gemifloxacin. The patient had the following laboratory values:

	SCR	OT	EOT	Reference Range
ALT	30	***112***	31	0-47 IU/L
AST	35	69	20	0-37 IU/L
ALK	97	151	74	40-135 IU/L
Total bilirubin	16.5	4.9	11.0	0-19.00 µmol/L
Monocytes	1.42	0.49	0.47	0-0.80 x 10^9/L
Lymphocytes	2.39	1.7	0.44	1.20-4.0 x 10^9/L
Eosinophils	0.02	0.10	0.04	0-0.50 x 10^9/L
Neutrophils	20.87	6.81	3.49	1.8-7.0 x 10^9/L
WBC	6.8	5.4	3.0	3.80-11.00 x 10^9/L

SCR = Screening; OT = On-Therapy; EOT = End of Therapy.
*Units are shown only in the reference range column.
Note: F2F3-flagged values are bolded and in italics.

PID 014.045.06541: This 30-year-old Caucasian female (country US) had a history of asthma, hay fever, and oral contraceptive use and presented with pruritus, characterized by itchy skin at night, on Day 0 lasting 11 days and of suspected relationship to gemifloxacin. The patient took gemifloxacin for 10 days. The patient developed a rash on Day 10 lasting 1 day described as mild and of suspected relationship to gemifloxacin. The patient developed hay fever on Day 18 lasting 2 days and considered unrelated to gemifloxacin.

	SCR	OT	EOT	Reference Range
ALT	51	***139***	50	0-42 IU/L
AST	28	40	27	0-37 IU/L
ALK	72	83	98	20-125 IU/L
Total bilirubin	10.26	8.55	10.26	0-22.23 µmol/L
Monocytes	0.98	0.5	0.01	0.20-1.10 x 10^9/L
Lymphocytes	1.19	1.42	1.45	0.85-4.10 x 10^9/L
Eosinophils	0.11	0.28	0.32	0.05-0.55 x 10^9/L
Neutrophils	5.17	3.24	2.6	1.8-7.0 x 10^9/L
WBC	7.5	5.5	4.4	3.80-10.80 x 10^9/L

SCR = Screening; OT = On-Therapy; EOT = End of Therapy.
*Units are shown only in the reference range column.
Note: F2F3-flagged values are bolded and in italics.

Although from a technical perspective these two patients may have met the eosinophil count criteria to be classified as having rash in association with systemic signs, neither of these two patients met the standard definition for peripheral eosinophilia of >500 cells/mm^3 at any time during or after therapy with gemifloxacin. Although both did develop mild liver function enzyme test abnormalities these were noted early in their course with gemifloxacin (on therapy

visit typically occurred on days 2-4 of treatment) and were already resolving by the end of therapy visit when the rash was just developing for both subjects. In addition, neither patient developed increased bilirubin concentrations either while on, or at the completion of therapy.

8.3.13 Immune System Reactions in Association With Rash

A total of 8/8119 (0.1%) patients taking gemifloxacin 320 mg PO and 2/5248 (<0.1%) patients in the all-comparators group who reported rash also concurrently experienced fever, arthralgia, and/or lymphadenopathy. This included 2.8% (8/283) of patients in the gemifloxacin group and 3.4% (2/59) of patients in the all-comparators group reporting rash AEs.

A total of 60/8119 (0.7%) of gemifloxacin treated patients reported fever, and of these, 4 (6.7%) patients developed rash. Two patients developed a transient fever during treatment or shortly thereafter, with a moderate rash developing after the last treatment. One patient developed a rash shortly thereafter the last treatment but fever occurred near the end of the rash episode. The other patient developed a fever and rash more than 2 weeks after treatment.

A total of 46/8119 (0.6%) of gemifloxacin treated patients reported arthralgia, and of these, 3 (6.5%) patients developed rash. Additionally, a total of 4/8119 (<0.1%) of patients reported lymphadenopathy, and of these, 1 (25.0%) patient developed rash. This particular patient with rash and lymphadenopathy also had arthralgia. There were 2 cases of arthralgia associated with rash in the all-comparators group.

In summary, the scope of the possible immune system reactions associated with rash included 8 cases of fever, arthralgia, and/or lymphadenopathy in patients receiving gemifloxacin 320 mg PO. Four patients had concurrent rash and fever, 3 patients had concurrent rash and arthralgia, and 1 patient had concurrent rash and arthralgia and lymphadenopathy. No patient had developed rash concurrently with lymphadenopathy alone. For the cases of fever, it preceded the development of the rash in three patients and occurred later in the course of rash in another patient, and for the cases of arthralgia, it occurred subsequent to the occurrence of rash, except for 1 case. In general, patients taking gemifloxacin do not appear to be at a higher risk for further adverse events involving the lymphatic system or the articular system as a result of developing a rash.

8.4 Study 344

Having observed that the rash rate was increased in patients taking gemifloxacin, a special clinical study, Study 344, was conducted to elicit and further characterize the gemifloxacin-associated rash. Specifically, Study 344 was designed to assess the following:

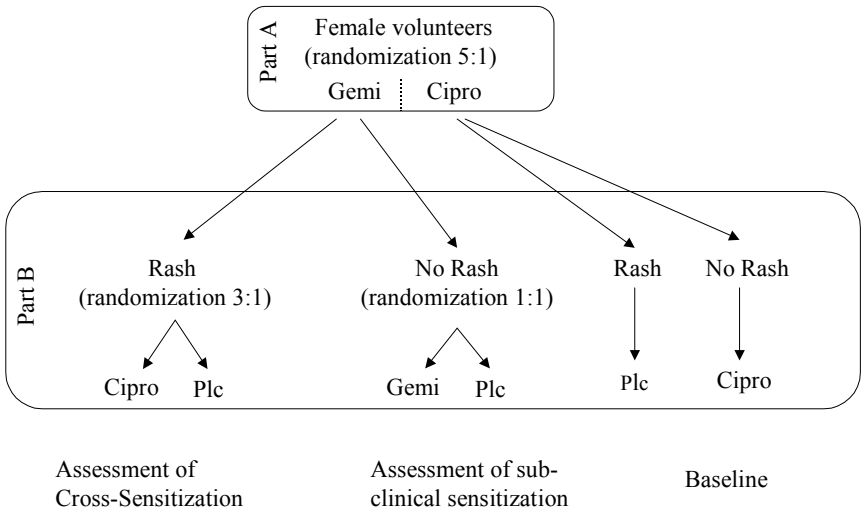
- The clinical and histological characteristics of gemifloxacin associated rash.
- The potential for cross-sensitization to other quinolones (as represented by ciprofloxacin) in subjects who experienced gemifloxacin-associated rash.
- The potential for sub-clinical sensitization in subjects not developing a rash on first exposure to gemifloxacin
- To explore the relationship between plasma levels of gemifloxacin and N-acetyl gemifloxacin and the incidence of rash.

Study 344 was intentionally designed with an enriched population considered to be at higher risk for development of rash treated for a longer duration than intended for CAP, ABECB (approved indications), and ABS (the subject of this briefing book) treatment, in order to elicit enough rashes to assess the possible immune basis, outcome of the rash, and to comprehensively characterize the rash. It therefore enrolled subjects most likely to develop a rash following exposure, namely female subjects aged <40 years, who were then exposed to 10 days of treatment, which was longer than the intended duration of treatment, 5 to 7 days (5 days for ABS), in order to maximize the incidence of rash.

8.4.1 Study Design

In order to maximize the occurrence of rash, the study exposed female subjects aged <40 years to 10 days of treatment with gemifloxacin. The study was performed in two parts, Part A and Part B (Figure 10). Both Part A and Part B were conducted to a double blind, double-dummy, repeat dose design. There was a washout period between Part A and Part B of 4 to 6 weeks.

Figure 10: Study Design for Study 344



Part A Study Design

Each subject participated in one repeat dose session and was administered 320 mg orally of gemifloxacin once daily or 500 mg orally of ciprofloxacin twice daily for 10 days or until a rash was reported. Subjects were randomized to receive gemifloxacin or ciprofloxacin in a 5:1 ratio.

Subjects in whom rash was reported underwent skin biopsies, standardized photographic assessment, dermatological and clinical examinations, blood sampling for immunoglobulin levels, drug levels, liver function tests, and eosinophil counts. Individuals who reported rash stopped dosing with study medication until enrolled in Part B of the study. All subjects with gemifloxacin-associated rash in Part A were expected to take part in Part B of this protocol, with the exception of those with Type I reactions (bronchospasm, angioedema, early onset, etc.) or other severe reactions (extensive, associated with systemic symptoms, abnormal labs, mucosal involvement etc.). An interim follow-up examination was conducted within 7 to 14 days of completion of dosing of Part A.

Part B Study Design

Subjects commenced Part B 4 to 6 weeks after their last dose in Part A. Depending on their Part A treatment allocation and occurrence of rash (see Figure 11), each subject entering Part B was re-randomized to receive 10 days dosing of either 320 mg orally of gemifloxacin PO, 500 mg orally of ciprofloxacin bid, or placebo. Subjects who received gemifloxacin in Part A and

reported rash were randomized to ciprofloxacin or placebo in a 3:1 ratio. Subjects who received gemifloxacin in Part A and did not report rash were randomized to gemifloxacin or placebo in a 1:1 ratio. Subjects who received ciprofloxacin in Part A and reported rash received placebo in Part B. Subjects who received ciprofloxacin in Part A and did not report rash received ciprofloxacin in Part B.

Drug administration was discontinued if rash occurred, and the same procedures as in Part A were conducted. A final follow-up examination was conducted 7 to 14 days after completion of the final dosing day in Part B.

8.4.2 Evaluation Criteria

Rash Assessment

The following assessments were made if a subject reported rash:

Clinical Rash Examination: A trained dermatologist assessed the rash using a standard Rash Questionnaire assessment within 24 hours of rash onset and prior to conducting the skin biopsy examinations. A Quality of Life assessment was conducted by subject questioning one week after the rash was reported.

Photography: Standardized photographs were taken of the rash sites.

Skin Biopsies: Three skin biopsy samples, each from unaffected and affected sites were taken. Biopsy sections underwent direct immunofluorescence examination for immunoglobulin in the skin and complement (C3) in the skin and immunophenotyping including ICAM-1, CD3 (all T lymphocytes), CD4 (T-helper lymphocytes), CD8 (T-cytotoxic lymphocytes), CD20 (all B lymphocytes) and HLA-DR (activated lymphocytes). These markers, along with any evidence of leukocytoclastic vasculitis, keratinocyte necrosis, immune complex deposition, or separation of the dermal/epidermal junction seen in conjunction with clinical signs of SJS or TEN, were used to judge the severity of any reaction observed. Histopathologists were blinded to subjects' drug regimen while reviewing the pathology.

Blood sampling: Blood samples for assessment of drug levels, liver function tests, eosinophils, and Epstein-Barr virus (EBV) screen were taken at time of assessment of rash.

Urine sampling: A sample was taken at the time of reporting of rash for urinalysis, including eosinophil counts.

Pharmacokinetic Parameters

Blood samples were collected for pharmacokinetic analysis in Part A only, on Days 1 and 6 (pre-dose and either at 1.5, 3, 6, and 12 hours or at 1, 2, 4, 8, and 24 hours following dosing.

8.4.3 Study Population

A total of 1011 healthy female subjects participated in Part A, and 873 subjects continued in Part B of the study. A total of 838 subjects completed the entire study as planned. The summary demographic statistics within and between regimens were similar.

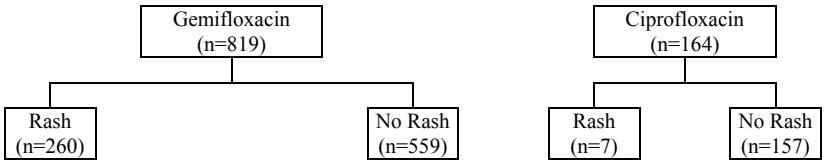
There were 138 withdrawals from Part A of this study. Of the subjects who withdrew from the study in Part A, 31 subjects withdrew due to non-rash related adverse events, and 25 withdrew due to rash related AEs. In Part B, 30 subjects withdrew; of these, 3 subjects withdrew due to rash related AEs. There were 12 non-rash related AE withdrawals. The most frequently reported AEs leading to withdrawal in the non-rash related AE group were abdominal pain, vomiting, nausea, diarrhea, and unintended pregnancy.

8.4.4 Incidence of Rash

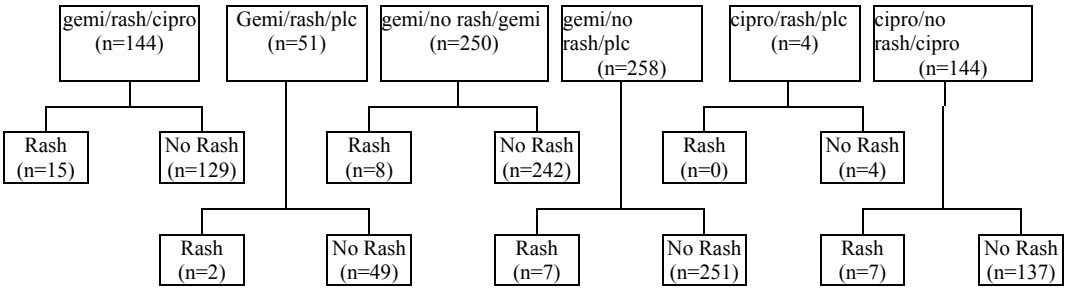
The subject disposition in the different study arms is summarized in Figure 11.

Figure 11: Subject Disposition in Part A and Part B

Part A



Part B



Part A

There were 1011 subjects entered into Part A, of which 983 were evaluable. Eight hundred and nineteen (819) subjects had received gemifloxacin (83%) and 164 (17%) received ciprofloxacin.

Two hundred and sixty (260) out of 819 (31.7%) evaluable subjects dosed with gemifloxacin and 7/164 (4.3%) evaluable subjects dosed with ciprofloxacin had a rash (this includes rash, rash erythematous and rash maculopapular) in Part A confirmed by the study dermatologist (Table 40).

Table 40: Point Estimates and 95% CI for Incidence of Rash in Part A

Regimen	Number of Subjects	Subjects with Rash	Point Estimate	95% CI	
				Normal Approximation	Exact Method
Gemifloxacin	819	260	0.317	(0.285, 0.350)	(0.286, 0.351)
Ciprofloxacin	164	7	0.043	(0.009, 0.077)	(0.017, 0.086)

This study was designed with an enriched population in order to elicit enough rashes to study and characterize. The incidence of gemifloxacin associated rash observed in Part A of this study was 31.7%, similar to the predicted incidence for this enriched population, given that the study was

specifically designed to elicit and describe skin reactions, which may have predisposed to detection bias. This may explain the relatively high incidence of rash reported in all arms of this study, including the ciprofloxacin (4.3% and 4.9%) and placebo arms (ranging from 2% to 4%).

Part B

There were 873 subjects entered into Part B, of which 851 were evaluable. Of these, 195 evaluable subjects had a gemifloxacin-associated rash in Part A. 144/195 (74%) of these subjects received ciprofloxacin and 51/195 (26%) received placebo.

Cross-sensitization

Of the subjects who experienced a gemifloxacin-associated rash in Part A and who received ciprofloxacin in Part B, 15/144 (10.4%) presented with rash, as did 2/51 subjects (3.9%) receiving placebo.

There were no reports of rash amongst the 4 subjects who received placebo after having experienced a ciprofloxacin rash in Part A. Of the 144 subjects who did not have a ciprofloxacin-associated rash in Part A and were then re-challenged with ciprofloxacin in Part B, 7 (4.9%) presented with rash.

The rate of rash in subjects randomized to ciprofloxacin following gemifloxacin-associated rash in Part A (10.4%) was approximately double that for subjects rechallenged with ciprofloxacin (4.9%). However, these results must be interpreted with caution for the following reasons:

> The study design included an inherent bias in the comparison of the two arms, as the cipro/no rash/cipro arm excludes all subjects known to have a rash with cipro on first exposure, whereas the gemi/rash/cipro arm does not. The impact of this bias was assessed statistically using a probability model to adjust for this bias.
>
> The observed difference (5.6%) was not statistically significant (95% CI: -1.2%, 12.4%); however, the study was not formally powered to show such a difference.
>
> During review of the data, it became evident that the rash rate in Part B at Center 027, was higher than at the other centers. There is currently no explanation for the high rash rates observed across all regimens at center 027. However, in light of the data observed, in particular the 100% rash rate with placebo (3/3 subjects), it was deemed appropriate to repeat the analysis, excluding this center.
>
> Removal of the data from this center reduces the incidence of rash in all subgroups and therefore does not affect the observed trends. However, the observed difference between

the two arms (gemifloxacin/rash/cipro/rash and cipro/no rash/cipro/rash) is reduced [10.4% versus 4.9% including Center 027 data and 5.9% versus 3.5% excluding center 027 data].

Sub-sensitization

Of the subjects who did not experience rash on gemifloxacin in Part A and who received gemifloxacin again in Part B, eight (8/250, 3.2%) had a rash in Part B. Similarly, for the 258 subjects who received placebo in Part B, 7/258 subjects (2.7%) had a rash in Part B, suggesting no risk for sub-clinical sensitization.

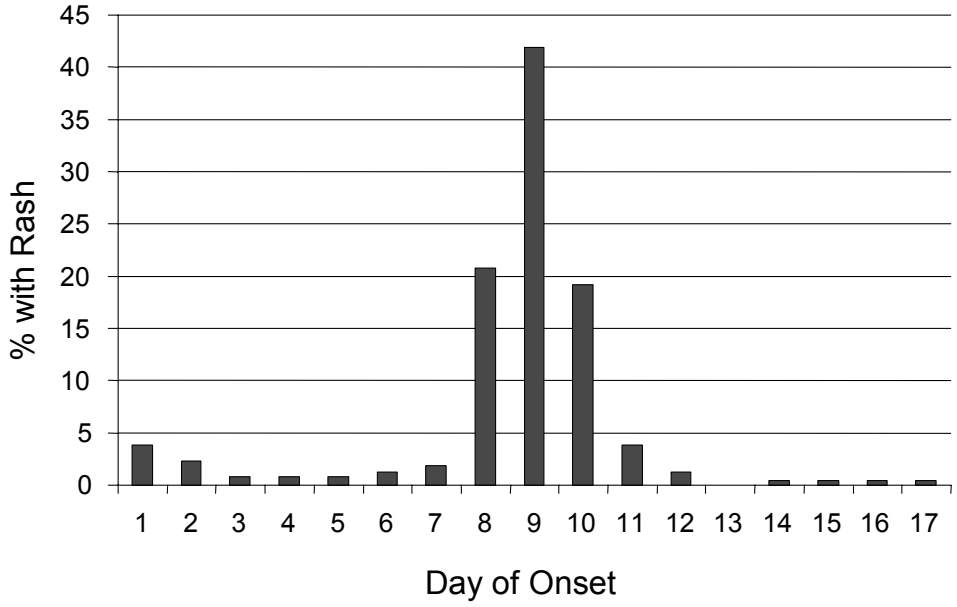
In conclusion, although this study cannot definitively establish the potential for or rate of cross-sensitization to ciprofloxacin in patients who had gemifloxacin-associated rash, the likelihood of cross-sensitization, if any, is low.

8.4.5 Description and Characteristics of Rash

Gemifloxacin Associated Rash in Part A

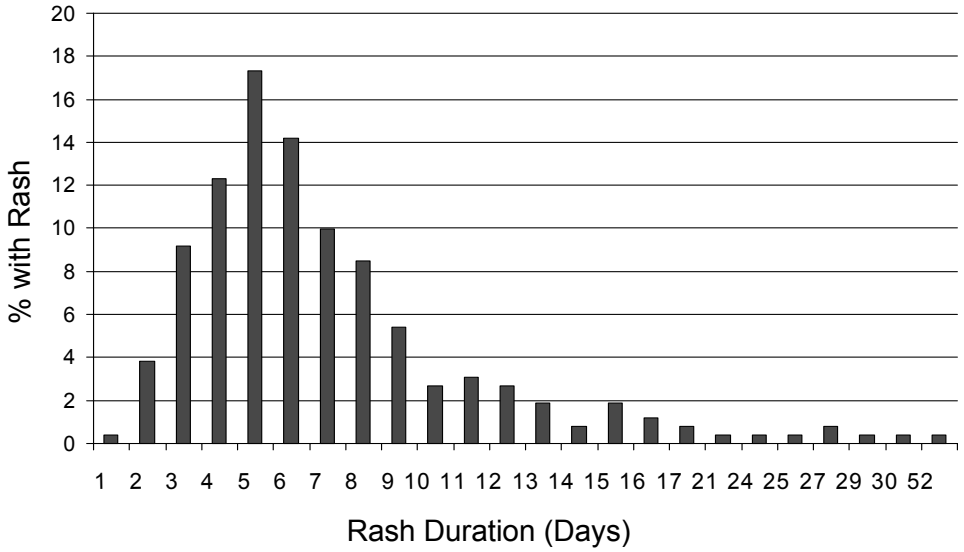
There were 260 reports of rash in the gemifloxacin arm in Part A. The majority of gemifloxacin-associated rashes occurred on days 8 to 10, with 213/260 (81.9%) subjects presenting with a rash during these three days of dosing (median day 9, range day 1 - 17) (Figure 12).

Figure 12: Gemifloxacin-Associated Rash in Part A: Distribution for Days to Onset



The median duration for gemifloxacin associated rash was 6 days (Figure 13). This is typical of the profile of rash previously observed following dosing with gemifloxacin.

Figure 13: Gemifloxacin-Associated Rash in Part A: Distributions for Duration of Rash

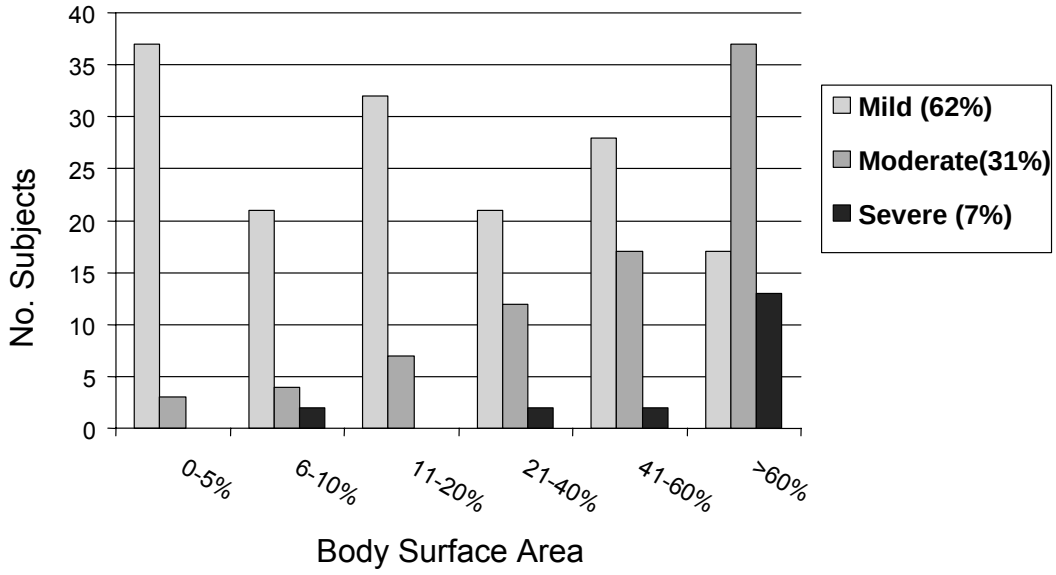


As expected, the majority (>80%) of the gemifloxacin-associated rashes were maculo-papular. In addition, many (69%) of the subjects experienced pruritus, and some of the subjects were described as having experienced urticaria (12%) plaques (11%), and skin tenderness (9%). There was no evidence of epidermal necrolysis or bullae in any of the subjects with rash.

The majority of the gemifloxacin-associated rashes were reported by the dermatologists to be mild (161/260, 62%) or moderate (80/260, 31%), and some (19/260, 7%) were considered to be severe. For the 7 subjects with ciprofloxacin-associated rash in Part A, 6 subjects reported mild rash and 1 subject reported moderate rash.

The body surface area involved varied from <5% to "total body rash" (Figure 14). Investigator opinion of severity (no guidance given) seemed to correlate with the extent of the rash.

Figure 14: Gemifloxacin-Associated Rash in Part A: Severity and Body Surface Area Affected



The incidence of rash by use of hormonal therapy and previous fluoroquinolone therapy was investigated; however, there was no clear evidence to suggest that the incidence of gemifloxacin-associated rash is changed with the use of hormonal therapy or related to previous fluoroquinolone therapy.

Investigators were asked to check for pre-defined systemic signs and symptoms. Findings were as summarized in Table 41. None of these individual signs and symptoms was associated with other signs or symptoms in a way suggestive of a clinical syndrome. There were no reports of rash associated with fever and eosinophilia or of rash associated with hepatitis and eosinophilia.

Table 41: Signs and Symptoms Associated with Rash in Part A

Sign or Symptom	Number (%)* of Subjects
Urticaria	26 (10)
Facial edema	12 (4.6)
Mucosal involvement	12 (4.6)

* Calculated as percentage of the 260 subjects with gemifloxacin-associated rash in Part A.

In only 0.6% of gemifloxacin-treated volunteers (4/819) in Study 344 was urticaria actually reported as an adverse event, as opposed to being scored as urticaria on the rash assessment form. Time to onset for these 4 volunteers was 9, 23, 40, and 46 days. In one of these patients the urticaria was reported on the day of re-challenge with ciprofloxacin, 46 days after the initial gemifloxacin dose. Thus, it would appear that the number of rashes recorded as urticaria (n = 26) in Part A via the rash assessment form is artificially elevated relative to the number of volunteers for whom the adverse event was actually reported as urticaria (n = 4). The clinical course, appearance (photos), biopsy findings, and cross sensitization experience in the subjects described as having urticaria are indistinguishable from those not described as having urticaria. This suggests these are not type I hypersensitivity findings but rashes that had an urticarial appearance. The incidence of urticaria as an adverse event was similar in both the clinical phase II/ III study database (0.5%), the overall phase I safety data pool (0.5%), and Study 344 (0.6%).

There were few subjects with mucous membrane involvement, symptoms associated with type I reactions or systemic symptoms. Mucous membrane involvement was recorded in 12 subjects. There were concomitant findings such as dryness or aphthae. Facial edema was part of the erythema on the face by and large. One had an urticarial rash and another had diarrhea. The case report forms (CRFs) were constructed to record symptoms and signs suggestive of angioedema. In neither case were these findings suggestive of angioedema.

No association with elevated liver function test results was observed in subjects who experienced a rash in Part A. The incidence of hepatic markers was extremely low (Table 42).

Table 42: Hepatic Markers in Part A

	Rash (n=260)	No Rash n=559
ALT	0	0
Alk Phos	0	0
AST	0	2 (0.4%)
Total Bilirubin	2 (0.8%)	4 (0.7%)
GGT	0	0

GGT = γ-glutamyl transpeptidase

Increases in peripheral eosinophil counts were infrequent in any of the subjects, regardless of treatment group or presence or absence of rash (Tables 43 and 44).

Table 43: Number (%) of Subject Sessions with Eosinophil Count Transitions, No Rash

x ULN	Part A		Part B		
	Gemifloxacin 320 mg	Ciprofloxacin 500 mg	Gemi/nrash/gemi 320 mg	Gemi/nrash/plc	Cipro/nrash/cipro 500 mg
>1	22/566 (3.9)	7/156 (4.5)	2/250 (2.0)	6/252 (2.4)	5/141 (3.5)
>1.5	6/566 (1.1)	1/156 (0.6)	3/250 (1.2)	2/252 (0.8)	1/141 (0.7)
>2	4/566 (0.7)	1/156 (0.6)	1/250 (0.4)	1/252 (0.4)	1/141 (0.7)
>3	2/566 (0.4)	0	0	1/252 (0.4)	0
>5	0	0	0	1/252 (0.4)	0
>8	0	0	0	0	0

ULN = upper limit of normal (normal is 0.05 to 0.55 x 10^9 cells/L)

Table 44: Number (%) of Subject Sessions with Eosinophil Count Transitions, Rash

x ULN	Part A		Part B				
	Gemi-floxacin 320 mg	Cipro-floxacin 500 mg	Gemi/rash/ cipro	Gemi/rash/ plc	Gemi/ nrash/gemi 320 mg	Gemi/ nrash/plc	Cipro/ nrash/cipro 500 mg
>1	12/260 (4.6)	0	0	0	0	1/7 (14.3)	0
>1.5	3/260 (1.2)	0	0	0	0	0	0

ULN = upper limit of normal (normal is 0.05 to 0.55 x 10^9 cells/L)

Gemifloxacin and Ciprofloxacin Associated Rashes in Part B

The median day of onset of rash for all dose groups in Part B was earlier than that seen in Part A of the study for subjects dosed with gemifloxacin (Table 45).

Table 45: Summary Statistics for Day of Rash Onset in Part B

	n	Mean	SD	Median	Min	Max
Gemi/rash/cipro	15	4	2.9	2	1	10
Gemi/rash/plc	2	6	4.9	6	2	9
Gemi/no rash/gemi	8	6	5.7	5	1	18
Gemi/no rash/plc	7	6	7.9	2	1	23
Cipro/rash/plc	0	-	-	-	-	-
Cipro/no rash/cipro	7	6	2.6	6	3	10

However, the median duration of rashes that occurred following dosing with gemifloxacin in Part B (i.e., gemi/no rash/gemi group) was similar as seen for gemifloxacin-associated rashes in Part A.

Similarly, for those subjects that received ciprofloxacin in Part B, the median rash duration was similar (i.e., 3 days in the gemi/rash/cipro group or 4 days in the cipro/no rash/cipro group) as was seen for ciprofloxacin-associated rashes in Part A. For those subjects that had a rash after receiving placebo in Part B (i.e., gemi/no rash/placebo), the median duration was 5 days, i.e., shorter than for subjects receiving gemifloxacin in Part B but longer than subjects receiving ciprofloxacin in Part B.

The appearance of the rashes seen in Part B was the same as for Part A, i.e., maculo-papular, and some subjects had pruritus.

Two subjects who experienced a rash following gemifloxacin in Part A were accidentally re-exposed to gemifloxacin in Part B. One of these subjects received a full 10-day course of gemifloxacin, while the other was withdrawn after one dose. Neither subject experienced a second rash.

Overall, rashes in Part B were milder than those described in Part A and were not associated with any systemic signs or symptoms. This further supports the view that gemifloxacin exposure does not result in a clinically significant sensitization to other members of the quinolone class.

Pruritus was reported as an AE in 11.4% (96/841) of subjects administered gemifloxacin versus 6.5% (11/170) of the ciprofloxacin group in Part A of the study. Although investigators described the rash as pruritic for many (69%) of the gemifloxacin subjects, it is of note than only 16.2% (42/260) of gemifloxacin subjects with a dermatologically confirmed rash in Part A also reported pruritus as an AE. In Part B, the frequency of reporting for pruritus as an AE was 4.3% (11/258) of gemifloxacin subjects, 7.1% (21/296) of ciprofloxacin subjects, and 4.8% (15/314) of placebo subjects. Medication was given to relieve itching in 3.2% (27/841) of gemifloxacin treated subjects compared to a single case on ciprofloxacin in Part A, 2% (6/296) on ciprofloxacin in Part B, and 1.6% (5/314) on placebo.

8.4.6 Histopathological Review of Rash

Biopsy samples were obtained from 288 subjects with rash from Parts A and B. A total of 576 slides (from unaffected and affected skin sites) were analyzed for routine histology. Immunofluorescence was done on 2880 slides (IgG, A, M & C3 plus negative and positive controls), and immunohistochemistry (immunophenotyping) was done on 4032 slides (CD3, 4, 8, 20, ICAM & HLADR plus negative and positive controls).

There were no pathological changes of clinical significance in unaffected skin. The most common finding in the affected skin was a mild superficial perivascular lymphocytic infiltrate. There were 10 cases of affected skin with moderate superficial or deep and superficial perivascular lymphocytic infiltrate. There were 10 cases with eosinophils in the infiltrate (9 affected skin samples and 1 unaffected). The lymphocytic infiltrate was T-cell type, both CD4 and CD8 cells present with no specific cell type predominance. There was activation of endothelial cells as indicated by their staining for ICAM and HLADR. This was in the absence of any evidence of vasculitis in all the biopsies. HLADR staining of dendritic cells was noted in a significant number of cases, although this was not part of the original components to be evaluated.

Immunofluorescence showed in some biopsies of affected and unaffected skin faint deposits of IgM & or C3 in dermal vessels "lumina." One case showed linear IgM along the basement membrane in both affected and unaffected skin.

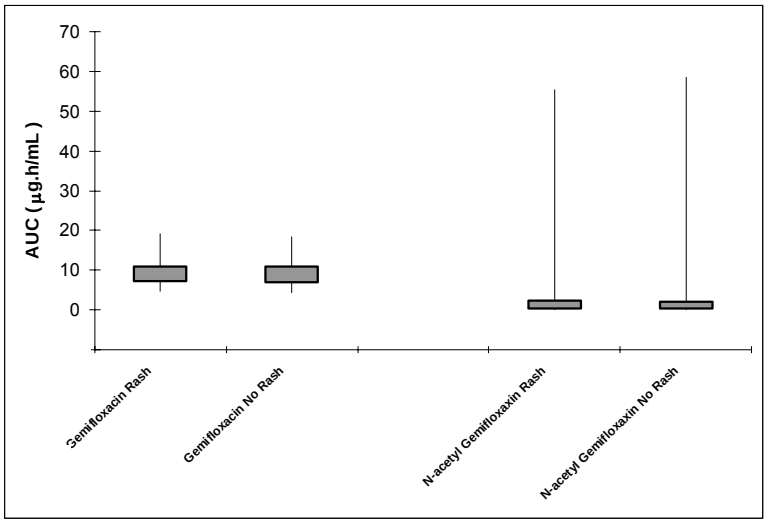
One case showed scratching excoriation, and there was one incidental case of miliaria pustulosa. It is important to note that there were no signs of epidermal necrosis, and no bulla formation in the epidermis or at the dermo-epidermal junction. There was no necrotizing vasculitis, and no pathological changes in the eccrine glands.

In summary, the histological evaluation of the biopsy samples showed a mild perivascular infiltrate of T cells without predominance of CD4 or CD8. There were no biopsy samples with signs of vasculitis, bulla formation, or epidermal or eccrine necrosis. The histopathology was consistent with the clinical observation of uncomplicated exanthematous morbilliform eruptions.

8.4.7 Pharmacokinetic Evaluation

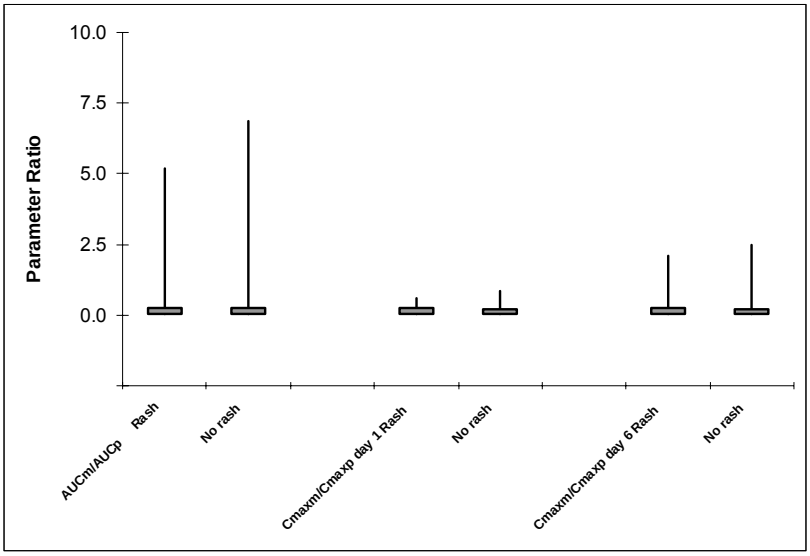
The use of sparse pharmacokinetic sampling in conjunction with population pharmacokinetic analysis of gemifloxacin and N-acetyl gemifloxacin provided accurate estimates of population pharmacokinetic parameters. Plasma concentration-time data were analyzed separately for gemifloxacin and N-acetyl gemifloxacin and included data from 838 and 837 subjects, respectively. A total of 7943 and 7934 plasma concentration-time data, respectively, were used in the final population pharmacokinetic analysis. The mean concentration-time course and 95%-confidence intervals for parent compound and metabolite concentrations were practically identical in subjects showing rash and no rash. The pharmacokinetic exposure parameters of gemifloxacin and N-acetyl gemifloxacin in subjects who experienced rash did not differ from those without rash. The summary statistics for these parameters are presented graphically as box [95% CI around geometric mean titer (GMT)] and whisker (range) plots in Figure 15.

Figure 15: AUC for Gemifloxacin and N-Acetyl Gemifloxacin in Subjects with and without Rash (Box-Whisker Plot)



As metabolic phenotype information was not formally evaluated in the pharmacokinetic model, the ratio between the AUC of the metabolite and parent compound (AUCmet/AUCpar) was used to identify potential differences between poor and fast metabolizers in terms of sensitivity to gemifloxacin. The AUC and C_{max} ratios were similar in subjects with and without rash. These results are summarized in Figure 16.

Figure 16: Pharmacokinetic Parameter Ratios in Subjects with and without Rash (Box-Whisker Plots)



The pharmacokinetic analysis showed that exposure to gemifloxacin and N-acetyl gemifloxacin in subjects who experienced rash was very similar to the exposure in subjects who had no rash, with nearly complete overlap of the 95% confidence intervals for AUC and C_{max} in these 2 sub-populations.

Despite the lack of information on the metabolic phenotype, the use of AUCmet/AUCparent ratios provided an accurate estimate of potential differences in poor and fast metabolizers. The mean ratios and 95%-confidence intervals in subjects who experienced rash were similar to those for subjects without rash.

These findings strongly suggest that neither the differences in drug exposure nor the extent of acetylation of gemifloxacin explained the occurrence of rash.

8.4.8 Laboratory Tests

Overall there was a very low frequency of subject sessions with laboratory test results of "potential clinical concern" in all subject populations, regardless of what dose regimen they received or whether they experienced a rash or not. There were also no clinically significant changes (F3 transitions) in LFTs and eosinophils in any of the dosing regimens examined, regardless of whether they experienced a rash or not.

8.4.9 Conclusions from Study 344

Study 344, involving 1,011 young adult females, was conducted to further characterize the gemifloxacin-associated rash. The study intentionally enrolled subjects most likely to develop a rash following exposure, namely female subjects aged <40 years, who were then exposed to 10 days of treatment, which was longer than the intended duration of treatment, up to 7 days (at the time of the 2003 approval and now only 5 days as proposed in the current sNDA), in order to maximize the incidence of rash. The incidence of gemifloxacin-associated rash in this enriched population was 31.7%. By comparison, the overall incidence of rash in the clinical trials was 3.5%.

The results of Study 344 could not definitively establish the potential for, or rate of, cross-sensitization to ciprofloxacin in patients who had gemifloxacin-associated rash because there was an inherent bias in comparing the 2 arms; the cipro/no rash/cipro arm excluded all subjects known to have a rash with ciprofloxacin on first exposure, whereas the gemi/rash/cipro arm did not. However, after proper statistical adjustment and evaluation, cross-sensitization, if any, was at a low rate. There was no evidence of sub-clinical sensitization in subjects who did not develop a rash on first exposure to gemifloxacin and who were re-exposed to a subsequent course of 10 days of gemifloxacin. The characteristics of rash observed in the study were consistent with those of rash observed in the clinical trial program. There were no reports of serious cutaneous reactions such as SJS or TEN and no known cases of other sequelae.

The nature of the rash was consistent with a typical, exanthematous drug eruption. The pathology seen in almost all cases was a mild, superficial, perivascular lymphocytic reaction, the classic pathology of mild drug rash. There was no evidence of pathology as seen with more severe skin reactions to drugs. The immunofluorescent findings were mild and of no clinical significance. The immunohistochemistry showed that infiltrating lymphocytes were mostly CD4+, with some CD8+ cells. There was no demonstrable predominance of CD8+ cells as is sometimes seen in serious rashes.

There was no notable difference in exposure to gemifloxacin or in extent of N-acetylation of gemifloxacin in subjects with or without rash, as indicated by AUCmet/AUCparent ratios. The occurrence of rash as an adverse event did not therefore appear to be related to the inter-individual differences in systemic exposure to gemifloxacin, or its N-acetyl metabolite.

8.5 Prescribing Use Study: Sensitization Analyses

As a post-marketing commitment to the FDA, Oscient is conducting an ongoing study to analyze the prescribing patterns and utilization of Factive® (gemifloxacin mesylate) tablets in the US. Oscient selected i3 Innovus, a subsidiary of Ingenix®, as the contract research organization to obtain the prescribing use data from its affiliated health plan, UnitedHealthcare. The first of three annual interim reports was prepared and submitted to FDA in June 2006 and contained data on 4,910 patients prescribed gemifloxacin during the first year of marketing (September 1, 2004 to August 31, 2005).

Analyses were performed on this study population to assess further the risk of cross-sensitization and sub-clinical sensitization with the use of gemifloxacin. The results of these analyses are provided below; additional detail can be found in the Executive Summary in Appendix 1. For all analyses, the occurrence of a rash associated with the use of gemifloxacin or other quinolones was determined by searching for the presence of any of a series of discrete ICD-9 codes during and up to 14 days after treatment.

8.5.1 Cross-Sensitization

Cross-sensitization was defined as the occurrence of rash upon subsequent exposure to another quinolone in patients who had previously developed a rash when treated with gemifloxacin.

147 out of the 4,910 patients in the dataset, or 3%, had at least one of these ICD-9 codes within 14 days of any gemifloxacin prescription. Notably, of the 147 patients with an initial gemifloxacin rash, 21 (14.3%) were subsequently treated with another quinolone. One of those 21 patients (4.8%) had an identified rash associated with the quinolone exposure.

Of the 4,763 patients who had no rash associated with use of gemifloxacin, there were 870 patients who had exposure to a quinolone after their initial exposure to gemifloxacin. Of the 870 patients, there were 9 patients (1.0%) who had an identified rash with the quinolone exposure. The subsequent quinolones received by the 9 patients were ciprofloxacin HCl (n=3), gatifloxacin (n=1), levofloxacin (n=3), and moxifloxacin HCl (n=2).

These findings are supportive of the conclusion from Study 344 that the risk with gemifloxacin of cross-sensitization to other quinolones is low and additionally that prior exposure to gemifloxacin even in patients without rash does not increase the risk of developing rash upon exposure to another quinolone.

8.5.2 Sub-clinical Sensitization

Sub-clinical sensitization was defined as the occurrence of rash in patients receiving gemifloxacin who had previously received gemifloxacin without developing a rash.

144 out of the 4,910 patients in the dataset, or 2.9%, had at least one of the rash ICD-9 codes during or up to 14 days after their initial gemifloxacin treatment episode. Of the 4,766 patients who had no rash associated with their first treatment episode, there were 244 patients who had subsequent exposure to gemifloxacin. Of those 244 patients, there was one patient (0.4%) with identified rash upon re-exposure to gemifloxacin.

This finding supports the conclusion from Study 344 that the risk of sub-clinical sensitization with gemifloxacin is low.

8.6 Cardiac Safety

8.6.1 Hypotension

A very small number of patients (≤0.2% out of 8119 gemifloxacin-treated patients treated and 0.3% of 5248 comparator treated patients) (≤0.2% of 1122 5-day ABS patients) reported hypotension. The level of severity was similar in the gemifloxacin treated patients and the comparators treated patients (gemifloxacin N=8119; total = 18 of which 13 mild, 3 moderate and 2 severe) (comparator group N= 5248; total = 15 of which 7 mild, 7 moderate, and 1 severe). There were no cases of either moderate or severe hypotension in the 5-day ABS group (gemifloxacin 5 day ABS group N=1122; total = 2 of which 2 mild, 0 moderate, and 0 severe).

8.6.2 QTc Interval Changes

Some fluoroquinolones are associated with prolongation of the electrocardiographic QT interval. Nonclinical studies, while not quantitatively predictive of clinical effect, can help to guide the level of definitive assessment of QT interval changes in the relevant species, man. Gemifloxacin caused reversible QT interval prolongation in dogs dosed intravenously, but not orally, at multiples of clinical exposure (Section 4.2). Comparative *in vitro* assays showed gemifloxacin to be of relatively low potency in prolonging APD_{90} in Purkinje fibers or inhibiting the hERG channel. However, in accordance with recommended best practice, gemifloxacin's potential to alter the QTc interval in humans was evaluated in substantial numbers of healthy volunteers and patients. As patients were not excluded from clinical trials because of risk factors for QT prolongation, the population studied is considered to be broadly representative of that expected in clinical use of gemifloxacin.

Only subjects with paired, manual QT recordings are included in the quantitative analyses. Electrocardiogram (ECG) waveforms were recorded (≥3 leads simultaneously) at 25 mm/sec (10 mm/mV) for at least 3-5 complexes. QT intervals were measured manually and corrected (QTc) using the most established formula, Bazett's, by two independent cardiologists. A third cardiologist reviewed traces showing treatment-emergent abnormalities. All ECGs were analyzed in a blinded fashion. "Off-therapy" ECGs in patients were recorded either before treatment or at least 5 half-lives after the last dose of gemifloxacin; on-therapy values were obtained approximately at plasma C_{max}.

Gemifloxacin's potential to alter QTc was assessed with regard to risk factors for QTc prolongation, both general (age, gender), and individual (co-morbidities, abnormal ECG, electrolyte status, concurrent medication known to affect QTc). Co-medications capable of prolonging the QTc interval, and which compete for or inhibit cytochromes P450, particularly CYP3A4, are potentially an issue. Gemifloxacin does not inhibit and is not cleared by cytochrome P450-dependent metabolism; therefore this type of drug-drug interaction is not of concern.

Surrogate evidence of potential arrhythmias (syncope, convulsions, cardiac arrest, sudden death), and treatment-emergent changes in waveform morphology, were evaluated. Mean and individual QTc intervals were considered. Reference upper limits for the absolute QTc interval in males (450 msec) and females (470 msec), for "marked" prolongation (absolute value >500 msec), and for change from baseline in QTc interval (>60 msec) were used. Individual changes from baseline of <30 msec are generally considered unlikely to raise significant concerns about the potential risk of arrhythmias (CPMP 1997).

8.6.3 Clinical Pharmacology Studies

Evaluable manual QTc measurements were available for 1395 healthy volunteer sessions. Study 344 contributed the largest amount of repeated dose volunteer ECG data (831 subjects receiving a single dose, and 788 receiving repeated doses), and in a female population; female gender is a risk factor for QTc prolongation.

8.6.3.1 Mean QTc Change

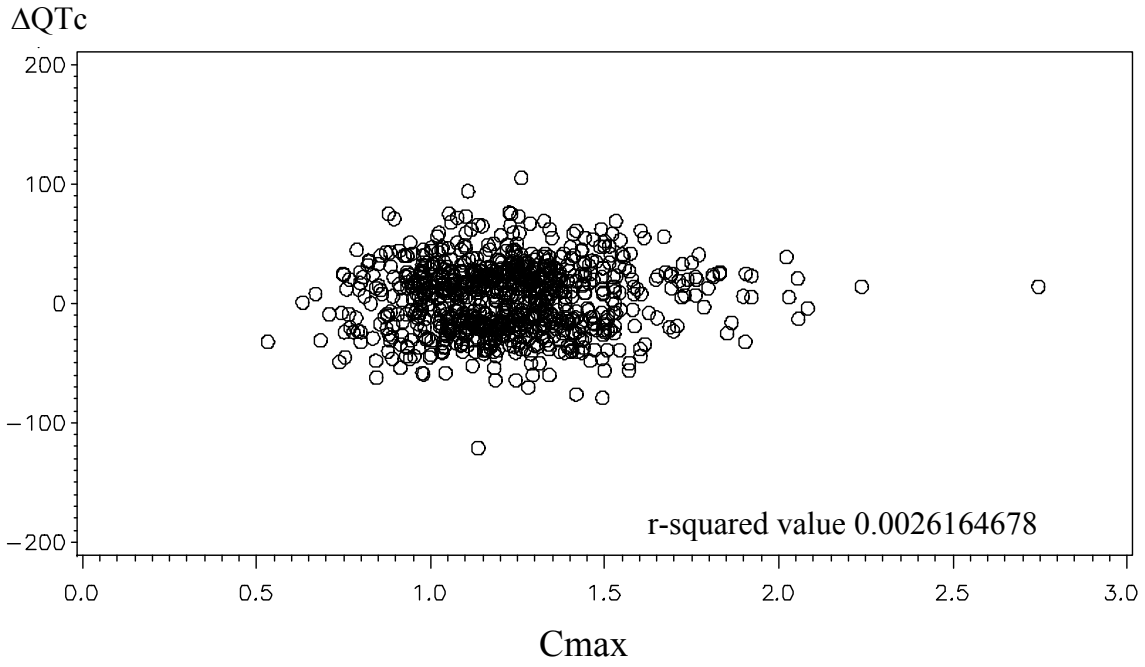
In Study 344, repeated administration of gemifloxacin or ciprofloxacin produced similar, minor increases (4.9 msec) in mean QTc compared with baseline (Table 46). Ciprofloxacin has not been associated clinically with consequences of QTc prolongation.

Table 46: Mean Change from Baseline in QTc Interval Following Repeated Dosing in Healthy Volunteers (Study 344)

	Gemifloxacin	**Ciprofloxacin**	
Part A	**N=788**	**N=160**	
Mean (msec)	4.9	4.9	
SD	25.10	23.85	
	Gemifloxacin	**Ciprofloxacin**	**Placebo**
Part B	**N=240**	**N=256**	**N=297**
Mean (msec)	8.3	12.7	5.8
SD	26.21	26.63	24.52

QTc prolongation in Study 344 subjects showed no evidence of correlation with plasma gemifloxacin C_{max} values, even when the largest observed change from baseline in QTc interval duration (i.e., on either Day 1 or Day 6) was plotted against the corresponding C_{max} value for each subject (Figure 17).

Figure 17: Highest Observed Change in QTc Interval (ΔQTc) versus Corresponding Maximum Plasma Gemifloxacin Concentration (C_{max}) for Subjects Given a Single or Repeated Dose of Gemifloxacin in Study 344



8.6.3.2 QTc Values Outside Pre-set Reference Limits

On-therapy QTc values of potential clinical concern in non-Study 344 volunteers were distributed similarly in subjects receiving gemifloxacin or placebo. There were no clear trends for values outside the reference ranges to be more frequent with increasing dose, repeated doses, or in elderly compared with younger subjects. There was no discernible relationship between QTc and plasma gemifloxacin C_{max} values. In Study 344, few subjects had QTc values >470 msec (Table 47), and of 28 with a change in QTc >60 msec, 8 had transient increases only after the first dose. No gemifloxacin-treated subject with a QTc outside normal limits in Part A showed any abnormal values in Part B. In the overall non-patient volunteer database of 1395 gemifloxacin subject sessions with manual QT recording, absolute QTc values exceeded 450 msec in males and 470 msec in females on 16 occasions (1.1%), compared with a placebo rate of 7/415 (1.6%). Increases in QTc of >60 msec occurred on 42/1395 (3.0%) sessions in subjects given gemifloxacin, and on 17/415 (4.0%) sessions in subjects given placebo.

Table 47: Number (%) of Healthy Volunteers with QTc >470msec On-Therapy, or Change in QTc >60msec from Baseline (Study 344)

		Gemifloxacin		Ciprofloxacin			
		N=788		N=160			
Part A	**Range**	**n**	**%**	**n**	**%**		
QTc on-therapy	>470msec	3	0.4	2	1.3		
Change in QTc	>60msec	28	3.6	3	1.9		
		Gemifloxacin		**Ciprofloxacin**		**Placebo**	
		N=240		**N=256**		**N=297**	
Part B	**Range**	**n**	**%**	**n**	**%**	**n**	**%**
QTc on-therapy	>470msec	0	-	6	2.3	3	1.0
Change in QTc	>60msec	7	2.9	23	9.0	10	3.4

8.6.4 Patient Studies

Paired ECG recordings were obtained in 436 of 8119 patients (407 with paired QTc) in the gemifloxacin group and 400 of 5248 patients (380 with paired QTc) in the all-comparators group. Females and older patients were well represented in both groups (Table 48).

Table 48: Distribution of Gender and Age of Patients with Paired QTc Recordings

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

Approximately 45% of patients with paired QTc recordings in both groups had at least one co-morbid condition predisposing to QT prolongation (Table 49). Off-therapy ECG abnormalities associated with risk factors for QT prolongation were present in 38.8% (169/436) of patients in the gemifloxacin group and 35.8% (143/400) of patients in the all-comparators group (Table 50).

Table 49: Proportion of Patients with Paired QTc Who had Co-morbid Conditions Known to Predispose to QTc Prolongation

Conditions	Treatment Group			
	Gemifloxacin 320 mg od		All Comparators	
	N=407		N=380	
	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)

Table 50: Number (%) of Patients with Selected Off-Therapy ECG Abnormalities

ECG Abnormality	Treatment Group			
	Gemifloxacin 320 mg PO N=436		All Comparators N=400	
	n	(%)	n	(%)
Patients ≥ 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)

Of patients with paired QTc values, 12.5% (51/407) patients in the gemifloxacin group and 16.1% (61/380) patients in the all-comparators group with paired QTc values were receiving concomitant medications associated with QT prolongation (identified from a list including antiarrhythmics, antidepressants, anti-infectives, antiprotozoals, neuroleptics, antihistamines, vasodilators, and other miscellaneous specific agents).

8.6.4.1 Mean QTc Change

Mean changes in QTc interval in all patients in the gemifloxacin and all-comparators groups for whom paired QTc measurements were available were very small and not statistically different (Table 51).

Table 51: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements

Change in QTc Interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	407	380
Mean	2.56	-0.39
SD	24.52	22.64
Mean Treatment Difference	2.95 msec	
95% Confidence Interval	(-0.36, 6.26)	
p value	0.08	

Further analysis of these patients by risk factors for QTc interval prolongation, including female gender (Table 52), age greater than 65 years (Table 53), presence of comorbid conditions known to predispose toward QTc interval prolongation (Table 54), and concomitant medications recognized as associated with QTc prolongation (Table 55), also showed that mean changes in QTc interval were clinically unimportant.

Table 52: Mean QTc Interval Change from Off-Therapy Value in Female Patients with Paired QTc Measurements

Change in QTc interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	179	156
Mean	4.45	-1.36
SD	23.31	24.04
Mean Treatment Difference	5.81 msec	
95% Confidence Interval	(0.72, 10.91)	

Table 53: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements, and Aged over 65 Years

Change in QTc interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	152	142
Mean	1.74	0.67
SD	26.87	23.08
Mean Treatment Difference	1.06 msec	
95% Confidence Interval	(-4.71, 6.83)	

Table 54: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements, and with Comorbid Conditions Known to Predispose to QTc Prolongation

Change in QTc interval (msec)	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	187	168
Mean	1.52	-1.68
SD	25.58	22.19
Mean Treatment Difference	3.20 msec	
95% Confidence Interval	(-1.83, 8.22)	

Table 55: Mean QTc Interval Change from Off-Therapy Value in Patients with Paired QTc Measurements who Received Concomitant Therapy Associated with QTc Prolongation

Change in QTc interval	Treatment Group	
	Gemifloxacin 320 mg PO	All Comparators
N	51	61
Mean	-0.56	7.42
SD	29.51	18.72
Mean Treatment Difference	-7.98 msec	
95% Confidence Interval	(-17.1, 1.13)	

8.6.4.2 Distribution of On-Therapy Changes in QTc in Patients

The proportions and distribution of patients with changes in QTc from off-therapy to on-therapy were generally similar in the gemifloxacin and all-comparators groups (Table 56).

Table 56: Number (%) of Patients with Changes in QTc from Off-Therapy Value in Patients with Paired QTc

QTc Change (msec)	Treatment Group			
	Gemifloxacin 320 mg PO N=407		All-Comparators N=380	
	n	(%)	n	(%)
≥ 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)

Of the 5 (1.2%) gemifloxacin patients with treatment-emergent increases in QTc of >60 msec, 2 had relevant co-morbid conditions, as did 1 of 2 patients in the all-comparators group. Four of 5 gemifloxacin-treated subjects with a QTc interval change of 51-60 msec also had co-morbidities.

Five patients (4 treatment-emergent) in the gemifloxacin group and one receiving amoxicillin-clavulanate had absolute QTc values >500 msec on-therapy (Table 57). Of those receiving gemifloxacin, one (207.057.31027) had a QTc of 512 msec off-therapy, and 503 msec on-therapy, with co-morbidity and relevant concomitant medication. Two with treatment-emergent values >500 msec had co-morbidities (011.182.25945, hypokalemia; 185.364.29739, hypertension, left ventricular hypertrophy and PVCs, chronic obstructive pulmonary disease (COPD), pleurisy, peripheral vascular disease, coronary artery disease, anemia, glaucoma, cataracts, depression and inguinal hernia), one (011.158.05533) was receiving concomitant medication (mianserin) associated with ventricular fibrillation and ectopic beats, and one (185.357.29796) had multiple co-morbidities (left bundle branch block, coronary artery disease, COPD, left ventricular diastolic dysfunction, pulmonary edema, anemia, osteoarthritis and dementia) and relevant concurrent medication. The patient with treatment-emergent QTc >500 msec while receiving amoxicillin-clavulanate also had a co-morbid condition.

Table 57: Number (%) of Patients with QTc >500 msec in Patients with Paired QTc

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

8.6.4.3 Treatment-Emergent Qualitative Changes in ECG Waveform Morphology

Changes in T wave and S-T segments, and treatment-emergent U waves, may indicate drug effects related to arrhythmias. Assessment of paired ECGs revealed no consistent pattern of change in patients with minor morphological alterations of ECG waveform in either the gemifloxacin or the all-comparators group (Table 58). No patient had more than one such abnormality. Two patients given gemifloxacin had treatment-emergent non-specific S-T changes or T wave inversion associated with an increase in QTc of >60 msec, but without sequelae.

Table 58: Number (%) of Patients With Paired ECGs Showing Qualitative Changes in T Wave or S-T segment, and Treatment-Emergent U Wave

ECG Abnormality	Treatment Group			
	Gemifloxacin 320 mg PO N=436		All-Comparators N=400	
	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)**

* Treatment-emergent T wave inversion in 1 patient (049.030.11483) was later confirmed by the reviewer as normal.
+ S-T segment depression was reported in 1 patient (011.038.05278) randomized to gemifloxacin who received 1 dose of study medication (placebo) and was withdrawn prior to receiving active study medication.
# Total number of patients with qualitative treatment-emergent changes in at least 1 of the tabulated ECG abnormalities

8.6.4.4 Clinical Conditions Associated with Arrhythmias

Incidences of syncope, convulsions, sudden death and cardiac arrest, which may be surrogates for drug-induced arrhythmias, are shown in Table 59.

Table 59: Number (%) of Patients with Syncope, Convulsions, Sudden Death, and Cardiac Arrest (Overall Safety Population)

Preferred Term	Gemifloxacin N=8119		All Comparators N=5248	
	n	%	N	%
Syncope	11	(0.1)	5	(0.1)
Convulsions*	1	(<0.1)	4	(0.1)
Sudden death	3	(<0.1)	0	(0.0)
Cardiac arrest	8	(0.1)	5	(0.1)

* Convulsions include the preferred terms convulsions and convulsions grand mal.

Rates of cardiac arrest reported as SAEs were low and similar in the gemifloxacin and all-comparators groups. Death occurred in 7 of 8 patients from the gemifloxacin group, and in 4 of 5 from the all-comparators group. In 6 patients (008.044.12477, 207.114.30425, 061.066.13701, 068.009.14233, 287.023.60078, and 112.012.35903) given gemifloxacin, cardiac arrest happened 1-31 days after completion of treatment. The investigator reported the event as unlikely to be related to study medication in one of these cases, and unrelated in the remainder, and to be associated with underlying disease. Five patients had serious pre-existing cardiac conditions, and in the fifth, respiratory insufficiency was associated with impregnation syndrome as a consequence of bronchogenic carcinoma. One ABECB patient (070.083.04405; male, aged 70), who had decided not to visit his doctor after a study x-ray showed right lobular pneumonia, died approximately two days after starting treatment with gemifloxacin. Cardiac arrest was linked to bronchopneumopathy of the right lobe; the investigator reported that neither event was related to treatment with gemifloxacin. The eighth patient (112.070.36346; female, aged 73), with a medical history including hypertension, supraventricular tachycardia and COPD, had chest pain 3 days after starting treatment with gemifloxacin. Cardiac arrest occurred 6 days after the last dose, during cardiac catheterization scheduled as a result of the earlier chest pain. The patient was stabilized, and the event resolved.

Cardiac arrest in the 5 patients given comparator drugs was also considered to be unrelated to study medication, or unlikely to be related. Two patients (049.086.10572 and 069.129.03278) died after cardiac arrest 7 and 22 days respectively after the last dose; in one of these, polytrauma from a suicide attempt was also cited as a cause of death. Of those in whom cardiac arrest occurred during treatment, two (185.601.29472 and 012.145.10215) had pre-existing cardiac conditions, and the third (112.800.35200) had a spontaneous pneumothorax suspected to be associated with perforation of an emphysematous bulla.

The 3 sudden deaths in the gemifloxacin group were all considered by the investigators to be unrelated to study medication. In one patient (012.077.10306; male, aged 62) found dead one day after the last dose, an autopsy indicated pericardial tamponade due to rupture of a cardiac

aneurysm related to an old myocardial infarction to be the cause of death. Another patient (013.047.02585; female, aged 90) died 8 days after the last dose of gemifloxacin; death was ascribed to natural causes. The patient's medical history included uterine fibroma and hysterectomy, glaucoma, arterial hypertension, anxiety, complicated cystitis and hypokalemia; the last is a potential risk factor for QTc prolongation, but there were no other pre-disposing conditions, or co-medications, of marked significance. The third (011.11.0511; male, aged 56), died on the day after the first dose of gemifloxacin. His history showed alcoholism and heavy smoking, and a fall at home prior to hospitalization for pneumonia. The study screening ECG indicated only sinus tachycardia, and the on-therapy ECG was normal. Blood parameters included only mildly elevated AST and creatine kinase, and a slightly low hemoglobin level. The investigator reported that death was unlikely to be related to study medication.

Convulsions were more frequent in the all-comparators group than in the gemifloxacin group. In the single patient (061.063.13589; female, aged 28) given gemifloxacin, self-resolving petit mal-like symptoms occurred 3 days after the last dose, and resolved without therapy. The event was described by the investigator as of suspected relationship to treatment, but non-serious, and the patient completed the course of gemifloxacin without further incident. In the all-comparators group, generalized tonic-clonic seizure occurred on the last day of administration of cefuroxime axetil to a male aged 35 (009.572.23940), and was considered possibly related to treatment, although the consequences of previous stroke could not be excluded. Convulsions lasting 5 days after 12 days' administration of cefuroxime/clarithromycin to a male aged 82 (012.090.17923) resolved without therapy, and were probably related to treatment. An epileptic crisis 2 days after the first dose of amoxicillin/clavulanate in a male aged 85 (011.125.05668) was considered to be associated with hyperthermia resulting from failure of treatment for CAP. Two episodes of epileptic convulsions, accompanying severe asthma, 7 days after the last dose of amoxicillin/clavulanate to a female aged 51 (070.010.20421) were also considered to be unrelated to treatment.

The incidences of syncope were low and similar in the gemifloxacin and all-comparators groups. In 10 of 11 patients receiving gemifloxacin and in the 5 patients receiving comparator regimens, syncope was considered to be both non-serious and unrelated to treatment. When the event occurred during treatment, in 6 of 7 patients from the gemifloxacin group, and in the single case from the all-comparators group, dosing was continued. The patient who was withdrawn had only a brief episode of mild symptoms. Syncope was generally considered by the investigator to be either mild or moderate in intensity, but severe in 2 patients given gemifloxacin, and in one given clarithromycin. Most occurrences resolved without treatment. Two patients given gemifloxacin had ongoing syncope at the time of the last study visit. Syncope (collapse) in the remaining patient (061.011.13158; male, aged 67) from the gemifloxacin group was considered to be a SAE. This patient, who had a history of pulmonary fibrosis, ischemic heart disease, right bundle branch block, emphysema, anasarca, cardiomyopathy, cardio-respiratory insufficiency, and auricular fibrillation, collapsed following the fifth dose, and treatment was discontinued. He was

diagnosed with left heart failure and respiratory failure, and after initial improvement, died of subtotal pulmonary embolism 6 days after medication was stopped. An autopsy showed chronic heart failure associated with bullous emphysema and chronic bronchitis. Both the initial collapse and death were considered to be unrelated to treatment with gemifloxacin, and to be associated with the patient's underlying condition.

No incidents of torsades de pointes were reported in patients from either group who exhibited cardiac arrest, sudden death, syncope, or convulsions. Concomitant medications potentially linked with QTc interval prolongation showed no evident relationship to incidence or severity of these adverse events.

8.6.4.5 QTc Prolongation for Other Quinolones

For comparison, mean prolongation QTc times for other quinolones are shown in Table 60. As can be seen, gemifloxacin resulted in a lesser effect on QTc duration, than any of the other quinolones for which data are available. It should also be noted that in Study 344, gemifloxacin had the same effect on QTc as did ciprofloxacin, a quinolone considered to have no torsades risk.

Table 60: QTc Interval Prolongation of Quinolone Antibiotics

	Spar-floxacin	Grepafloxacin	Moxifloxacin	Levofloxacin	Trovafloxacin	Gemifloxacin
QTc interval prolongation in humans	Yes	Yes	PO minimal	Minimal	No	Minimal
Mean ± SD QTc interval prolongation in humans	PO 10.3 ± 27.6 msec	PO 8 msec	PO 6 ± 26 msec, IV 12.1 msec	4.6 ± 23 msec	No data	PO 2.6 ± 24.6 msec
Number of subjects	1489		787			407

(Ball et al. 1999; Samaha 1999; Iannini et al. 2000; Levaquin (levofloxacin) 2000)

8.6.5 Conclusion

Oral dosing of gemifloxacin, 320 mg PO, was associated with only a small, clinically insignificant, mean increase in QTc interval in a substantial population of patients assessed using paired, manual ECG measurements. The distribution of changes in QTc was also consistent with that in non-patient volunteers, and with the distribution of changes produced by comparators. The QTc changes were equal to or less than those resulting from the use of other quinolones.

The few patients with treatment-emergent QTc values greater than 500 msec had significant co-morbidities and/or concomitant medications known to cause QT prolongation. Neither these predisposing factors, age, gender (both risk factors for QTc prolongation), nor higher systemic concentrations of gemifloxacin associated with intravenous administration had any significant influence on the overall distribution of QTc changes.

There was no evidence of effect of pre-existing minor waveform abnormalities on QTc, and no treatment-emergent pattern of such abnormalities. Patterns of clinical conditions potentially associated with arrhythmia generally did not differ between the gemifloxacin and all-comparators groups, and both sudden deaths and cardiac arrests after gemifloxacin administration were considered by investigators not to be related to study medication. There were no cases of torsades de pointes in any group.

Overall, in-depth evaluation of mean and individual measurements, with regard to known risk factors, supports the conclusion that oral gemifloxacin is very unlikely to cause clinically significant QTc prolongation in a wider patient population and that with respect to QTc, it is as safe or safer than other quinolones.

8.7 Hepatic Safety

Hepatotoxicity was observed in pre-clinical studies conducted in dogs. The hepatotoxicity seen in dogs likely depended on deposition of crystals of gemifloxacin in the biliary tract, followed by local impedance of bile flow and resulting damage by bile salts to principally periportal hepatocytes ('cholate stasis'). Humans are predicted to be protected, both by a lesser burden on biliary secretion and by biliary pH favoring maintenance of gemifloxacin in solution, however the occasional rise in liver function tests may be explained by the mechanism of reversible “injury” seen in dogs. This may have been more evident in the human pharmacology studies where subjects were treated with 640 mg daily of gemifloxacin and 2.1% were noted to demonstrate elevation of liver transaminases, more than twice the upper limit of normal, quite often in association with demonstrable rises in alkaline phosphatase. In no cases did any of these subjects exposed to this higher dose of gemifloxacin (or any of the 8119 patients exposed to the 320 mg dose of gemifloxacin) exhibit laboratory findings consistent with Hy’s Law (elevation of bilirubin above 3 mg/dL in conjunction with significant elevation of liver transaminases), which has been identified as a potential sentinel for the risk of severe and irreversible drug-induced hepatocellular injury.

Gemifloxacin treatment was not associated with any consistent liver clinical chemistry finding. Treatment-emergent changes of potential clinical concern in liver values were very infrequent. No marked or consistent differences between the gemifloxacin 320 mg PO and the all-comparator groups for patients with in-range values at screening were seen (Table 61).

Table 61: Number (%) of Patients with Treatment-Emergent Liver Function Tests within the Specified Ranges at the On-Therapy and End-of-Therapy Visits for Patients with In-Range Values at Screening

Visit/ Laboratory Test	Range	Gemifloxacin 320 mg PO N=8000*		All Comparators N=5175*	
		n	(%)	n	(%)
On-Therapy Visit					
Alanine Aminotransferase	<=ULN	4165	(94.9)	3457	(96.0)
	>ULN to <2xULN	192	(4.4)	125	(3.5)
	2 to <4xULN	32	(0.7)	15	(0.4)
	4 to <6xULN	1	(<0.1)	2	(0.1)
	≥8xULN	0	(0)	1	(<0.1)
Alkaline Phosphatase	<=ULN	4475	(98.4)	3616	(98.2)
	>ULN to <2xULN	63	(1.4)	64	(1.7)
	2 to <4xULN	7	(0.2)	4	(0.1)
	4 to <6xULN	1	(<0.1)	0	(0)
Aspartate Aminotransferase	<=ULN	4205	(95.6)	3529	(96.8)
	>ULN to <2xULN	164	(3.7)	99	(2.7)
	2 to <4xULN	29	(0.7)	15	(0.4)
	4 to <6xULN	1	(<0.1)	1	(<0.1)
	6 to <8xULN	1	(<0.1)	0	(0)
Total Bilirubin	<=ULN	4579	(99.0)	3665	(99.4)
	>ULN to <2xULN	41	(0.9)	22	(0.6)
	2 to <4xULN	3	(0.1)	0	(0)
End-of-Therapy Visit					
Alanine Aminotransferase	<=ULN	5706	(94.6)	3566	(95.8)
	>ULN to <2xULN	278	(4.6)	129	(3.5)
	2 to <4xULN	39	(0.6)	27	(0.7)
	4 to <6ULN	6	(0.1)	2	(0.1)
Alkaline Phosphatase	<=ULN	6146	(98.4)	3729	(98.4)
	>ULN to <2xULN	91	(1.5)	60	(1.6)
	2 to <4xULN	7	(0.1)	2	(0.1)
Aspartate Aminotransferase	<=ULN	5880	(97.1)	3690	(98.0)
	>ULN to <2xULN	151	(2.5)	68	(1.8)
	2 to <4xULN	22	(0.4)	6	(0.2)
Total Bilirubin	<=ULN	6220	(98.7)	3742	(98.8)
	>ULN to <2xULN	76	(1.2)	47	(1.2)
	2 to <4xULN	5	(0.1)	0	(0)

* Total includes all patients who had values within the normal range at screening but at least one abnormal value at either the on-therapy or end-of-therapy visit.

Not unexpectedly, treatment-emergent changes of potential clinical concern in liver values were more frequent in patients with out of range values at screening since these values likely reflected the already elevated values the patients exhibited at baseline. Taking into account the variability that the elevations at baseline would more than likely exhibit, no marked or consistent differences between the gemifloxacin 320 mg PO and the all-comparator groups for patients with out-of-range values at screening were seen (Table 62).

Table 62: Number (%) of Patients with Liver Function Tests within the Specified Ranges at the On-Therapy and End-of-Therapy Visits for Patients with Out- of-Range Values at Screening

Visit/ Laboratory Test	Range	Gemifloxacin 320 mg PO N=1468		All Comparators N=720	
		n	(%)	n	(%)
On-Therapy Visit					
Alanine Aminotransferase	<=ULN	119	(26.5)	71	(29.2)
	>ULN to <2xULN	207	(46.1)	121	(49.8)
	2 to <4xULN	97	(21.6)	44	(18.1)
	4 to <6xULN	17	(3.8)	6	(2.5)
	6 to <8xULN	5	(1.1)	1	(0.4)
	>=8xULN	4	(0.9)	0	(0.0)
Alkaline Phosphatase	<=ULN	85	(25.1)	39	(20.0)
	>ULN to <2xULN	218	(64.3)	136	(69.7)
	2 to <4xULN	34	(10.0)	18	(9.2)
	4 to <6xULN	2	(0.6)	0	(0.0)
	6 to <8xULN	0	(0.0)	2	(1.0)
Aspartate Aminotransferase	<=ULN	150	(34.3)	78	(39.2)
	>ULN to <2xULN	205	(46.9)	83	(41.7)
	2 to <4xULN	59	(13.5)	33	(16.6)
	4 to <6xULN	13	(3.0)	3	(1.5)
	6 to <8xULN	5	(1.1)	2	(1.0)
	>=8xULN	5	(1.1)	0	(0.0)
Total Bilirubin	<=ULN	184	(73.3)	144	(77.0)
	>ULN to <2xULN	55	(21.9)	38	(20.3)
	2 to <4xULN	9	(3.6)	5	(2.7)
	4 to <6xULN	2	(0.8)	0	(0.0)
	6 to <8xULN	1	(0.4)	0	(0.0)
End-of-Therapy Visit					
Alanine Aminotransferase	<=ULN	268	(45.6)	126	(57.0)
	>ULN to <2xULN	228	(38.8)	73	(33.0)
	2 to <4xULN	75	(12.8)	19	(8.6)
	4 to <6xULN	14	(2.4)	3	(1.4)
	6 to <8xULN	3	(0.5)	0	(0.0)

Visit/ Laboratory Test	Range	Gemifloxacin 320 mg PO N=1468		All Comparators N=720	
		n	(%)	n	(%)
Alkaline Phosphatase	<=ULN	157	(39.3)	81	(41.8)
	>ULN to <2xULN	224	(56.0)	108	(55.7)
	2 to <4xULN	17	(4.3)	4	(2.1)
	4 to <6xULN	2	(0.5)	1	(0.5)
Aspartate Aminotransferase	<=ULN	323	(57.9)	118	(66.3)
	>ULN to <2xULN	184	(33.0)	46	(25.8)
	2 to <4xULN	41	(7.3)	12	(6.7)
	4 to <6xULN	6	(1.1)	1	(0.6)
	6 to <8xULN	2	(0.4)	1	(0.6)
	≥8xULN	2	(0.4)	0	(0.0)
Total Bilirubin	<=ULN	255	(76.8)	154	(81.9)
	>ULN to <2xULN	68	(20.5)	29	(15.4)
	2 to <4xULN	9	(2.7)	5	(2.7)

An earlier quinolone, temafloxacin, demonstrated a cluster of clinical effects, including hepatotoxicity, the so called "temafloxacin syndrome". Patients are defined as having temafloxacin syndrome if a single blood specimen meets all of the following criteria:

Bilirubin increase from baseline greater than or equal to 1.0 mg/dL or greater than or equal to 17 µmol/L

Serum creatinine increase from baseline greater than or equal to 0.8 mg/dL or greater than or equal to 73 µmol/L

Hemoglobin decrease from baseline greater than or equal to 2 g/dL or greater than or equal to 1.24 mmol /L.

None of the gemifloxacin treated subjects met these criteria.

8.7.1 Independent Review of Liver Findings

Dr. Paul Watkins, Professor of Pharmacotherapy, University of North Carolina, Chapel Hill, NC reviewed the liver findings of gemifloxacin. Dr. Watkins reviewed all cases in the gemifloxacin safety database using conservative criteria, ALT ≥2 x ULN or total bilirubin ≥1.5 mg/dL. His analysis of liver functions after dosing with gemifloxacin is summarized as follows.

The most sensitive and specific test available to detect hepatocellular injury is serum ALT; serum bilirubin elevations associated with hepatocellular injury occur only when that injury is

severe. There were no patients in the gemifloxacin clinical trials database who experienced bilirubin elevations to > 1.5 mg/dL as a result of treatment-emergent hepatocellular injury. At the 320 mg dose, there were no treatment-associated ALT elevations exceeding 8 x ULN among those patients with normal ALT at screening. Among patients with abnormal ALT at screening, there was only one patient who experienced an ALT elevation exceeding 8 x ULN and where gemifloxacin may have contributed to the injury observed. In this case, the incremental injury attributable to gemifloxacin is over estimated based on ALT alone due to the elevation at baseline.

The available data are most consistent with first pass liver exposure (and not systemic exposure) as being the most relevant determinant of toxic response. For a drug that is well absorbed like gemifloxacin, first pass liver exposure should be chiefly a function of oral dose, with relatively little interpatient variability.

In the recently completed gemifloxacin study OP-634-001, which compared a 5-day course of gemifloxacin against a 7-day course in the treatment of mild to moderate CAP, the sponsor noted a trend for higher serum ALT in the 5-day group when compared to the 7-day group and a trend for higher serum ALT overall versus prior NDA studies. The sponsor requested Dr. Watkins perform a specific analysis of the liver safety data from the study itself and in comparison to prior gemifloxacin studies.

Dr. Watkins concluded that his review of the OP-634-001 laboratory data did not raise new concerns regarding the liver safety of gemifloxacin. Treatment-emergent increases in serum ALT were modest and consistent with that observed with other antibiotics used to treat CAP. More importantly, there were no cases that fit the criteria for Hy's Rule (i.e., simultaneous elevations in serum ALT and bilirubin). The trend for higher incidence of serum ALT elevations among the patients treated for 5 days versus 7 days is not consistent with an increased hepatotoxic effect of gemifloxacin and can be explained by a higher mean serum ALT at baseline in those randomized to 5 day treatment. Dr. Watkins also determined that the trend toward higher incidence of ALT elevation in the study versus the prior NDA studies likewise appears to be artifactual. It likely results from two factors: higher mean baseline ALT and lower absolute value for the upper limits of normal in the study relative to the prior NDA studies.

Dr. Watkins has concluded that the gemifloxacin liver safety data reviewed in aggregate do not suggest a significant hepatotoxicity risk with gemifloxacin. The clinical trials database, which now includes 8,119 treated patients, does not contain a single case that would fit current criteria for a liver safety signal. The substantial safety data that has accumulated since his last review in 2002 continues to support his prior conclusion that the risk of significant liver injury during treatment with gemifloxacin appears to be very low.

8.8 Phase IV Force Study

The FORCE Study is a study designed to fulfill a post-marketing commitment to the FDA. The commitment is to conduct a prospective, randomized study comparing gemifloxacin mesylate (5,000 patients) to an active control (2,500 patients) in patients with mild-to-moderate CAP or ABECB. Patients are evaluated for clinical and laboratory safety. In order to gain safety information on selected ethnic groups (African Americans, Asians, and Hispanics), the sponsor will attempt to enroll and randomize each ethnic group at a rate of 10% of the total enrollment. It is anticipated that the study will be completed within 4 years of study start, with interim analyses submitted annually with the Factive NDA Annual Report. As of July 31, 2006, 4,969 of 7,500 patients have been enrolled.

The primary objective of this study is to evaluate and compare the overall safety in patients with mild-to-moderate CAP treated with gemifloxacin versus clarithromycin XL and patients with ABECB treated with gemifloxacin versus amoxicillin/clavulanate. The secondary objectives of this study are to evaluate the following: the incidence of rash; hepatic and creatine phosphokinase (CPK) changes in patients with pre-existing liver disease; and the effect on QTc duration in patients with CAP.

For this second planned interim reporting period, safety data from 1,821 gemifloxacin patients (413 CAP, 1,408 ABECB), 214 clarithromycin XL patients (all CAP), and 686 amoxicillin/clavulanate patients (all ABECB) were available for analysis.

8.8.1 Demographics

Demographics for all indications are presented in Table 63. There were no statistically or clinically significant differences between the treatment groups in mean age, mean body weight, mean body mass index (BMI), or the distribution of patients by gender or race. Although the treatment groups each were primarily Caucasian, the study has been close to meeting its stated objective of ensuring a 10% minority enrollment for each minority population. There has also been a greater percentage of females than males enrolled. The mean age of each group was 55 years, and the BMI was 30 kg/m^2.

The subgroup of patients at higher risk of rash (females <40 years old) (gemifloxacin N=191, combined controls N=98) was also primarily Caucasian (72% of the subgroup), with an overall mean age of 31 years and an overall mean BMI of 30 kg/m^2.

The small subgroup of patients with pre-existing liver disease (gemifloxacin N=16, combined controls N=4) was primarily female (60% of the subgroup) and Caucasian (85% of the subgroup), with an overall mean age of 51 years and an overall mean BMI of 31 kg/m^2.

Table 63: Demographics for Interim Safety Population FORCE Study

Demographic Characteristics	All Gemifloxacin N=1,821	Combined Controls N=900
Age (years, mean ±SD)	55.3 ±16.19	54.8 ±16.27
Age range (years, min-max)	18.0-102.0	18.0-91.0
Gender (no. [%] of patients)		
Male	735 (40.4)	362 (40.2)
Female	1086 (59.6)	538 (59.8)
Race (no. [%] of patients)		
American Indian/Alaska Native	18 (1.0)	4 (0.4)
Asian or Pacific Islander	38 (2.1)	12 (1.3)
Black or African American	168 (9.2)	93 (10.3)
Hispanic or Latino	184 (10.1)	77 (8.6)
White or Caucasian	1395 (76.6)	702 (78.0)
Other	15 (0.8)	10 (1.1)
Missing	3 (0.2)	2 (0.2)
Body weight (kg, mean ±SD)	84.4 ±22.89	84.4 ±22.38
BMI (kg/m^2, mean ±SD)	30.0 ± 7.65	30.1 ± 7.44

8.8.2 Patient Adverse Event Profile

8.8.2.1 Overall

Gemifloxacin has been associated with a low incidence of AEs, generally similar or lower than rates in comparators and with a majority of mild to moderate severity. Rash was the only AE that was greater than the comparator group although the rate was low (1.8%).. These results are consistent with the safety from the overall clinical trial database (Table 64).

Table 64: Treatment Emergent Adverse Events that Occurred in ≥ 1% of any Treatment Group (Interim Safety Population)

Preferred Term	Treatment Group			
	Gemifloxacin 320 mg PO		All Comparators	
	N=1821		N=900	
	N	(%)	N	(%)
Patients with at least one treatment emergent AE	301	16.5	192	21.3
Diarrhea	35	1.9	61	6.8
Nausea	34	1.9	33	3.7
Rash*	33	1.8	5	0.6
Headache	24	1.3	19	2.1
Cough	14	0.8	12	1.3
Vomiting	11	0.6	11	1.2
Dysgeusia	5	0.3	12	1.3

*Combined incidence of adverse events coded to rash, rash generalized, maculopapular rash and urticaria.

8.8.2.2 Serious Adverse Events (SAEs)

The analysis of SAE incidence by treatment group is summarized in Table 65 for all patients, and in Table 66 for women < 40 years of age. In the second interim reporting period, SAE incidence for each treatment group was similar for all indications, for CAP patients, for ABECB patients, and for women < 40 years of age (all indications, CAP, and ABECB).

None of the 20 patients with pre-existing liver disease experienced an SAE.

Table 65: Primary Safety Analysis of SAE of All Patients (Interim Safety Population)

Statistic	CAP		ABECB		All Indications	
	Gemifloxacin 7 day	Clarithro-mycin XL	Gemifloxacin 5 day	Amoxicillin/ Clavulanate	All Gemifloxacin	Combined Controls
	(N=413)	(N=214)	(N=1,408)	(N=686)	(N=1,821)	(N=900)
No. (%) of patients with SAE	4 (1.0)	3 (1.4)	31 (2.2)	18 (2.6)	35 (1.9)	21 (2.3)
Odds ratio	0.69		0.84		0.82	
95% CI	0.15,3.14		0.46,1.50		0.47,1.41	
P-value	0.6340		0.5487		0.4650	

Across indication: odds ratio and 95% confidence interval (CI) calculated using the Cochran Mantel-Haenszel method stratified by indication.
Within indication: odds ratio and 95% confidence interval (CI) calculated using the Cochran Mantel-Haenszel method.
P-value: calculated using the Cochran Mantel-Haenszel method.

Table 66: Primary Safety Analysis of SAE of Women <40 Years Old (Interim Safety Population

Statistic	CAP		ABECB		All Indications	
	Gemifloxacin	Clarithro-mycin XL	Gemifloxacin	Amoxicillin/ Clavulanate	All Gemifloxacin	Combined Controls
	(N=50)	(N=24)	(N=141)	(N=74)	(N=191)	(N=98)
No. (%) of women <40 years with SAE	0	0	3 (2.1)	2 (2.7)	3 (1.6)	2 (2.0)
Odds ratio	--		0.78		0.78	
95% CI	--		0.13,4.79		0.13,4.79	
P-value	--		0.7909		0.7909	

--: Statistical testing not performed because there were no events in either treatment group.
Across indication: odds ratio and 95% confidence interval (CI) calculated using the Cochran Mantel-Haenszel method stratified by indication.
Within indication: odds ratio and 95% confidence interval (CI) calculated using the Cochran Mantel-Haenszel method.
P-value: calculated using the Cochran Mantel-Haenszel method.

8.8.2.3 Withdrawals Due to AEs

There were fewer withdrawals due to AEs 39/1821 (2.1%) in the gemifloxacin group that in the all comparator group 39/900 (4.3%).

8.8.2.4 Deaths

There was one death during the trial. The death occurred in amoxicillin/clavulanate ABECB patient 17405, and it was not related to the study medication per the investigator.

8.8.3 Rash

The analysis of the incidence of rash by treatment group is summarized in Table 67 for all patients and for females < 40 years. The incidence of rash was higher in each gemifloxacin group compared to the respective control group.

Table 67: Incidence of Adverse Experiences of Rash for Both Treatment Groups

Type of AE	Treatment Group				Subgroup Female <40 Years			
	Gemifloxacin 320 mg PO N=1821		All Comparators N=900		Gemifloxacin 320 mg PO CAP N=50		Gemifloxacin 320 mg PO ABECB N=191	
	N	(%)	N	(%)	N	(%)	N	(%)
Rash*	33	(1.8)+	5	(0.6)	4	(8.0%)	4	(2.8%)
SAE of rash	0	(0)	0	(0)	0	(0)	0	(0)
Rash* leading to withdrawal	5	(0.3)	3	(0.3)	-	-	-	-

*Rash includes the combined terms of MedDRA 7.1 PTs rash, rash generalized, maculopapular rash, and urticaria)

The data presented in this second interim analysis support the finding that gemifloxacin continues to be well-tolerated. Although interim data, the following observations are noted:

- The incidence of SAEs in the gemifloxacin groups was slightly lower than the incidence in the respective control groups, even in the subgroup of females < 40 years.
- In females <40 years the incidence of rash in the gemifloxacin groups was higher than the incidence in the respective control groups.
- The majority of rashes (38 of 39 total occurrences) seen with the use of gemifloxacin were of mild-to-moderate intensity.

- The one reported rash of severe intensity was determined to be non-serious by the Investigator.

These findings are consistent with the original clinical trial database.

8.8.4 Cardiac Safety

A secondary objective of the FORCE study is to evaluate the effect of gemifloxacin versus clarithromycin XL on QTc duration in patients with CAP. This report covers ECG data for 280 CAP patients from the period from 14 September 2004 (study start) to data cut-off on 04 April 2006. The protocol originally specified that this analysis would not be performed until 300 paired ECGs were available on the safety population, however an interim analysis was performed to maximize the amount of data available for the committee and the FDA.

The changes seen in QTc corrected using both the Bazett's correction (QTcB) and the Fridericia's correction formula (QTcF) are summarized in Table 68. As can be seen, gemifloxacin had minimal effects on QTc using either correction formula, and this was similar to the effects seen in patients treated with clarithromycin XL.

It should also be noted that no patients in the FORCE study were found to have QTc values in excess of 500 msec while on gemifloxacin and similar percentages of patients in each treatment group had an absolute increase from baseline in QTcB or QTcF of 30 or 60 msec. These data are summarized in Table 69.

Table 68: Number (%) of Patients with Clinically Significant Increases from Baseline to End of Treatment for QTcB and QTcF (ECG Study Population)

Clinically Significant Change	QTcB		QTcF	
	Gemifloxacin (N=184)	Clarithromycin XL (N=96)	Gemifloxacin (N=184)	Clarithromycin XL XL (N=96)
Shift from ≤500 msec at baseline to >500 msec at EOT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Absolute increase ≥30 msec	13 (7.1)	6 (6.3)	23 (12.5)	11 (11.5)
Absolute increase ≥60 msec	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)

P-values for each comparison were <0.05 (Cochran Mantel-Haenzel method).

Table 69: Summary Statistics for Change from Baseline to End of Treatment for QTcB and QTcF (Interim ECG Study Population)

Time Point and Statistic	QTcB		QTcF	
	Gemifloxacin (N=184)	Clarithromycin XL (N=96)	Gemifloxacin (N=184)	Clarithromycin XL (N=96)
Baseline				
Mean	412.7	416.7	395.0	399.3
SD	22.85	20.18	21.33	19.61
Median	414.0	418.5	395.0	401.0
Min-max	356 – 469	355 – 457	342 – 451	349 – 461
EOT				
Mean	412.6	418.6	399.9	402.6
SD	23.43	22.08	21.69	20.19
Median	413.0	417.0	400.5	402.5
Min-max	357 – 483	354 – 469	344 – 464	358 – 452
EOT absolute change				
Mean	-0.1	1.9	4.9	3.4
SD	21.70	20.88	20.09	20.33
Median	0.0	3.0	5.0	4.0
Min-max	-58 – 66	-57 – 57	-53 – 81	-63 – 51

Notes: EOT = end of treatment

There were no statistically significant treatment group differences in absolute or percentage change from baseline for QTcB or QTcF for subjects with co-morbidities (Table 70). Additionally no statistically significant treatment group differences in absolute change from baseline were noted when the two treatment groups were analyzed by race, age, gender and gender by age.

Table 70: Analysis of Change from Baseline to End of Treatment for QTcB and QTcF (Interim ECG Study Population, ECG Subjects with Co-morbidities)

Statistic	QTcB		QTcF	
	Gemifloxacin	Clarithromycin XL	Gemifloxacin	Clarithromycin XL
	N=53	N=24	N=53	N=24
LSM baseline	412.8	413.8	398.2	397.5
LSM absolute change (SE)	7.8 (4.88)	3.9 (5.48)	8.5 (4.69)	3.1 (5.38)
LSM percentage change (SE)	1.9 (1.16)	0.9 (1.33)	2.2 (1.16)	0.9 (1.33)
Analysis of absolute change[a]				
Diff. between treatments[b] (95% CI)	4.5 (-5.2,14.2)		5.7 (-3.5,14.9)	

Notes: CI = confidence interval; LSM = least square mean; SE = standard error of the mean
[a] Analysis by ANCOVA with treatment as factor and baseline, age, gender, and race as covariates.
[b] Point estimate of the difference in mean change; gemifloxacin - clarithromycin XL.

8.9 Safety Data from Post Marketing Sources

Since approved for use in the treatment of mild-to-moderate CAP and ABECB in 2003 in the US, gemifloxacin has been approved by health authorities marketed in several countries, including the US, Korea, South Africa, Jordan, and Russia. Safety data from post marketing sources are estimated at nearly one million (205,821 outside of the US and 764,861 in the US).

This significant exposure with commercial use allows for a comparison of the safety profile observed in the clinical trials for gemifloxacin and assessment of the potential for rare adverse events.

The crude reporting rate is defined as the number of adverse events reported divided by the exposure. In the case of gemifloxacin, that exposure is approximately 764,861 patients in the US. The crude reporting rate of all AEs was 0.19%. The post-marketing experience has not revealed any safety signals to date and has a profile similar to what was seen in the clinical trials. Some quinolone class effects have been reported (e.g., cases of anaphylaxis and of increased International Normalized Ratio (INR) or prothrombin time (PT) and/or clinical episodes of bleeding with concurrent administration of warfarin), and importantly to date there have been no spontaneous reports of torsades des pointes.

Cutaneous cases of potential clinical significance

Dr. Neil Shear, Professor and Chief of Dermatology, and Director Drug Safety Group, University of Toronto Medical School conducted a review of spontaneous (MEDWATCH)

reports of cutaneous cases of potential clinical significance, which revealed three cases of potential concern.

1. 0400083: This is a 67-year-old woman who had been on levofloxacin for four days for sinusitis and came back to the doctor on the last day of levofloxacin saying it was not working. The physician then put her on a course of gemifloxacin. On day 3 or 4 of gemifloxacin therapy the patient developed a diffuse macular papular rash with mucosal and vaginal lesions. The patient was referred to the emergency room, was then hospitalized and treated with intravenous steroids, and discharged 2-3 days later. **Comment by Dr Shear: What was not given was a description that is compatible with SJS. There were no target lesions, no hemorrhagic or painful erosions on the lips, no conjunctivitis. The information that was given, and the obvious information that could have been given, lead me to believe that this was NOT SJS. The timing is acceptable for a maculopapular exanthem from gemifloxacin. The levofloxacin could also be involved but less likely. In summary, the report is not very compelling as a case of SJS. The exanthematous rash is most like due to gemifloxacin, but there are other possibilities.**

2. 466205: This report includes the preferred terms of maculopapular rash, pruritus, flushing, and SJS. The sponsor became aware of this case during a routine search of the AERS database through the use of a licensed database called QScan®. There is no information on patient age, gender, concomitant medications, or other health information. The sponsor contacted FDA in an effort to obtain additional information regarding this case. FDA stated that the sponsor was not notified of this case through the MEDWATCH to Manufacturers Program because FDA received the direct report as a letter, not on a MEDWATCH form, which made it confidential and not disclosable (even under the Freedom of Information Act). The sponsor requested FDA to contact the reporter to obtain permission to share all information regarding this report. The FDA has not granted this request. FDA advised the sponsor to submit a freedom of information request, which the sponsor did on July 7, 2006. No additional information is available. The sponsor believes the report does not fulfill the WHO criteria for an adverse event report. **Comment by Dr Shear: This did not meet the minimum requirements to be considered a case. There is no data to support the diagnosis of SJS.**

3. 0600069: This is an 18-year-old female patient. The medical history includes no known allergies. The patient was not taking any concomitant medications. The patient was prescribed a 7–day course of gemifloxacin for “strep throat”. One day after taking the first dose of gemifloxacin the patient reportedly complained of itchiness. Her physician instructed the patient to take Benadryl. The itchiness worsened, and her physician instructed the patient to increase her dose of Benadryl. The patient’s symptoms reportedly worsened to where she developed what the reporter called ‘hives”. The patient

was brought to the emergency room, admitted to the hospital, treated with steroids, and continued on Benadryl. The reporter stated that the patient had "discolored skin, blisters in her mouth and vaginal blisters". The reporter mentioned that his niece had "SJS" as told to him by his sister (the patient's mother) and also stated that this diagnosis was not medically confirmed as far as he was aware. The patient was discharged after being hospitalized for 7 days. **Comment by Dr. Shear: Primary diagnosis is erythema multiforme major (EMM). Without seeing the rash or a biopsy it is of course difficult. But the features fit this best. This is NOT a drug-induced reaction and is most often a sign of reacting to a reactivation of herpes simples (something that is not a surprise in the setting of a cold, hence cold sores, or similar disease). This disease response is usually seen in younger patients, so the age is actually supportive. SJS low, <5%: The timing is week, this is usually delayed by more than 1 day. The description of the lesions and the itch also make it less likely. If it is SJS, it is not necessarily due to drug, but could also be post infectious. Urticaria plus: This is possible and it could be urticaria due to a successful response to treatment, due to the infection, or due to the gemifloxacin. Probability overall of due to gemifloxacin <5% HSS: Timing is wrong, but if we include this it is much less than 1% as a possible diagnosis. Probability of causation if EMM is primary diagnosis: Possible causes of EMM are herpes reactivation, strep, drug. But drug is very low on this list. The likelihood it is post strep is >80%. Overall this is EMM and NOT a drug eruption. The probability that gemifloxacin caused any of these likely diagnoses is <10%.**

In summary, Dr. Shear concluded of the three cases, the first is unlikely to be SJS because none of the hallmarks of SJS are described, in the second there is insufficient information, and the third appears appears to be a non-drug-related EMM.

Hepatic cases of potential clinical significance

Dr. Paul Watkins, Professor of Pharmacotherapy, University of North Carolina, Chapel Hill, NC conducted a review of 11 spontaneous (MEDWATCH) reports of possible hepatic injury up through July 5, 2006, which revealed only two cases involving hepatocellular injury and jaundice:

1. 0500453 – This is a 33-year-old man who developed multiorgan failure including jaundice (bilirubin of 9 mg/dL) after receiving a 5-day course of gemifloxacin. His serum ALT was only 274 and this may have been largely of skeletal muscle origin as his CPK was 14,000 and his AST was 937. Of note is that he was also taking acetaminophen 4 grams/day X 10-12 days for fevers and myalgias, and such a treatment with acetaminophen has been recently shown to frequently cause ALT elevations > 3 x ULN. The patient was demonstrated to have splenomegaly, low serum albumin (2.2), low

platelet count, renal failure, and a skin rash. The skin rash was biopsied and thought to be consistent with a drug reaction. ERCP did not reveal biliary blockage, but the ampulla was lacerated suggesting possible recent passage of a gallstone. Liver biopsy showed patchy necrosis and mild lobular mononuclear inflammation consistent with an infectious process. Full liver work up was negative (virus, autoantibody). The patient died and autopsy revealed hemophagocytic syndrome (HSP). **Comment by Dr. Watkins: This is not a case of drug induced liver injury.**

2. 060071 – a 26-year-old woman who took clarithromycin for 5 days, then switched to gemifloxacin. One day later she started vomiting and 3 days later, with continued vomiting, she noted dark urine. She, went to an ER and received IV fluids, and was sent home. She completed the 5-day course of gemifloxacin, and then saw her physician who told her she was having a drug reaction. Five days later with continued vomiting, she was seen in the ER and was noted to be jaundiced. Her serum liver chemistries were: ALT 771 IU, alkaline phosphatase 378 IU, bilirubin 12.5 mg/dL, and her serum lipase was 3500, suggesting pancreatitis. Full hepatitis work was up negative including imaging of biliary tree. She was discharged and 9 days later was noted to have a serum bilirubin of 22 mg/dL and a serum ALT of 196 IU. Liver biopsy performed about 2 weeks after discontinuing gemifloxacin showed intrahepatic cholestasis and a paucity of bile ducts, which was thought to be a sampling artifact given the acute history of the event. Five months after discontinuing therapy she remains jaundiced with bilirubin ~20 mg/dL and elevated alkaline phosphatase. Event has been attributed to either gemifloxacin or clarithromycin by the reporter. **Comment by Dr. Watkins: I agree that this appears to be a drug reaction to clarithromycin or gemifloxacin. Clarithromycin treatment has been rarely associated with both cholestatic and hepatocellular injury and the timing of the onset of symptoms seems more consistent with clarithromycin (6 days) versus gemifloxacin (1 day) exposure. It is important to note that this is largely a cholestatic reaction based on the alkaline phosphatase elevation and the liver biopsy. Because this is not hepatocellular jaundice, it is not a Hy's Law case.**

Of the other 9 cases reviewed by Dr. Watkins, he noted that there were 2 cases that represented hepatocellular injury without jaundice, 5 cases where there was insufficient data to assign causation, none of which clearly represented severe liver injury, and 2 cases that did not appear to document significant liver injury.

In summary, Dr. Watkins concluded there have been no fatalities or liver transplantations among the 11 MEDWATCH reports provided. The most severe liver injury reported (060071) was largely cholestatic, and it is not possible to exclude a role for clarithromycin in the injury observed. The post-marketing experience to date is also reassuring. The substantial safety data that has accumulated since Dr. Watkin's last review in 2002 continues to support his prior

conclusion that the risk of significant liver injury during treatment with gemifloxacin appears to be very low.

8.10 Safety Conclusions

Overall, gemifloxacin 320 mg PO was well tolerated in the clinical studies.

The incidence of rash in the overall population was higher for the gemifloxacin group (all durations) than for the all-comparators group, 3.5% versus 1.1%, respectively. However in the 5-day ABS studies, the rash rate was 2.6%. Most cases of rash were of mild or moderate intensity. The rash is self-limiting and not associated with any of the features of a more severe cutaneous drug reaction, which carries a risk of significant morbidity or mortality. The cross sensitization potential to other quinolones is low, and there is no subclinical sensitization potential. There were no clinically consistent reports of SJS or TEN, and no other known sequelae to any of the reported rashes.

Except for rash, the overall adverse events profile, including serious adverse events, was better or similar in gemifloxacin treated patients compared to those receiving other therapies.

Use of gemifloxacin was associated with small prolongations in the ECG QTc interval. These prolongations were not clinically meaningful and are equal to or less than those seen with other quinolones.

Gemifloxacin treatment was not associated with any consistent liver clinical chemistry finding. Treatment-emergent changes of potential clinical concern in liver values were very infrequent in those with in-range values at screening. No marked or consistent differences between the gemifloxacin 320 mg PO and the all-comparator groups were seen at either the on-therapy or end of therapy visits in those with in-range or out-of-range values at screening.

The post marketing experience with gemifloxacin, close to a million patient exposures, is consistent with the findings in the clinical trial database in terms of overall safety, rash, cardiac, and hepatic findings. Of the three cases of cutaneous cases of potential clinical significance the first is unlikely to be SJS because none of the hallmarks of SJS are described. In the second there is insufficient information. In the third it appears to be a non-drug related EMM (which is oftened misdiagnosed as SJS but is clinically distinct and rarely fatal). The drug utilization study [Prescribing Patterns and Use Study of Factive® (gemifloxacin mesylate); Appendix 1] further addresses the question of cross and subclinical sensitization with gemifloxacin. Again the findings of this study are consistent with the original clinical trial database demonstrating a low rate of cross sensitization and low or no subclinical sensitization.

9. DISCUSSION

Multidrug resistance in many pathogenic bacteria is a widely reported phenomenon of increasing concern both to the individual patient and to society as a whole (Butler et al. 1996; Doern et al. 1998; Cunha & Shea 1998). Increasing usage of each antibiotic class has been accompanied by an increase in bacterial resistance to that class of antibiotic over time.

Since the 1990s, fluoroquinolone resistance among strains of *S. pneumoniae* has been emerging worldwide. The increasing use of fluoroquinolones for the treatment of a variety of community-acquired infections has led to an increased prevalence of the fluoroquinolone-resistant strains, ranging from 1 to 15% (Chen et al. 1999; Jones et al. 2000; Empey et al. 2001; Zheng et al. 2001; Ho et al. 2001; Ferraro 2002; Davidson et al. 2002; Ross et al. 2002; Anderson et al. 2003). Indeed, recently the results were presented of a nationwide surveillance program that showed pockets of high prevalence of resistance in some regions of the US with rates as high as 22% (Ferraro 2002).

This has been in large part due to the use of fluoroquinolones with marginal activity against the pneumococcus including ciprofloxacin and levofloxacin; both having AUC/MIC ratios just at or below those necessary to eradicate the infecting organism and prevent the emergence of strains either resistant to current fluoroquinolones (first and second step mutations) or having reduced susceptibility (first-step mutants). Decreased susceptibility to fluoroquinolones results mainly from amino acid substitutions in the QRDR, either in the TOPO IV, preferentially in the *parC* subunit, or in the DNA gyrase, preferentially in the *gyrA* subunit (first-step mutants), or in both (first- and second-step mutants).

Fluoroquinolones resistance associated with target mutations is acquired through a stepwise process. First-step mutants (or mutants with reduced susceptibility) generally result from mutations in the preferential target for a given fluoroquinolones, *parC* for ciprofloxacin and levofloxacin or *gyrA* for moxifloxacin and gatifloxacin. In the second-step mutants, amino acid substitutions are present in both TOPO IV and gyrase, most frequently affecting *parC* and *gyrA*, and less so *parE* and *gyrA*. They result in resistance to all the currently available antipneumococcal fluoroquinolones (levofloxacin and moxifloxacin).

Outbreaks of respiratory tract infections due to fluoroquinolone- and multidrug-resistant pneumococci have been reported, reflecting the propensity of these strains to spread. Furthermore, first-step mutants with TOPO IV or gyrase mutations have been shown to be associated with treatment failures in some cases of pneumonia. Since fluoroquinolones can be used as first-line drugs for the treatment of community-acquired pneumonia, it is essential that they use fluoroquinolones with activity that ensures the effective treatment of patients and prevents the emergence of resistance. With the increasing prevalence of first-step mutants

(Doern et al. 2005), the use of agents with marginal activity may not result in the selection of resistant strains, but may also result in clinical failure.

This scenario is exactly how pneumococcal resistance to penicillin emerged in the 1980s. The overall penicillin-resistance prevalence rates were only 2% in the early 80s. But even then, there were regions in the country where resistance was between 15-20%, foreshadowing the high across-the-board rates we have today.

With the continuing increase in the prevalence of community-acquired respiratory pathogens with resistance to a variety of antimicrobial agents, more agents with enhanced activity, particularly versus *S. pneumoniae*, are clearly needed. Because of the frequency of ABS and its antibiotic therapy, appropriate antibiotic treatment of this condition is important since the same organisms are implicated in more serious respiratory conditions such as CAP. Drs. Sande and Gwaltney recommend short course therapy of the most potent agent (Sande & Gwaltney 2004). Only three drugs (azithromycin, levofloxacin, and telithromycin) still currently marketed have been shown to be effective when given in a short course in this disease. Azithromycin-has shown problems with resistance and produces gastrointestinal side effects when given in large doses, levofloxacin has-already shown problems with resistance generation, and telithromycin-has a new boxed warning for severe life-threatening hepatic toxicity.

Gemifloxacin, by virtue of its inherent *in vitro* potency, pharmacokinetics, and proven clinical efficacy against both antibiotic sensitive and resistant strains of bacteria responsible for common respiratory diseases, has represented an important new therapeutic option for treatment of CAP and ABECB and holds promise to provide the same advantages for the treatment of ABS.

Gemifloxacin has a favorable benefit/risk and represents the "best in class" quinolone for the treatment of respiratory infections in an era of increasing antibiotic resistance.

Mechanisms of quinolone resistance in *S. pneumoniae* include mutations in the *parC* or *gyrA* gene (step one mutation) or both genes (step two or double mutation). Quinolone resistance is a class phenomenon and quinolone-resistant *S. pneumoniae* exhibit increased MICs to all quinolones. In the case of a single mutation, most *S. pneumoniae* isolates become resistant to the currently marketed quinolones. Gemifloxacin by virtue of its low MIC to *S. pneumoniae* remains below its predicted breakpoint. Only the *gyrA/parC* double mutant caused a significant increase in gemifloxacin MIC. Gemifloxacin is the only quinolone to retain significant anti-pneumococcal activity in the face of quinolone resistance.

Gemifloxacin was found to have the lowest MICs of all the marketed quinolones to both penicillin- and macrolide-resistant *S. pneumoniae*. AUC_{24}/MIC and C_{max}/MIC parameters for gemifloxacin predict that gemifloxacin will have the highest efficacy and lowest resistance generation compared to the currently marketed quinolones for these drug-resistant bacteria.

Gemifloxacin also has excellent activity against the other major respiratory pathogens, *H. influenzae*, *M. catarrhalis*, and is active methicillin-sensitive *S. aureus*, with activity against these pathogens being comparable to the activity seen with other marketed quinolones. Thus based upon *in vitro* data, gemifloxacin can be expected to be efficacious against the usual respiratory tract pathogens.

In large clinical trials gemifloxacin's anti-bacterial activity and pharmacokinetic parameters have translated into convincing efficacy versus multiple comparator drugs in ABS. Gemifloxacin for 5 days has excellent clinical and bacteriological efficacy for the treatment of ABS, with favorable outcomes for all the major pathogens associated with ABS including infections due to MDRSP. The combined results from the controlled studies of gemifloxacin demonstrated that the efficacy of 7 days of gemifloxacin was as effective as each of the approved comparators. Furthermore, the efficacy of 5 days of gemifloxacin was as effective as 7 days of gemifloxacin in ABS.

Multiple drugs are frequently prescribed for underlying cardiovascular and chronic respiratory conditions. Renal and hepatic impairment may also occur in this population. Physicians thus face difficult choices in selecting drugs without potential for drug or concomitant disease interactions in this group. The lack of CYP450-mediated drug interaction or dosage modification requirement in hepatic and mild-moderate renal impairment, strongly favor the benefit/risk for the use of gemifloxacin.

Gemifloxacin has been documented to have a favorable safety profile among the population as a whole. Among the 8119 patients who have received gemifloxacin at 320 mg in clinical trials, the overall adverse event profile was equivalent to that seen in the control groups: cutaneous adverse events were more common with gemifloxacin; the remaining adverse events were similar or less common with gemifloxacin. This was confirmed in both the phase IV FORCE Study and with the post marketing experience.

As evidenced by the lack of any cases of severe ALT elevation or significant total bilirubin elevation, the hepatic problems occasionally reported with other fluoroquinolones do not appear to be a problem with gemifloxacin. Similarly, the lack of a significant increase in QTc duration indicates that gemifloxacin does not possess cardiac arrhythmogenic potential.

The only adverse event consistently reported to occur more frequently with gemifloxacin than with control therapy was rash, occurring in 2.6% of patients treated for 5 days for ABS. Importantly in the overall clinical trial database, in approximately 87% of cases, the rash was either mild or moderate in severity. The clinical, histopathological and immunofluorescence findings are those of a mild exanthematous drug eruption. None of the hallmarks presaging more severe skin reactions (lichenoid or dense lesions, significant IgM levels in lesions or CD8-predominant lymphocyte infiltrates) was observed. None of the subjects developed more

serious dermatologic reactions known to be associated with significant morbidity or mortality such as SJS or TEN. Therefore, although the rash was not an uncommon event, it was rarely clinically severe. More importantly, in no cases was it serious, using either clinical or regulatory criteria. This has been confirmed in both the post-marketing experience of the drug in approximately 760,000 exposures and in the phase IV FORCE safety study.

The sponsor believes that given the unique attributes of gemifloxacin and its demonstrated clinical activity in treatment of respiratory diseases, even in cases involving bacterial organisms resistant to other antibiotics, the risk/benefit ratio for gemifloxacin strongly favors treatment with this agent in ABS with 320 mg PO 5-day dosing, in addition to the already approved indications of mild-to-moderate CAP and ABECB.

10. RISK MANAGEMENT PLAN

10.1 Introduction

In the post-marketing period, Oscient has continued working to optimize gemifloxacin's safety through a number of techniques. These include monitoring of spontaneous adverse event reports, minimizing the risks of off label use through the use of fixed dose packs and physician education, and the implementation of phase IV safety and drug utilization studies. FDA approved gemifloxacin for CAP and ABECB in 2003. Oscient is now requesting in 2006 marketing approval for the ABS indication (5 days treatment). This is based on evaluation of the 5-day ABS clinical trial data (1,122 patients), the phase IV FORCE study (1,821 patients) and the post marketing data (764,861 patients). These data all support an acceptable safety profile, and demonstrate a safety profile that has been consistent across the board with the clinical trials, ABS clinical subpopulation, phase IV and finally the post marketing data. There is an acceptable risk/benefit for gemifloxacin in ABS even in the patient population that is under 40 years of ago and in females.

10.2 Minimization of Prolonged Duration of Therapy

The current label for gemifloxacin states that the indication is 5 days for use in patients with ABECB, and 7 days for patients with CAP. The company proposes to migrate use of gemifloxacin to 5-day use following the approval of the pending supplement for mild-to-moderate CAP of 5 days duration. Reducing all treatment course of gemifloxacin to 5 days will further reduce the rash rate, which has been shown to be duration dependent.

The company has conducted a drug utilization study [Prescribing Patterns and Use of Factive® (gemifloxacin mesylate)]. Oscient selected i3 Innovus, a subsidiary of Ingenix®, as the contract research organization to obtain the prescribing use data from its affiliated health plan, UnitedHealthcare. During the study period of the first annual interim report (September 2004 through August 2005), gemifloxacin was prescribed for 4,910 patients contained in the Ingenix® database. This program enables Oscient to monitor the prescribing patterns of gemifloxacin and determine the effectiveness of its risk minimization strategy. The data collected demonstrates that fixed dose packs of gemifloxacin led to <7% prescribing of extended courses of treatment (executive summary of the planned analysis after one year is included in Appendix 1).

Marketing representatives will continue to emphasize the importance of prescribing gemifloxacin according to the label during all meetings with prescribing physicians and pharmacists, thus further decreasing the risk of patients receiving gemifloxacin for longer than the labeled duration.

10.3 Phase IV Study

Oscient is continuing to enroll patients into the phase IV safety study (FORCE). This study's objectives are to better define the incidence and outcome of rash in patients with CAP and ABECB who are treated with gemifloxacin. The planned 2-year interim report on this study has enabled Oscient to better characterize the rash and provided further support and statistical power to the conclusion that the rash associated with gemifloxacin does not result in significant morbidity.

Through the use of these various methods, Oscient intends to continue to minimize the risks of toxicity from the use of gemifloxacin. These methods will also allow for early identification of any safety issues that need to be addressed and thereby allow them to be resolved in a timely manner.

11. CONCLUSION

In conclusion, gemifloxacin, by virtue of its inherent *in vitro* potency, pharmacokinetics, and proven clinical efficacy against both antibiotic sensitive and resistant strains of bacteria responsible for common respiratory diseases, offers unique benefits, while possessing a risk profile equivalent to that of currently marketed antibiotics, including other fluoroquinolones. Gemifloxacin represents an important new therapeutic option for treatment of ABS, particularly those cases involving resistant organisms.

On the basis of these observations, the sponsor believes gemifloxacin has a benefit/risk profile justifying adding the ABS indication with 320 mg PO 5-day dosing to the currently approved prescribing information.

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Appendix 1: Executive Summary - Prescribing Patterns and Use of Factive® (gemifloxacin Mesylate)

EXECUTIVE SUMMARY

STUDY TITLE: Prescribing Patterns and Use of Factive® (gemifloxacin mesylate)

Introduction

As a post-marketing commitment to the FDA, Oscient Pharmaceuticals is conducting an ongoing study to analyze the prescribing patterns and utilization of Factive® (gemifloxacin mesylate) tablets in the United States. When completed in 2008, the final study report will include data from the commercial launch of gemifloxacin in September 2004 through the first three years of marketing.

Oscient has selected i3 Innovus, a subsidiary of Ingenix®, as the contract research organization to obtain the prescribing use data from its affiliated health plan, UnitedHealthcare. For 2004, data relating to approximately 13 million individuals with both medical and pharmacy benefit coverage were available. An additional 8 million enrollees with medical benefits only are also available. Underlying information is geographically diverse across the United States, and is updated frequently. Ingenix research activities utilize de-identified data from the research database except in limited instances where applicable law allows the use of patient identifiable data.

The first of three annual interim reports was prepared and submitted to FDA in June 2006, containing data on gemifloxacin prescription use during the first year of marketing (1 Sep 2004 to 31 August 2005). A summary of the data from this report, including the demographics of the population, the types of diagnoses associated with use of gemifloxacin, the duration of gemifloxacin treatment, the number and duration of refills, and the number of subsequent gemifloxacin treatment episodes are provided in this document.

In addition, analyses of the study population were performed to assess the risk of cross-sensitization and sub-clinical sensitization with the use of gemifloxacin. A summary of these analyses is also provided herein.

Demographics of Study Population

During the study period of the first annual interim report (September 2004 through August 2005), gemifloxacin was prescribed for 4,910 patients contained in the Ingenix® database. Table 1 provides an overview of the characteristics of these patients.

Sixty-three percent (63%) of the patients were in the 40-64 years age group. Nine percent (9%) of the patients were 65 years of age or older and only 0.5% of the patients were less than 18

years old. A majority (56%) of the patients were female. An analysis by both age and gender not included here showed that 16.2% (797) of all patients prescribed gemifloxacin were women less than 40 years of age [First Interim Annual Report, Table 5].

TABLE 1. Characteristics of Overall Study Population

Population Variables	No. of Patients N=4,910
	n (%)
Age (mean, SD)	47.21 (13.1)
Age Group	
Less than 18 years	22 (0.5)
18-39	1,376 (28.0)
40-64	3,086 (62.9)
65 or older	426 (8.7)
Gender	
Female	2,769 (56.4)
Male	2,141 (43.6)
Health Plan Region	
Northeast	618 (12.6)
Midwest	1,047 (21.3)
South	3,140 (64.0)
West	105 (2.1)
Insurance Type	
Commercial	4,788 (97.5)
Medicaid	6 (0.1)
Medicare	116 (2.4)

Data: First Interim Annual Report, Table 1
Percentages within categories may not sum to 100.0 due to rounding.

Diagnoses Associated with Gemifloxacin Prescriptions

For each patient who obtained a gemifloxacin prescription, the study searched for the presence of ICD-9 diagnostic codes three days prior to and including the date of the patient's gemifloxacin prescription. An Oscient physician reviewed and categorized these ICD-9 codes in aggregate into eight infectious disease (ID) groups. Any patient who did not have an ID code identified with their prescription was placed into the non-ID diagnostic group. Table 2 presents all patients by diagnostic group.

A majority (72.3%) of patients had an identifiable infectious disease diagnosis code. The three most common ID diagnostic code groups associated with a gemifloxacin prescription were the "bronchitis" (33.0%), "sinusitis" (27.5%) and "URI, excluding sinusitis" (18.8%) groups.

TABLE 2. All Patients by Diagnostic Group

Diagnostic Group	No. of Patients N=4,910*
	n (%)
ID Diagnostic Group	**3,548 (72.3)**
Upper Respiratory Infection (URI), excluding Sinusitis	924 (18.8)
Sinusitis	1,349 (27.5)
Otitis	214 (4.4)
Bronchitis	1,621 (33.0)
Pneumonia	316 (6.4)
Other Infections	212 (4.3)
Genitourinary (GU) Infection	78 (1.6)
Skin Infection	96 (2.0)
Non-ID Diagnostic Group†	**1,362 (27.7)**

*A patient with more than one diagnosis within a particular ID diagnostic group is only counted once. Patients can be counted in more than one ID diagnostic group. Therefore, the total number of patients in all ID diagnostic groups does not equal the total number of patients in the ID Diagnostic Group row.

† The Non-ID Diagnostic Group consists of 1,362 patients who took gemifloxacin and who did not have an infectious disease diagnosis identified during medical review. These patients are exclusive of the 8 ID diagnostic groups.

Data: First Interim Annual Report, Table 2

Subsequent Treatment Episodes

A new treatment episode was considered to have begun whenever a subsequent gemifloxacin prescription was filled for the same patient greater than 14 days after the end of the previous gemifloxacin fill. Table 3 presents the number of subsequent treatment episodes for the 4,910 patients who received a gemifloxacin fill.

Most patients (95.0%) had only a single treatment episode of gemifloxacin. This rate was similarly high across all ID diagnostic groups. Only 36 patients (0.7%) had more than two treatment episodes with gemifloxacin.

TABLE 3. Number of Subsequent gemifloxacin Treatment Episodes by Patient

Diagnostic Group	Number of Subsequent Treatment Episodes (n=number of patients)						
	0	**1**	**2**	**3**	**4**	**7**	**Total**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ALL Patients	**4,662 (95.0)**	**212 (4.3)**	**29 (0.6)**	**4 (0.1)**	**2 (0.0)**	**1 (0.0)**	**4,910 (100)**
ID Diagnostic Group	**3,361 (95.3)**	**142 (4.0)**	**20 (0.6)**	**2 (0.1)**	**-**	**1 (0.0)**	**3,526 (100)**
URI (excl. sinus)	866 (95.3)	38 (4.2)	5 (0.6)	-	-	-	909 (100)
Sinusitis	1,250 (94.3)	63 (4.8)	11 (0.8)	1 (0.1)	-	1 (0.1)	1,326 (100)
Otitis	195 (93.8)	12 (5.8)	1 (0.5)	-	-	-	208 (100)
Bronchitis	1,522 (95.2)	68 (4.3)	6 (0.4)	2 (0.1)	-	-	1,598 (100)
Pneumonia	301 (96.2)	10 (3.2)	2 (0.6)	-	-	-	313 (100)
Other Infection	198 (96.1)	7 (3.4)	1 (0.5)	-	-	-	206 (100)
GU Infection	70 (95.9)	3 (4.1)	-	-	-	-	73 (100)
Skin infection	85 (95.5)	4 (4.5)	-	-	-	-	89 (100)
Non-ID Diagnostic Group	**1,301 (94.0)**	**70 (5.1)**	**9 (0.7)**	**2 (0.1)**	**2 (0.1)**	**-**	**1,384 (100)**

Source: Addendum Source Table 4A

For all subsequent treatment episodes, the average time to the next treatment episode was 69.86 days (SD: ± 52.69 days; median: 56; range: 15 to 322 days).

Length of Gemifloxacin Prescriptions

Table 4 presents all patients by the length of the initial gemifloxacin prescription and stratified by diagnostic group. Overall, 90% of patients received either 5 or 7 days of therapy with their initial gemifloxacin prescription. A total of 2,292 patients (46.7%) received a 5-day course of treatment and 2,127 patients (43.3%) received a 7-day course. The percentage of patients who received a prescription for a duration longer than 7 days was low and similar across all diagnostic groups.

TABLE 4. Number of Patients by Days of Treatment of Initial Gemifloxacin Prescription

Diagnostic Group	Length of Initial Index Prescription in Days							
	<5	5	7	10	14	>14	Other*	Total
ALL PATIENTS	**139 (2.8)**	**2292 (46.7)**	**2127 (43.3)**	**244 (5.0)**	**47 (1.0)**	**19 (0.4)**	**42 (0.9)**	**4,910 (100)**
ID Diagnostic Group	**100 (2.8)**	**1637 (46.1)**	**1559 (43.9)**	**177 (5.0)**	**33 (0.9)**	**14 (0.4)**	**28 (0.8)**	**3,548 (100)**
URI (excl. Sinusitis)	15 (1.6)	492 (53.2)	375 (40.6)	31 (3.4)	5 (0.5)	1 (0.1)	5 (0.5)	924 (100)
Sinusitis	35 (2.6)	545 (40.4)	637 (47.2)	91 (6.7)	22 (1.6)	8 (0.6)	11 (0.8)	1,349 (100)
Otitis	8 (3.7)	88 (41.1)	97 (45.3)	13 (6.1)	4 (1.9)	0	4 (1.9)	214 (100)
Bronchitis	53 (3.3)	774 (47.7)	708 (43.7)	65 (4.0)	6 (0.4)	4 (0.2)	11 (0.7)	1,621 (100)
Pneumonia	11 (3.5)	93 (29.4)	185 (58.5)	17 (5.4)	5 (1.6)	1 (0.3)	4 (1.3)	316 (100)
Other Infections	4 (1.9)	108 (50.9)	78 (36.8)	14 (6.6)	3 (1.4)	3 (1.4)	2 (0.9)	212 (100)
GU Infection	4 (5.1)	36 (46.2)	31 (39.7)	3 (3.8)	1 (1.3)	1 (1.3)	2 (2.6)	78 (100)
Skin Infection	4 (4.2)	41 (42.7)	41 (42.7)	6 (6.3)	3 (3.1)	0	1 (1.0)	96 (100)
Non-ID Diagnostic Group‡	**39 (2.9)**	**655 (48.1)**	**568 (41.7)**	**67 (4.9)**	**14 (1.0)**	**5 (0.4)**	**14 (1.0)**	**1,362 (100)**

*"Other" includes a total of the patients receiving a duration of 6, 8, 9, 11, 12 or 13 days.
‡ The Non-ID Diagnostic Group consists of 1,362 patients who took gemifloxacin and who did not have an infectious disease diagnosis identified during medical review. These patients are exclusive of the 8 ID diagnostic groups.
Source: First Interim Annual Report, Table 8, consolidated

Number and Timing of Refills

A refill was defined as a subsequent gemifloxacin prescription filled for the same patient within 14 days of the end of the previous gemifloxacin fill. Table 5 presents the number of refills of the initial prescription for all 4,910 patients who received gemifloxacin.

The refill rate for the initial gemifloxacin fill was low (2.8%). Only 11 patients (0.2%) had >1 refill of their initial fill. Across all treatment episodes, the refill rate was 3.1%.

TABLE 5. Number of Refills by Treatment Episode

Diagnostic Group	Number of Refills Per Patient				
	0	1	2	3	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Index (Initial) Treatment Episode	4,774 (97.2)	125 (2.6)	7 (0.1)	4 (0.1)	4,910 (100)
2nd Treatment Episode	228 (91.9)	19 (7.7)	1 (0.4)	-	248 (100)
3rd Treatment Episode	30 (83.3)	5 (13.9)	1 (2.8)	-	36 (100)
4th Treatment Episode	6 (85.7)	1 (14.3)	-	-	7 (100)
5th Treatment Episode	3 (100)	-	-	-	3 (100)
6th Treatment Episode	1 (100)	-	-	-	1 (100)
7th Treatment Episode	1 (100)	-	-	-	1 (100)
8th Treatment Episode	1 (100)	-	-	-	1 (100)
ALL Treatment Episodes	**5,044 (96.9)**	**150 (2.9)**	**9 (0.2)**	**4 (0.1)**	**5,207 (100)**

Source: Addendum Source Table 1C

Due to the small numbers of patients with a refill of a subsequent treatment episode, the number of refills was stratified by diagnostic group for the index gemifloxacin fill only (Table 6). Across all ID diagnostic groups, the rate of refills was low (<6%) with a slightly higher incidence of refills of the index fill for patients in the Sinusitis, Pneumonia, GU Infection and Skin Infection diagnostic groups.

TABLE 6. Number of Refills of Index Gemifloxacin Fill by ID Diagnostic Group

Diagnostic Group	Number of Refills of Index gemifloxacin Fill				
	0	**1**	**2**	**3**	**Total**
	n (%)	n (%)	n (%)	n (%)	n (%)
ALL Patients	**4,774 (97.2)**	**125 (2.6)**	**7 (0.1)**	**4 (0.1)**	**4,910 (100)**
ID Diagnostic Group	**3,428 (97.2)**	**92 (2.6)**	**5 (0.1)**	**1 (0.0)**	**3,526 (100)**
URI (excl. sinus)	892 (98.1)	14 (1.5)	2 (0.2)	1 (0.1)	909 (100)
Sinusitis	1,282 (96.7)	41 (3.1)	2 (0.2)	1 (0.1)	1,326 (100)
Otitis	203 (97.6)	5 (2.4)	-	-	208 (100)
Bronchitis	1,560 (97.6)	35 (2.2)	2 (0.1)	1 (0.1)	1,598 (100)
Pneumonia	299 (95.5)	14 (4.5)	-	-	313 (100)
Other Infection	201 (97.6)	5 (2.4)	-	-	206 (100)
GU Infection	69 (94.5)	4 (5.5)	-	-	73 (100)
Skin infection	84 (94.4)	5 (5.6)	-	-	89 (100)
Non-ID Diagnostic Group	**1,346 (97.3)**	**33 (2.4)**	**2 (0.1)**	**3 (0.2)**	**1,384 (100)**

Source: Addendum Source Table 1A

As described above, 90% (4419/4910) of patients received 5 or 7 days for their initial gemifloxacin fill. The refill rate for patients who received either 5 or 7 days for their initial prescription was low (2.1% [48/2292] and 3.1% [65/2127], respectively). The combined refill rate for patients receiving approved durations for their initial prescription (5 or 7 days) was 2.6% (113/4419).

The majority of patients in the three ID diagnostic groups with >5 patients (Upper Respiratory Infection (excluding Sinusitis), Sinusitis, Bronchitis and Pneumonia received their refill between 0 and 4 days after the end of therapy. Only 17/4910 patients (0.003%) had their gemifloxacin prescription refilled before it had ended.

Length of Refills

Addendum Table 7 presents the number of patients who received at least one refill of their initial fill by the duration of the refill. 86.0% of patients receiving a refill received either 5 or 7 days duration.

Patients receiving a refill more commonly received a refill of the same duration as their initial fill. 72.9% of patients who received an initial 5 days of therapy received a refill of another 5

days of therapy vs. 20.8% who received 7; similarly, 76.9% of patients receiving an initial 7 days of therapy received a refill of 7 days vs. 15.4% who received 5 days.

TABLE 7. Duration of First Gemifloxacin Refill by ID Diagnostic Group

Diagnostic Group	Number of Days of First Index Refill (n=number of patients)								
	3	**4**	**5**	**7**	**10**	**14**	**15**	**30**	**Total**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ALL Patients	**1 (0.7)**	**2 (1.5)**	**55 (40.4)**	**62 (45.6)**	**5 (3.7)**	**8 (5.9)**	**2 (1.5)**	**1 (0.7)**	**136 (100)**
ID Diagnostic Group	**1 (1.0)**	**2 (2.0)**	**40 (40.8)**	**42 (42.9)**	**5 (5.1)**	**5 (5.1)**	**2 (2.0)**	**1 (1.0)**	**98 (100)**
URI (excl. sinus)	-	-	5 (29.4)	9 (52.9)	2 (11.8)	1 (5.9)	-	-	17 (100)
Sinusitis	1 (2.3)	1 (2.3)	14 (31.8)	20 (45.5)	1 (2.3)	4 (9.1)	2 (4.6)	1 (2.3)	44 (100)
Otitis	-	-	1 (20.0)	4 (80.0)	-	-	-	-	5 (100)
Bronchitis	-	1 (2.6)	18 (47.4)	18 (47.4)	1 (2.6)	-	-	-	38 (100)
Pneumonia	-	-	7 (50.0)	6 (42.9)	-	1 (7.1)	-	-	14 (100)
Other Infection	-	-	3 (60.0)	2 (40.0)	-	-	-	-	5 (100)
GU Infection	-	-	3 (75.0)	1 (25.0)	-	-	-	-	4 (100)
Skin infection	-	-	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)	-	-	5 (100)
Non-ID Diagnostic Group	**-**	**-**	**15 (39.5)**	**20 (52.6)**	**-**	**3 (7.9)**	**-**	**-**	**38 (100)**

Source: Addendum Source Table 3B

Assessment of Cross-Sensitization

Oscient Pharmaceuticals requested i3 Innovus to perform an additional analysis of the dataset created for the first interim annual report to determine the risk of cross-sensitization to other quinolones with the use of gemifloxacin. Cross-sensitization was defined as the occurrence of rash upon subsequent exposure to another quinolone in patients who had previously developed a rash when treated with gemifloxacin.

Figure 1 presents a schematic overview of the cross-sensitization analysis.

An assessment was first made of the number of patients with an occurrence of rash associated with use of gemifloxacin by searching for the occurrence of any of a series of ICD-9 diagnostic codes from the first day of any gemifloxacin fill up to 14 days after the fill. The ICD-9 codes that were chosen for the search are listed in Table 8.

TABLE 8. List of ICD-9 Codes Used to Determine Occurrence of Rash

693.0 Due to drugs and medicines
Dermatitis medicamentosa NOS
693.8 Due to other specified substances taken internally
693.9 Due to unspecified substance taken internally
695.0 Toxic erythema
Erythema venenatum
695.1 Erythema multiforme
Erythema iris
Herpes iris
Lyell's syndrome
Scalded skin syndrome
Stevens-Johnson syndrome
Toxic epidermal necrolysis
695.9 Unspecified erythematous condition
Erythema NOS
Erythroderma (secondary)
782.1 Rash and other non-specific skin eruption
Exanthem
995.2 Unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered
Adverse effect to correct medicinal substance properly administered
Allergic reaction to correct medicinal substance properly administered
Hypersensitivity to correct medicinal substance properly administered
Idiosyncrasy due to correct medicinal substance properly administered
Drug:
hypersensitivity NOS
reaction NOS
995.3 Allergy, unspecified
Allergic reaction NOS
Hypersensitivity NOS
Idiosyncrasy NOS

147 out of the 4,910 patients in the dataset, or 3%, had at least one of these ICD-9 codes within 14 days of any gemifloxacin prescription.

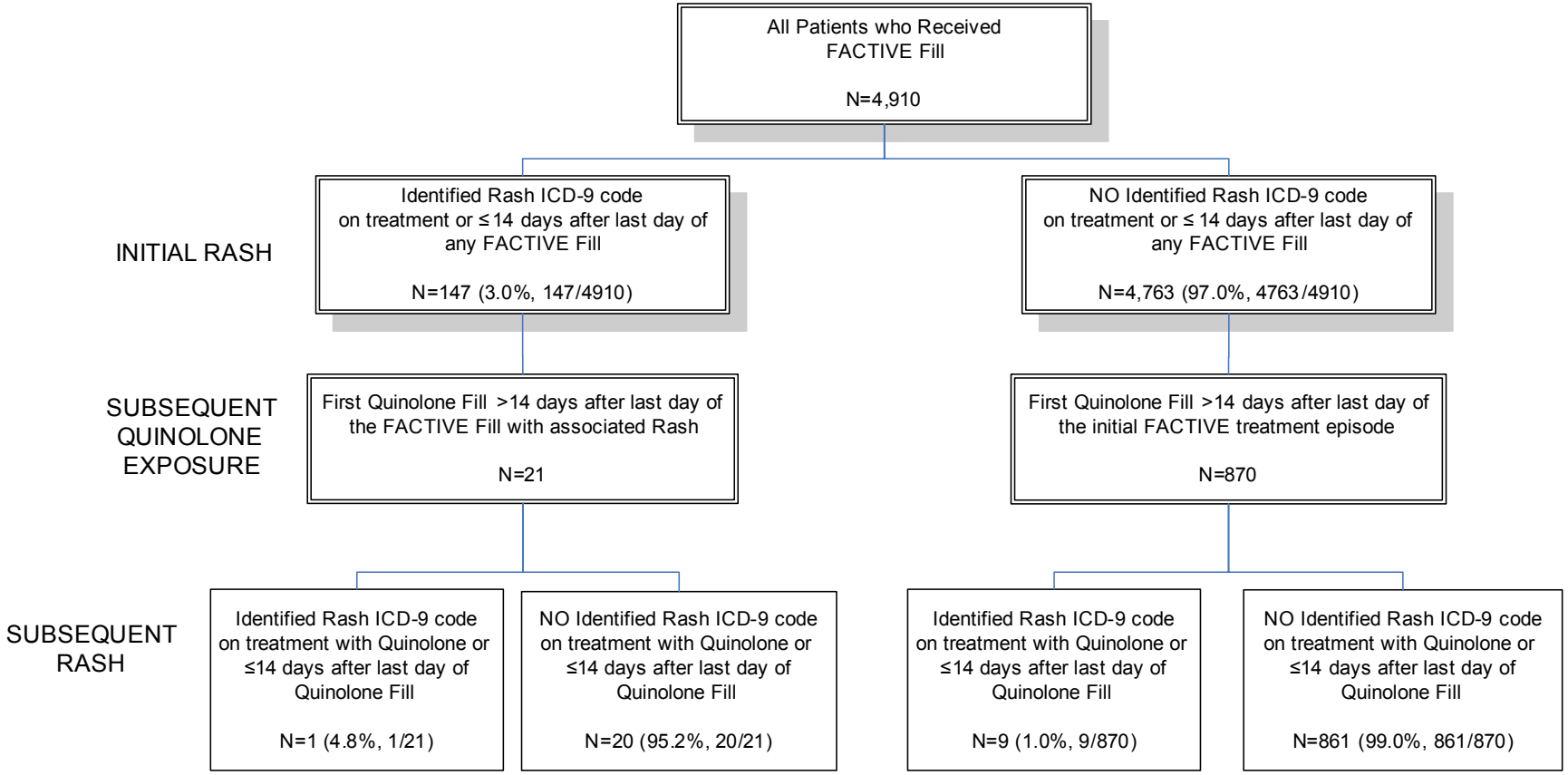
Notably, of the 147 patients with an initial gemifloxacin rash, 21 (14.3%) were subsequently treated with another quinolone. One of those 21 patients had an identified rash associated with the quinolone exposure.

The remaining patients without an associated rash (4763/4910) were then assessed for subsequent quinolone exposure by searching for the first occurrence of a quinolone prescription >14 days after the end of their initial gemifloxacin prescription. Quinolones included in the search were alatrofloxacin, cinoxacin, ciprofloxacin, enoxacin, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin and trovafloxacin. Of the 4763 patients who had no rash associated with use of gemifloxacin, there were 870 patients who had exposure to a quinolone after their initial exposure to gemifloxacin.

This subset of 870 patients was assessed for an occurrence of a rash associated with the subsequent quinolone exposure by searching for the occurrence of any of the same series of ICD-9 diagnostic codes from the first day of the subsequent quinolone prescription up to 14 days after the end of the quinolone prescription. Of the 870 patients with no rash associated with use of gemifloxacin who then had subsequent exposure to a quinolone, there were 9 patients (1.0%) who had an identified rash with the quinolone exposure. The cross-sensitization rate in women < 40 years was similar to the overall population (0.8%, 1/131). The subsequent quinolones received by the 9 patients were ciprofloxacin HCL (n=3), gatifloxacin (n=1), levofloxacin (n=3) and moxifloxacin HCL (n=2).

These findings are supportive of the conclusion that the risk with gemifloxacin of cross-sensitization to other quinolones is low and additionally that prior exposure to gemifloxacin even in patients without rash does not increase the risk of developing rash upon exposure to another quinolone.

FIGURE 1: Gemifloxacin Cross-Sensitization Analysis



Assessment of Sub-clinical Sensitization

To determine the risk of sub-clinical sensitization with use of gemifloxacin, an additional analysis was performed on the dataset created for the first interim annual report. Sub-clinical sensitization was defined as the occurrence of rash in patients receiving gemifloxacin who had previously received gemifloxacin without developing a rash.

Figure 2 presents a schematic overview of the sub-clinical sensitization analysis.

The number of patients with an occurrence of rash associated only with their first treatment episode of gemifloxacin was determined by searching for the occurrence of any of the rash ICD-9 diagnostic codes (see Table 8 above) from the first day of the initial gemifloxacin prescription up to 14 days after the end of the treatment episode (i.e., including any refills of the initial fill).

144 out of the 4,910 patients in the dataset, or 2.9%, had at least one of the rash ICD-9 codes during or up to 14 days after their initial gemifloxacin treatment episode. Notably, of the 144 patients with an initial gemifloxacin rash, 4 were retreated with gemifloxacin and none had an identified rash.

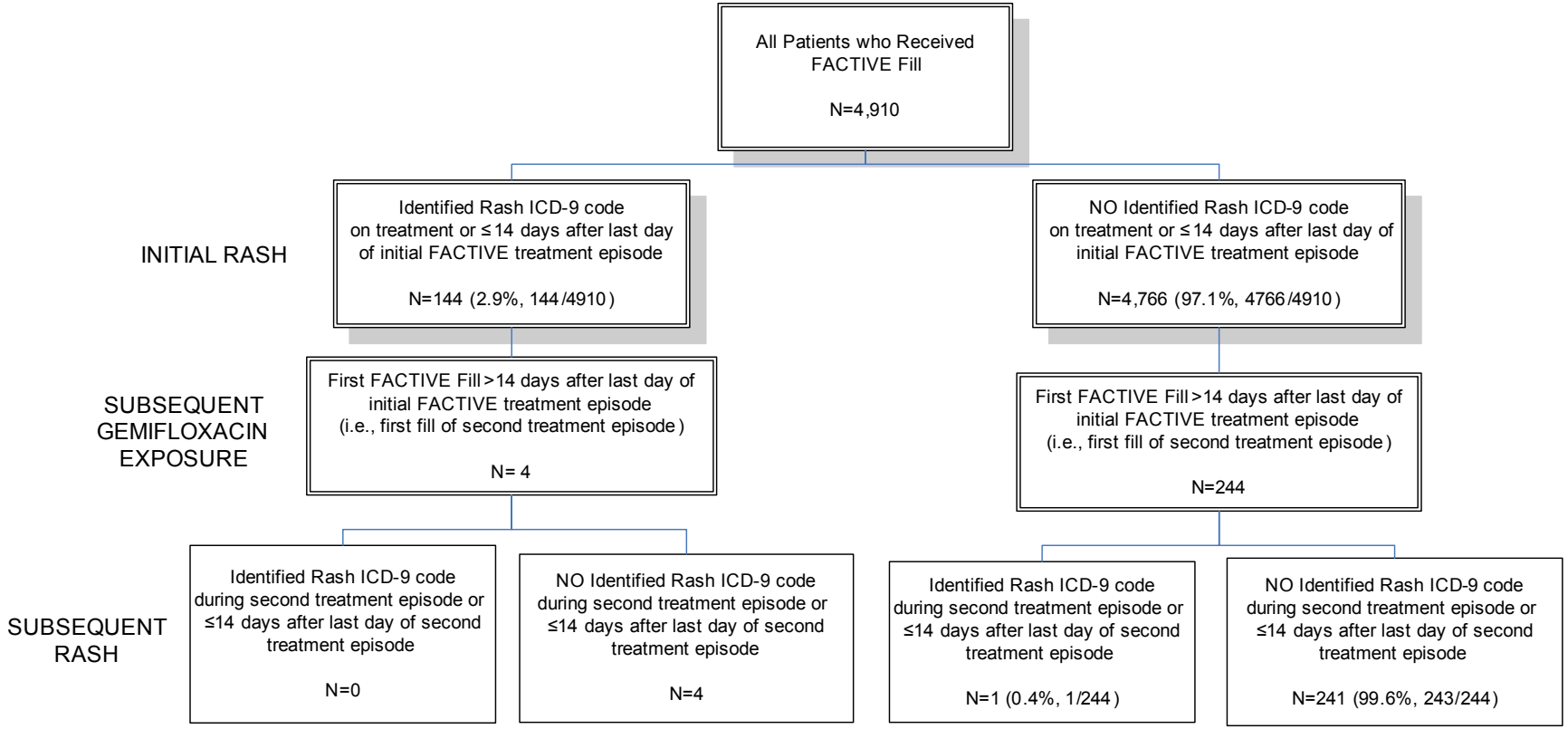
The remaining patients without an associated rash (4766/4910) were then assessed for subsequent gemifloxacin exposure by searching for the first occurrence of a gemifloxacin prescription >14 days after the end of their initial gemifloxacin treatment episode. Of the 4,766 patients who had no rash associated with their first treatment episode, there were 244 patients who had subsequent exposure to gemifloxacin.

This subset of 244 patients was assessed for an occurrence of a rash associated with the subsequent gemifloxacin treatment episode by searching for the occurrence of any of the same series of ICD-9 diagnostic codes from the first day of the subsequent gemifloxacin exposure up to 14 days after the end of the episode.

Of the 244 patients with no rash associated with a first gemifloxacin treatment episode who then had a re-exposure to gemifloxacin, there was one patient (0.4%) with identified rash upon re-exposure to gemifloxacin.

This finding supports the conclusion that the risk of sub-clinical sensitization with gemifloxacin is low.

FIGURE 2: Gemifloxacin Sub-Clinical Sensitization Analysis



Conclusions

- Of those patients with an identified infectious disease diagnosis code prior to their gemifloxacin prescription, the three most commonly occurring infectious disease groups were respiratory tract infections: bronchitis (33.0%), sinusitis (27.5%), and URI, excluding sinusitis (18.8%).
- Most patients (95.0%) took gemifloxacin for a single treatment episode. Only 36 patients (0.7%) had more than two treatment episodes with gemifloxacin.
- Most patients (90%) received either 5 or 7 days of treatment for their initial prescription. The percentage of patients who received treatment longer than 7 days was low and similar across all ID diagnostic groups.
- The refill rate for the initial prescription was 2.8%. Across all treatment episodes, the refill rate was 3.1%. Only 11 patients (0.2%) had >1 refill of their initial prescription.
- Across all indications, the mean number of days of the refill was 6.93 days. The respiratory tract ID diagnostic group with the longest mean refill duration was the Sinusitis group (7.80 days); the shortest was the Bronchitis group (6.05 days). 86.0% of patients receiving a refill received treatment of 5 or 7 days duration.
- Patients most commonly received a refill of the same duration as their initial prescription.
- Of the 147 patients with a gemifloxacin rash, 21 (14.3%) were subsequently treated with another quinolone. One of those 21 patients (4.8%) developed a rash. This finding supports the conclusion that the risk of cross-sensitization to other quinolones with the use of gemifloxacin is low.
- Of the 244 patients with no identified rash associated with their first gemifloxacin treatment episode who then had subsequent re-exposure to gemifloxacin, there was 1 patient (0.4%) who developed a rash. This finding supports the conclusion that the risk of sub-clinical sensitization with the use of gemifloxacin is low.

Appendix 2: Package Insert For Factive (Gemifloxacin Mesylate)

PRESCRIBING INFORMATION

FACTIVE®

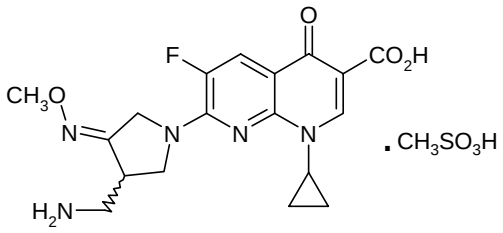
(gemifloxacin mesylate) Tablets

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

FACTIVE (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically, gemifloxacin is (*R,S*)-7-[(4Z)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

The mesylate salt is a white to light brown solid with a molecular weight of 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 μg/mL at 37°C, pH 7.0). Its empirical formula is $C_{18}H_{20}FN_5O_4 \bullet CH_4O_3S$ and its chemical structure is:



Each white to off-white, oval, film-coated FACTIVE tablet has breaklines and GE 320 debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of gemifloxacin are approximately linear over the dose range from 40 mg to 640 mg. There was minimal accumulation of gemifloxacin following multiple oral doses up to 640 mg a day for 7 days (mean accumulation <20%). Following repeat oral

administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing.

Absorption and Bioavailability

Gemifloxacin, given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (Cmax) and systemic drug exposure (AUC(0-24)) were 1.61 ± 0.51 μg/mL (range 0.70-2.62 μg/mL) and 9.93 ± 3.07 μg•hr/mL (range 4.71-20.1 μg•hr/mL), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC(0-24), 8.36 μg•hr/mL; range 3.2 – 47.7 μg•hr/mL.

The pharmacokinetics of gemifloxacin were not significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore FACTIVE tablets may be administered without regard to meals.

Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects is approximately 60 to 70% and is concentration independent. After repeated doses, the *in vivo* plasma protein binding in healthy elderly and young subjects ranged from 55% to 73% and was unaffected by age. Renal impairment does not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 L/kg (range, 1.66 – 12.12 L/kg).

Gemifloxacin is widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the plasma. Gemifloxacin penetrates well into lung tissue and fluids. After five daily doses of 320 mg gemifloxacin, concentrations in plasma, bronchoalveolar macrophages, epithelial lining fluid and bronchial mucosa at approximately 2 hours were as in Table 1:

Table 1. Gemifloxacin Concentrations in Plasma and Tissues (320 mg Oral Dosing)

Tissue	Concentration (mean ± SD)	Ratio compared with plasma (mean±SD)
Plasma	1.40 (0.442) μg/mL	---
Bronchoalveolar Macrophages	107 (77) μg/g	90.5 (106.3)
Epithelial Lining Fluid	2.69 (1.96) μg/mL	1.99 (1.32)
Bronchial Mucosa	9.52 (5.15) μg/g	7.21 (4.03)

Metabolism

Gemifloxacin is metabolized to a limited extent by the liver. The unchanged compound is the predominant drug-related component detected in plasma (approximately 65%) up to 4 hours after dosing. All metabolites formed are minor (<10% of the administered oral dose); the principal ones are N-acetyl gemifloxacin, the E-isomer of gemifloxacin and the carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes do not play an important role in gemifloxacin metabolism, and the metabolic activity of these enzymes is not significantly inhibited by gemifloxacin.

Excretion

Gemifloxacin and its metabolites are excreted via dual routes of excretion. Following oral administration of gemifloxacin to healthy subjects, a mean (±SD) of 61 ± 9.5% of the dose was excreted in the feces and 36 ± 9.3% in the urine as unchanged drug and metabolites. The mean (±SD) renal clearance following repeat doses of 320 mg was approximately 11.6 ± 3.9 L/hr (range 4.6-17.6 L/hr), which indicates active secretion is involved in the renal excretion of gemifloxacin. The mean (±SD) plasma elimination half-life at steady state following 320 mg to healthy subjects was approximately 7 ± 2 hours (range 4-12 hours).

Special Populations

Pediatric: The pharmacokinetics of gemifloxacin in pediatric subjects have not been studied.

Geriatric: In adult subjects, the pharmacokinetics of gemifloxacin are not affected by age.

Gender: There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin,

AUC values were approximately 10% higher in healthy female patients compared to males. Males and females had mean AUC values of 7.98 μg·hr/mL (range, 3.21 – 42.71 μg·hr/mL) and 8.80 μg·hr/mL (range, 3.33 – 47.73 μg·hr/mL), respectively. No gemifloxacin dosage adjustment based on gender is necessary.

Hepatic Insufficiency: The pharmacokinetics following a single 320 mg dose of gemifloxacin were studied in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) liver disease. There was a mean increase in AUC (0-inf) of 34% and a mean increase in Cmax of 25% in these patients with hepatic impairment compared to healthy volunteers.

The pharmacokinetics of a single 320 mg dose of gemifloxacin were also studied in patients with severe hepatic impairment (Child-Pugh Class C). There was a mean increase in AUC (0-inf) of 45% and a mean increase in Cmax of 41% in these subjects with hepatic impairment compared to healthy volunteers.

These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic impairment patients. No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. (See **DOSAGE AND ADMINISTRATION**.)

Renal Insufficiency: Results from population pharmacokinetic and clinical pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin Cmax was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. (See **DOSAGE AND ADMINISTRATION.)** Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Photosensitivity Potential: In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg b.i.d., or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg b.i.d. and the photosensitivity potential for both drugs were statistically greater than that of placebo. Photosensitivity reactions were

reported rarely in clinical trials with gemifloxacin (0.039%). (See **ADVERSE REACTIONS**.)

Drug-Drug Interactions

Antacids/Di- and Trivalent Cations: The systemic availability of gemifloxacin is significantly reduced when an aluminum- and magnesium- containing antacid is concomitantly administered (AUC decreased 85%; Cmax decreased 87%). Administration of an aluminum- and magnesium- containing antacid or ferrous sulfate (325 mg) at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the systemic availability of gemifloxacin. Therefore, aluminum- and/or magnesium- containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after taking FACTIVE tablets.

Calcium carbonate (1000 mg) given either 2 hr before or 2 hr after gemifloxacin administration showed no notable reduction in gemifloxacin systemic availability. Calcium carbonate administered simultaneously with gemifloxacin resulted in a small, not clinically significant, decrease in gemifloxacin exposure [AUC (0-inf) decreased 21% and Cmax decreased].

Sucralfate: When sucralfate (2 g) was administered 3 hours prior to gemifloxacin, the oral bioavailability of gemifloxacin was significantly reduced (53% decrease in AUC; 69% decrease in Cmax). When sucralfate (2 g) was administered 2 hours after gemifloxacin, the oral bioavailability of gemifloxacin was not significantly affected; therefore FACTIVE should be taken at least 2 hours before sucralfate. (See **PRECAUTIONS.**)

In Vitro Metabolism: Results of *in vitro* inhibition studies indicate that hepatic cytochrome P450 (CYP450) enzymes do not play an important role in gemifloxacin metabolism. Therefore gemifloxacin should not cause significant *in vivo* pharmacokinetic interactions with other drugs that are metabolized by CYP450 enzymes.

Theophylline: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of theophylline (300 to 400 mg b.i.d. to healthy male subjects).

Digoxin: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of digoxin (0.25 mg once daily to healthy elderly subjects).

Oral Contraceptives: The effect of an oral estrogen/progesterone contraceptive product (once daily for 21 days) on the pharmacokinetics of gemifloxacin (320 mg once daily for 6 days) in healthy female subjects indicates that concomitant administration caused an average reduction in gemifloxacin AUC and Cmax of 19% and 12%. These changes are not considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the

repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive product (30 μg/150 μg once daily for 21 days to healthy female subjects).

Cimetidine: Co-administration of a single dose of 320 mg gemifloxacin with cimetidine 400 mg four times daily for 7 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 6%, respectively. These increases are not considered clinically significant.

Omeprazole: Co-administration of a single dose of 320 mg gemifloxacin with omeprazole 40 mg once daily for 4 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 11%, respectively. These increases are not considered clinically significant.

Warfarin: Administration of repeated doses of gemifloxacin (320 mg once daily for 7 days) to healthy subjects on stable warfarin therapy had no significant effect on warfarin-induced anticoagulant activity (i.e., International Normalized Ratios for Prothrombin Time). (See **PRECAUTIONS: Drug Interactions**.)

Probenecid: Administration of a single dose of 320 mg gemifloxacin to healthy subjects who also received repeat doses of probenecid (total dose = 4.5 g) reduced the mean renal clearance of gemifloxacin by approximately 50%, resulting in a mean increase of 45% in gemifloxacin AUC(0-inf) and a prolongation of mean half-life by 1.6 hours. Mean gemifloxacin Cmax increased 8%.

Microbiology

Gemifloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms. Gemifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs). Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. *Streptococcus pneumoniae* showing mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S. pneumoniae* (dual targeting), and has MIC values that are still in the susceptible range for some of these double mutants.

The mechanism of action of quinolones, including gemifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to gemifloxacin and other quinolones. There is no known cross-resistance between gemifloxacin and the above mentioned classes of antimicrobials.

The main mechanism of fluoroquinolone resistance is due to mutations in DNA gyrase and/or TOPO IV. Resistance to gemifloxacin develops slowly via multistep mutations and efflux in a manner similar to other fluoroquinolones. The frequency of spontaneous mutation is low (10^{-7} to $<10^{-10}$). Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gemifloxacin.

Gemifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP])[*],[*]MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae (many strains are only moderately susceptible)
Moraxella catarrhalis

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following data are available, **but their clinical significance is unknown**.

Gemifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.25 μg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic gram-positive microorganisms
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Acinetobacter lwoffii
Klebsiella oxytoca
Legionella pneumophila
Proteus vulgaris

Susceptibility Tests

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gemifloxacin powder. The MICs should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

MIC (µg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5	Intermediate (I)
≥1.0	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[b]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)
0.25	Intermediate (I)
≥0.5	Resistant (R)

[b]These interpretive standards are applicable only to broth microdilution susceptibility tests using cation–adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gemifloxacin powder should provide the following MIC values:

Microorganism		MIC Range (µg/mL)
Enterococcus faecalis	ATCC 29212	0.016-0.12
Escherichia coli	ATCC 25922	0.004-0.016
Haemophilus influenzae	ATCC 49247[c]	0.002-0.008
Streptococcus pneumoniae	ATCC 49619[d]	0.008-0.03

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5µg gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5µg gemifloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
16-19	Intermediate (I)
≤15	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[e]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)

[e] This interpretive standard is applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[f]:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
20-22	Intermediate (I)
≤19	Resistant (R)

[f] These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gemifloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5µg gemifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29-36
Haemophilus influenzae	ATCC 49247[g]	30-37

Streptococcus pneumoniae	ATCC 49619[h]	28-34

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2] .

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

FACTIVE is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES**.)

Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae*, *Haemophilus parainfluenzae,* or *Moraxella catarrhalis*.

Community-acquired pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae (*including multi-drug resistant strains [MDRSP]) *, *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae, or Klebsiella pneumoniae***.*

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g. cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

** In clinical trials, there were 13 subjects with *Klebsiella pneumoniae,* primarily from non-comparative studies. Ten subjects had mild disease, two had moderate disease, and one had severe disease. There were two clinical failures in subjects with mild disease (one subject with bacteriologic recurrence).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Gemifloxacin is contraindicated in patients with a history of hypersensitivity to gemifloxacin, fluoroquinolone antibiotic agents, or any of the product components.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF FACTIVE IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy and Nursing Mothers subsections.)

QT Effects: Fluoroquinolones may prolong the QT interval in some patients. Gemifloxacin should be avoided in patients with a history of prolongation of the QTc interval, patients with uncorrected electrolyte disorders (hypokalemia or hypomagnesemia), and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents.

Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gemifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with gemifloxacin treatment in over 6775 patients, including 653 patients concurrently receiving drugs known to prolong the QTc interval and 5 patients with hypokalemia.

The likelihood of QTc prolongation may increase with increasing dose of the drug; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the Cmax and AUC are slightly higher. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. The maximal change in the QTc interval occurs approximately 5-10 hours following oral administration of gemifloxacin.

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

Gemifloxacin should be discontinued immediately at the appearance of any sign of an immediate type I hypersensitivity skin rash or any other manifestation of a hypersensitivity reaction**;** the need for continued fluoroquinolone therapy should be evaluated. As with other drugs, serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines,

corticosteroids, pressor amines and airway management as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and occasionally fatal events, some due to hypersensitivity and/or some of uncertain etiology, have been reported in patients receiving fluoroquinolones. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations usually include new onset fever and one or more of the following: rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Peripheral Neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones.

Tendon Effects: Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Gemifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones.

CNS Effects: In clinical studies with gemifloxacin, central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, gemifloxacin should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in gemifloxacin clinical trials, convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving other fluoroquinolones. CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions occur in patients receiving gemifloxacin, the drug should be discontinued and appropriate measures instituted.

Antibiotic Associated Colitis: Pseudomembranous colitis has been reported with nearly all antibacterial agents, including gemifloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. (See **ADVERSE REACTIONS.**)

PRECAUTIONS

General*:* Prescribing FACTIVE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Rash: In clinical studies, the overall rate of drug-related rash was 2.8%. The most common form of rash associated with gemifloxacin was described as maculopapular and mild to moderate in severity; 0.3% was described as urticarial in appearance. Rash usually appeared 8 to 10 days after start of therapy; 60% of the rashes resolved within 7 days, and 80% resolved within 14 days. Approximately 10% of those patients developing rash had a rash described as of severe intensity. Histology was evaluated in a clinical pharmacology study and was consistent with an uncomplicated exanthematous skin reaction and showed no evidence of phototoxicity, vasculitis, or necrosis. There were no documented cases in the clinical trials of more serious skin reactions known to be associated with significant morbidity or mortality.

Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days). Prolonging duration of therapy beyond 7 days causes the incidence of rash to increase significantly in all subgroups except men over the age of 40 (see Table 2). Gemifloxacin therapy should be discontinued in patients developing a rash while on treatment. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES.**)

Table 2. Rash Incidence in FACTIVE Treated Patients from the Clinical Studies Population* by Gender, Age, and Duration of Therapy

Gender & Age (yr) Category	Duration of Gemifloxacin Therapy 5 days	7 days	10 days**	14 days**
Female < 40	5/242 (2.1%)	39/324 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
Female ≥ 40	19/1210 (1.6%)	30/695 (4.3%)	19/308 (6.2%)	10/126 (7.9%)
Male < 40	4/218 (1.8%)	20/318 (6.3%)	7/74 (9.5%)	3/39 (7.7%)
Male ≥ 40	9/1321 (0.7%)	23/776 (3.0%)	9/345 (2.6%)	3/116 (2.6%)
Totals	37/2991 (1.2%)	112/2113 (5.3%)	55/858 (6.4%)	23/312 (7.4%)

*includes patients from studies of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and other indications
exceeds the recommended duration of therapy (see **DOSAGE AND ADMINISTRATION)

Photosensitivity reactions have been reported very rarely in clinical trials with FACTIVE. (See **CLINICAL PHARMACOLOGY.**) However, as with all drugs of this class, it is recommended that patients avoid unnecessary exposure to strong sunlight or artificial UV rays (e.g., sunlamps, solariums), and should be advised of the appropriate use of broad spectrum sun block if in bright sunlight. Treatment should be discontinued if a photosensitivity reaction is suspected.

Hepatic Effects: Liver enzyme elevations (increased ALT and/or AST) occurred at similar rates in patients receiving gemifloxacin 320 mg daily relative to comparator antimicrobial agents (ciprofloxacin, levofloxacin, clarithromycin/cefuroxime axetil, amoxicillin/clavulanate potassium, and ofloxacin). In patients who received gemifloxacin at doses of 480 mg per day or greater there was an increased incidence of elevations in liver enzymes. (See **ADVERSE REACTIONS**.)

There were no clinical symptoms associated with these liver enzyme elevations. The liver enzyme elevations resolved following cessation of therapy. The recommended dose of gemifloxacin 320 mg daily should not be exceeded and the recommended length of therapy should not be exceeded. (See **DOSAGE AND ADMINISTRATION**.)

Alteration of the dosage regimen is necessary for patients with impairment of renal function (creatinine clearance ≤40 mL/min). (See **DOSAGE AND ADMINISTRATION.**)

Adequate hydration of patients receiving gemifloxacin should be maintained to prevent the formation of a highly concentrated urine.

Information for Patients
Patients should be counseled:

- that antibacterial drugs including FACTIVE should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When FACTIVE is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by FACTIVE or other antibacterial drugs in the future;

- that FACTIVE has been associated with rash. Patients should discontinue drug and call their healthcare provider if they develop a rash;

- that FACTIVE may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose; patients should immediately discontinue the drug at the sign of a rash or other allergic reaction and seek medical care;

- that FACTIVE may cause changes in the electrocardiogram (QTc interval prolongation);

- that FACTIVE should be avoided in patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents;

- that FACTIVE should be used with caution in patients receiving drugs that affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants;

- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia;

- to inform their physician of any other medications when taken concurrently with FACTIVE, including over-the-counter medications and dietary supplements;

- to contact their physician if they experience palpitations or fainting spells while taking FACTIVE;

- that FACTIVE may be taken with or without meals;

- to drink fluids liberally;

- not to take antacids containing magnesium and/or aluminum or products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or

Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution within 3 hours before or 2 hours after taking FACTIVE tablets;

- that FACTIVE should be taken at least 2 hours before sucralfate;

- that phototoxicity has been reported with certain quinolones. The potential for FACTIVE to cause phototoxicity was low (3/7659) at the recommended dose in clinical studies. In keeping with good clinical practice, avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds). If a sunburn-like reaction or skin eruption occurs, contact your physician; (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);

- that FACTIVE may cause dizziness; if this occurs, patients should not operate an automobile or machinery or engage in activities requiring mental alertness or coordination;

- that they should discontinue FACTIVE therapy and inform their physician if they feel pain, tenderness or rupture of a tendon. Patients should rest and avoid exercise until the diagnosis of tendonitis or tendon rupture has been excluded;

- that convulsions have been reported in patients receiving quinolones; and they should notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: Administration of repeat doses of FACTIVE had no effect on the repeat dose pharmacokinetics of theophylline, digoxin or an ethinylestradiol/levonorgestrol oral contraceptive product in healthy subjects. (See **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**.)

Concomitant administration of FACTIVE and calcium carbonate, cimetidine, omeprazole, or an estrogen/progesterone oral contraceptive produced minor changes in the pharmacokinetics of gemifloxacin, which were considered to be without clinical significance. (See **CLINICAL PHARMACOLOGY.**)

Concomitant administration of FACTIVE with probenecid resulted in a 45% increase in systemic exposure to gemifloxacin. (See **CLINICAL PHARMACOLOGY**.)

FACTIVE had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy. However, because some quinolones have been reported to enhance the anticoagulant effects of warfarin or its derivatives in patients, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Quinolones form chelates with alkaline earth and transition metals. The absorption of oral gemifloxacin is significantly reduced by the concomitant administration of an antacid containing aluminum and magnesium. Magnesium- and/or aluminum-containing antacids, products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after FACTIVE. Sucralfate should not be taken within 2 hours of FACTIVE. (See **CLINICAL PHARMACOLOGY.**)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long term studies in animals to determine the carcinogenic potential of gemifloxacin have not been conducted.

Photocarcinogenesis: Gemifloxacin did not shorten the time to development of UVR-induced skin tumors in hairless albino (Skh-1) mice; thus, it was not photocarcinogenic in this model. These mice received oral gemifloxacin and concurrent irradiation with simulated sunlight 5 days per week for 40 weeks followed by a 12-week treatment-free observation period. The daily dose of UV radiation used in this study was approximately 1/3 of the minimal dose of UV radiation that would induce erythema in Caucasian humans. The median time to the development of skin tumors in the hairless mice was similar in the vehicle control group (36 weeks) and those given up to 100 mg/kg gemifloxacin daily (39 weeks). Following repeat doses of 100 mg/kg gemifloxacin per day, the mice had skin gemifloxacin concentrations of approximately 7.4 μg/g. Plasma levels following this dose were approximately 1.4 μg/mL in the mice around the time of irradiation. There are no data on gemifloxacin skin levels in humans, but the mouse plasma gemifloxacin levels are in the expected range of human plasma Cmax levels (0.7-2.6 μg/mL, with an overall mean of about 1.6 μg/mL) following multiple 320 mg oral doses.

Mutagenesis: Gemifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in an Ames *Salmonella* reversion assay. It did not induce micronuclei in the bone marrow of mice following intraperitoneal doses of up to 40 mg/kg and it did not induce unscheduled DNA synthesis in hepatocytes from rats which received oral doses of up to 1600 mg/kg. Gemifloxacin was clastogenic *in vitro* in the mouse lymphoma and human lymphocyte chromosome aberration assays. It was clastogenic *in vivo* in the rat micronucleus assay at oral and intravenous dose levels (≥800 mg/kg and ≥40 mg/kg, respectively) that produced bone marrow toxicity. Fluoroquinolone clastogenicity is apparently due to inhibition of mammalian topoisomerase activity which has threshold implications.

Impairment of Fertility: Gemifloxacin did not affect the fertility of male or female rats at AUC levels following oral administration (216 and 600 mg/kg/day) that were approximately 3- to 4-fold higher than the AUC levels at the clinically recommended dose.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Gemifloxacin treatment during organogenesis caused fetal growth retardation in mice (oral dosing at 450 mg/kg/day), rats (oral dosing at 600 mg/kg/day) and rabbits (IV dosing at 40 mg/kg/day) at AUC levels which were 2-, 4- and 3-fold those in women given oral doses of 320 mg. In rats, this growth retardation appeared to be reversible in a pre- and postnatal development study (mice and rabbits were not studied for the reversibility of this effect). Treatment of pregnant rats at 8-fold clinical exposure (based upon AUC comparisons) caused fetal brain and ocular malformations in the presence of maternal toxicity. The overall no-effect exposure level in pregnant animals was approximately 0.8 to 3-fold clinical exposure.

The safety of gemifloxacin in pregnant women has not been established. Gemifloxacin should not be used in pregnant women unless the potential benefit to the mother outweighs the risk to the fetus. There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers: Gemifloxacin is excreted in the breast milk of rats. There is no information on excretion of gemifloxacin into human milk. Therefore, gemifloxacin should not be used in lactating women unless the potential benefit to the mother outweighs the risk.

Pediatric Use: Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Fluoroquinolones, including gemifloxacin, cause arthropathy and osteochondrosis in immature animals. (See **WARNINGS.**)

Geriatric Use: Of the total number of subjects in clinical studies of gemifloxacin, 30% (2064) were 65 and over, while 12% (779) were 75 and over. No overall difference in effectiveness was observed between these subjects and younger subjects; the adverse event rate for this group was similar to or lower than that for younger subjects with the exception that the incidence of rash was lower in geriatric patients compared to patients less than 40 years of age.

ADVERSE REACTIONS

In clinical studies, 6775 patients received daily oral doses of 320 mg gemifloxacin. In addition, 1797 healthy volunteers and 81 patients with renal or hepatic impairment received single or repeat doses of gemifloxacin in clinical pharmacology studies. The majority of adverse reactions experienced by patients in clinical trials were considered to be of mild to moderate severity.

Gemifloxacin was discontinued because of an adverse event (possibly or probably related) in 2.2% of patients, primarily due to rash (0.9%), nausea (0.3%), diarrhea (0.3%), urticaria (0.3%) and vomiting (0.2%). Comparator antibiotics were discontinued because of an

adverse event at an overall comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.3%), vomiting (0.3%) and rash (0.3%).

Drug-related adverse events, classified as possibly or probably related with a frequency of ≥1% for patients receiving 320 mg of gemifloxacin versus comparator drug (beta-lactam antibiotics, macrolides or other fluoroquinolones) are as follows: diarrhea 3.6% vs. 4.6%; rash 2.8% vs. 0.6%; nausea 2.7% vs. 3.2%; headache 1.2% vs. 1.5%; abdominal pain 0.9% vs. 1.1%; vomiting 0.9% vs. 1.1%; dizziness 0.8% vs. 1.5%; and taste perversion 0.3% vs. 1.9%.

Gemifloxacin appears to have a low potential for photosensitivity. In clinical trials, treatment-related photosensitivity occurred in only 0.039% (3/7659) of patients.

Additional drug-related adverse events (possibly or probably related) in >0.1% to 1% of patients who received 320 mg of gemifloxacin were: abdominal pain, anorexia, arthralgia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, hyperglycemia, insomnia, leukopenia, moniliasis, pruritus, somnolence, taste perversion, thrombocythemia, urticaria, vaginitis, and vomiting.

Other adverse events reported from clinical trials which have potential clinical significance and which were considered to have a suspected relationship to the drug, that occurred in ≤0.1% of patients were: abnormal urine, anemia, asthenia, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, flushing, gastroenteritis, granulocytopenia, hot flashes, increased GGT, leg cramps, myalgia, nervousness, non-specified gastrointestinal disorder, pain, pharyngitis, pneumonia, thrombocyotopenia, tremor, vertigo, and vision abnormality.

In clinical trials of acute bacterial exacerbation of chronic bronchitis (ABECB) and community acquired pneumonia (CAP), the incidences of rash were as follows (Table 3):

Table 3. Incidence of Rash by Clinical Indication in Patients Treated with Gemifloxacin

	ABECB (5 days) N = 2284		**CAP (7 days) N = 643**	
	n/N	%	n/N	%
Totals	27/2284	1.2	26/643	4.0
Females, < 40 years	NA*		8/88	9.1
Females, ≥ 40 years	16/1040	1.5	5/214	2.3
Males, < 40 years	NA*		5/101	5.0
Males, ≥ 40 years	11/1203	0.9	8/240	3.3

* insufficient number of patients in this category for a meaningful analysis.

(See **PRECAUTIONS**).

Laboratory Changes: The percentages of patients who received multiple doses of gemifloxacin and had a laboratory abnormality are listed below. It is not known whether these abnormalities were related to gemifloxacin or an underlying condition.

Clinical Chemistry: increased ALT (1.5%), increased AST (1.1%), increased creatine phosphokinase (0.6%), increased potassium (0.5%), decreased sodium (0.3%), increased gammaglutamyl transferase (0.5%), increased alkaline phosphatase (0.3%), increased total bilirubin (0.3%), increased blood urea nitrogen (0.3%), decreased calcium (0.2%), decreased albumin (0.3%), increased serum creatinine (0.2%), decreased total protein (0.1%) and increased calcium (<0.1%).

CPK elevations were noted infrequently: 0.8% in gemifloxacin patients vs. 0.4% in the comparator patients.

Hematology: increased platelets (0.9%), decreased neutrophils (0.5%), increased neutrophils (0.5%), decreased hematocrit (0.3%), decreased hemoglobin (0.2%), decreased platelets (0.2%), decreased red blood cells (0.1%), increased hematocrit (0.1%), increased hemoglobin (0.1%), and increased red blood cells (0.1%).

In clinical studies, approximately 7% of the gemifloxacin treated patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 10% showed a further elevation of their ALT at the on-therapy visit and 5% showed a further elevation at the end of therapy visit. None of these patients demonstrated evidence of hepatocellular jaundice. For the pooled comparators, approximately 6% of patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 7% showed a further elevation of their ALT at the on-therapy visit and 4% showed a further elevation at the end of therapy visit.

In a clinical trial where 638 patients received either a single 640 mg dose of gemifloxacin or 250 mg bid of ciprofloxacin for 3 days, there was an increased incidence of ALT elevations in the gemifloxacin arm (3.9%) vs. the comparator arm (1.0%). In this study, two patients experienced ALT elevations of 8 to10 times the upper limit of normal. These elevations were asymptomatic and reversible.

OVERDOSAGE

Any signs or symptoms of overdosage should be treated symptomatically. No specific antidote is known. In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage; the patient should be carefully observed and treated symptomatically with appropriate hydration maintained. Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Mortality occurred at oral gemifloxacin doses of 1600 mg/kg in rats and 320 mg/kg in mice. The minimum lethal intravenous doses in these species were 160 and 80 mg/kg, respectively. Toxic signs after administration of a single high oral dose (400 mg/kg) of gemifloxacin to rodents included ataxia, lethargy, piloerection, tremor, and clonic convulsions.

DOSAGE AND ADMINISTRATION

FACTIVE can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of FACTIVE is 320 mg daily, according to the following table (Table 4).

Table 4. Recommended Dosage Regimen of FACTIVE

INDICATION	DOSE	DURATION
Acute bacterial exacerbation of chronic bronchitis	One 320 mg tablet daily	5 days
Community-acquired pneumonia (of mild to moderate severity)	One 320 mg tablet daily	7 days

The recommended dose and duration of FACTIVE should not be exceeded (see Table 2).

Renally Impaired Patients: Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. Table 5 provides dosage guidelines for use in patients with renal impairment:

Table 5. Recommended Doses for Patients With Renal Impairment

Creatinine Clearance (mL/min)	Dose
>40	See Usual Dosage
≤40	160 mg q24h

Patients requiring routine hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) should receive 160 mg q24h.

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men

Use in Hepatically Impaired Patients: No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Use in Elderly: No dosage adjustment is recommended.

HOW SUPPLIED

FACTIVE (gemifloxacin mesylate) is available as white to off-white, oval, film-coated tablets with breaklines and GE 320 debossed on both faces. Each tablet contains gemifloxacin mesylate equivalent to 320 mg of gemifloxacin.

320 mg Unit of Use (CR*) 5's	NDC 67707-320-05
320 mg Unit of Use (CR*) 7's	NDC 67707-320-07
320 mg Hospital Pack (NCR**) 30's	NDC 67707-320-30

*Child Resistant ** Not Child Resistant

STORAGE

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

ANIMAL PHARMACOLOGY

Quinolones have been shown to cause arthropathy in immature animals. Degeneration of articular cartilage occurred in juvenile dogs given at least 192 mg/kg/day gemifloxacin in a 28-day study (producing about 6 times the systemic exposure at the clinical dose), but not in mature dogs. There was no damage to the articular surfaces of joints in immature rats given repeated doses of up to 800 mg/kg/day.

Some quinolones have been reported to have proconvulsant properties that are potentiated by the concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs). Gemifloxacin alone had effects in tests of behavior or CNS interaction typically at doses of at least 160 mg/kg. No convulsions occurred in mice given the active metabolite of the NSAID, fenbufen, followed by 80 mg/kg gemifloxacin.

Dogs given 192 mg/kg/day (about 6 times the systemic exposure at the clinical dose) for 28 days, or 24 mg/kg/day (approximately equivalent to the systemic exposure at the clinical dose) for 13 weeks showed reversible increases in plasma ALT activities and local periportal liver changes associated with blockage of small bile ducts by crystals containing gemifloxacin.

Quinolones have been associated with prolongation of the electrocardiographic QT interval in dogs. Gemifloxacin produced no effect on the QT interval in dogs dosed orally to provide about 4 times human therapeutic plasma concentrations at Cmax, and transient prolongation after intravenous administration at more than 4 times human plasma levels at Cmax.

Gemifloxacin exhibited weak activity in the cardiac I_{Kr} (hERG) channel inhibition assay, having an IC_{50} of approximately 270 μM.

Gemifloxacin, like many other quinolones, tends to crystallize at the alkaline pH of rodent urine, resulting in a nephropathy in rats that is reversible on drug withdrawal (oral no-effect dose 24 mg/kg/day).

Gemifloxacin was weakly phototoxic to hairless mice given a single 200 mg/kg oral dose and exposed to UVA radiation. However, no evidence of phototoxicity was observed at 100 mg/kg/day dosed orally for 13 weeks in a standard hairless mouse model, using simulated sunlight.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

FACTIVE (320 mg once daily for 5 days) was evaluated for the treatment of acute bacterial exacerbation of chronic bronchitis in three pivotal double-blind, randomized, actively-controlled clinical trials (studies 068, 070, and 212). The primary efficacy parameter in these studies was the clinical response at follow-up (day 13 to 24). The results of the clinical response at follow-up for the principal ABECB studies demonstrate that FACTIVE 320 mg PO once daily for 5 days was at least as good as the comparators given for 7 days. The results are shown in Table 6 below.

Table 6. Clinical Response at Follow-Up (Test of Cure): Pivotal ABECB Studies

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)
Study 068		
FACTIVE 320 mg x 5 days	86.0 (239/278)	1.2 (-4.7, 7.0)
Clarithromycin 500 mg bid x 7 days	84.8 (240/283)	
Study 070		
FACTIVE 320 mg x 5 days	93.6 (247/264)	0.4 (-3.9, 4.6)
Amoxicillin/clavulanate 500 mg/125 mg tid x 7 days	93.2 (248/266)	
Study 212		
FACTIVE 320 mg x 5 days	88.2 (134/152)	3.1 (-4.7, 10.7)
Levofloxacin 500 mg x 7 days	85.1 (126/148)	

Community Acquired Pneumonia (CAP)

The clinical program to evaluate the efficacy of gemifloxacin in the treatment of community acquired pneumonia in adults consisted of three double-blind, randomized, actively-controlled clinical studies (studies 011, 012, and 049) and one open, actively-controlled study (study 185). In addition, two uncontrolled studies (studies 061 and 287) were conducted. Three of the studies, pivotal study 011 and the uncontrolled studies, had a fixed 7-day duration of treatment for FACTIVE. Pivotal study 011 compared a 7-day course of FACTIVE with a 10-day treatment course of amoxicillin/clavulanate (1g/125 mg tid) and clinical success rates were similar between treatment arms. The results of comparative studies 049, 185, and 012 were supportive although treatment duration could have been 7 to 14 days. The results of the clinical studies with a fixed 7-day duration of gemifloxacin are shown in Table 7:

Table 7. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7 Day Duration of Treatment

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)*
Study 011		
FACTIVE 320 mg x 7 days	88.7 (102/115)	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 500 mg/125 mg tid x 10 days	87.6 (99/113)	
Study 061		
FACTIVE 320 mg x 7 days	91.7 (154/168)	(86.1, 95.2)
Study 287		
FACTIVE 320 mg x 7 days	89.8 (132/147)	(84.9, 94.7)

* For uncontrolled studies, the 95% CI around the success rate is shown

The combined bacterial eradication rates for patients treated with a fixed 7-day treatment regimen of FACTIVE are shown in Table 8:

Table 8. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Studies with a Fixed 7-day Duration of Treatment

Pathogen	n/N	%
S. pneumoniae	68/77	88.3
M. pneumoniae	21/22	95.5
H. influenzae	30/35	85.7
C. pneumoniae	13/14	92.9
*K. pneumoniae**	11/13	84.6
M. catarrhalis	10/10	100

* Subjects with *Klebsiella pneumoniae* included in this table were from non-comparative studies 061 and 287. Ten of these subjects had mild disease, two had moderate disease, and

one had severe disease. Both failures were in subjects with mild disease (one of these had a bacteriologic recurrence).

FACTIVE was also effective in the treatment of CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP*). Of 22 patients with MDRSP treated for 7 days, 19 (86.5%) achieved clinical and bacteriological success at follow-up. The clinical and bacteriological success for the 22 patients with 22 MDRSP isolates are shown in Table 9.

*MDRSP: Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Table 9. Clinical and Bacteriological Success for 22 Patients Treated with FACTIVE in Studies with a 7-day Duration of Treatment for MDRSP

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N[a]	%	n/N[b]	%
Penicillin-resistant	11/11	100	11/11	100
2nd generation cephalosporin-resistant	14/14	100	14/14	100
Macrolide-resistant[c]	16/19	84.2	16/19	84.2
Trimethoprim/sulfamethoxazole-resistant	16/16	100	16/16	100
Tetracycline-resistant	13/16	81.3	13/16	81.3

a) n = the number of patients successfully treated; N = number of patients with MDRSP (from a total of 22 patients)
b) n = the number of bacteriological isolates successfully treated; N = number of isolates studied (from a total of 22 isolates)
c) Macrolide antibiotics tested include clarithromycin and erythromycin

Cutaneous Manifestations (Rash)

In clinical trials of 6,775 patients, the incidence of rash was higher in patients receiving gemifloxacin than in those receiving comparator drugs (see **PRECAUTIONS** and **ADVERSE REACTIONS**). Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days, see Table 2).

To further characterize gemifloxacin-associated rash, a clinical pharmacology study was conducted. The study enrolled 1,011 healthy female volunteers less than 40 years of age. Subjects were randomized to receive either FACTIVE 320 mg po daily or ciprofloxacin 500

mg po twice daily for 10 days. The objective of the study was to assess the characteristics of rash. The majority of rashes in subjects receiving FACTIVE were maculopapular and of mild to moderate severity; 7% of the rashes were reported as severe, and severity appeared to correlate with the extent of the rash. In 68% of the subjects reporting a severe rash and approximately 25% of all those reporting rash, >60% of the body surface area was involved; the characteristics of the rash were otherwise indistinguishable from those subjects reporting a mild rash. The histopathology was consistent with the clinical observation of uncomplicated exanthematous morbilliform eruption. There were no documented cases of hypersensitivity syndrome or findings suggestive of angioedema or other serious cutaneous reactions.

The majority of rash events (81.9%) occurred on days 8 through 10 of the planned 10 day course of gemifloxacin; 2.7% of rash events occurred within one day of the start of dosing. The median duration of rash was 6 days. The rash resolved without treatment in the majority of subjects. Approximately 19% received antihistamines and 5% received steroids, although the therapeutic benefit of these therapies is uncertain.

In the second part of this study after a 4 to 6 week wash out period, subjects developing a rash on gemifloxacin were treated with ciprofloxacin or placebo; 5.9% developed rash when treated with ciprofloxacin and 2.0% developed rash when treated with placebo. The characteristics of rash in subjects receiving ciprofloxacin following gemifloxacin were similar to those described in subjects who only received ciprofloxacin. The cross sensitization rate to other fluoroquinolones was not evaluated in this clinical study. There was no evidence of sub-clinical sensitization to gemifloxacin (i.e. subjects who had not developed a rash to gemifloxacin in the first part of the study were not at higher risk of developing a rash to gemifloxacin with a second exposure).

There was no relationship between the incidence of rash and systemic exposure (Cmax and AUC) to either gemifloxacin or its major metabolite, N-acetyl gemifloxacin.

REFERENCES: 1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January 2003. **2.** National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Eighth Edition. Approved Standard NCCLS Document A2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January 2003.

DATE OF REVISION AUGUST 2004

Rx only

Manufactured for:
Oscient Pharmaceuticals Waltham, MA 02451-1478 USA

Licensed from LG Life Sciences, Ltd. Seoul, Korea

Patient Information

FACTIVE®
(gemifloxacin mesylate) Tablets

This leaflet summarizes the most important information about FACTIVE. Read the Patient Information that comes with FACTIVE each time you get a new prescription. There may be new information. This leaflet does not list all benefits and risks of treatment and does not take the place of talking with your healthcare provider about your condition or your treatment. FACTIVE can only be prescribed by a healthcare professional. If you would like more information, talk with your healthcare provider or pharmacist.

What is FACTIVE?
FACTIVE is an antibiotic. It is used to treat adults 18 years or older with bronchitis or pneumonia (lung infections) caused by certain bacteria (germs).

Sometimes, other germs called viruses infect the lungs. The common cold is a virus. FACTIVE, like other antibiotics, does not treat viruses.

FACTIVE tablets are white to off white and imprinted with GE 320 on both sides.

Who should not take FACTIVE?
- **Do not take FACTIVE if you are allergic to any of the ingredients in FACTIVE or to any antibiotic called a "quinolone".** If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, stop taking FACTIVE and call your healthcare professional. The ingredients in FACTIVE are listed at the end of this leaflet. Ask your healthcare provider or pharmacist if you need a list of quinolones.

FACTIVE may not be right for you. Tell your healthcare provider if you:
- are pregnant, planning to become pregnant, or are breast feeding. The effects of FACTIVE on unborn children and nursing infants are unknown;
- or any family members have a rare heart condition known as congenital prolongation of the QTc interval;
- have low potassium or magnesium levels;
- have a slow heart beat called bradycardia;
- have had a recent heart attack;
- have a history of convulsions;
- have kidney problems.

FACTIVE has not been studied in children under the age of 18. Quinolones may cause joint problems (arthropathy) in children.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and dietary supplements. **Be sure to tell your healthcare provider if you take:**

- medicines for your heart rhythm called "antiarrhythmics"
- erythromycin
- medicines for your mental health called "antipsychotics" or "tricyclic antidepressants"
- medicines called "corticosteroids", taken by mouth or by injection
- medicines called diuretics such as furosemide and hydrochlorothiazide.

How should I take FACTIVE?

- Take 1 FACTIVE tablet a day for 5 or 7 days, exactly as prescribed.
- Take FACTIVE at the same time each day.
- FACTIVE can be taken with or without food.
- Swallow the FACTIVE tablet whole, and drink plenty of fluids with it. Do not chew the FACTIVE tablet.
- If you miss a dose of FACTIVE, take it as soon as you remember. **Do not take more than 1 dose of FACTIVE in a day.**
- To make sure all bacteria are killed, take all the medicine that was prescribed for you even if you begin to feel better.
- Call your healthcare provider if your condition does not improve while taking FACTIVE.

Do not take the following medicines within 3 hours before FACTIVE or 2 hours after FACTIVE. They may interfere with the absorption of FACTIVE and may prevent it from working properly:

- antacids that contain magnesium or aluminum
- ferrous sulfate (iron)
- multivitamin that contains zinc or other metals
- Videx® (didanosine)

FACTIVE should be taken at least 2 hours before sucralfate.

What are possible side effects of FACTIVE?

FACTIVE is generally well tolerated. The most common side effects with FACTIVE include diarrhea, rash, nausea, headache, vomiting, stomach pain, dizziness, and a change in the way things taste in your mouth. If you get a rash while taking FACTIVE, stop FACTIVE, and call your healthcare provider right away. Do not drive or operate heavy machinery until you know how FACTIVE affects you. FACTIVE can make you dizzy.

FACTIVE and other quinolone antibiotics may cause the following serious side effects:

- a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and result in sudden death. You should call your healthcare provider right away if you have any symptoms of prolongation of the QTc interval including heart palpitations (a change in the way your heart beats) or fainting spells;
- central nervous system problems including body shakes (tremors), restless feeling, lightheaded feelings, confusion, and hallucinations (seeing or hearing things that are not there);
- tendon problems including tendonitis or rupture ("tears") of a tendon. If you experience pain, swelling, or rupture of a tendon, stop taking FACTIVE and call your healthcare professional;
- phototoxicity. This can make your skin sunburn easier. Do not use a sunlamp or tanning bed while taking FACTIVE. Use a sunscreen and wear protective clothing if you must be out in the sun.

These are not all the side effects you may experience with FACTIVE. If you get any side effects that concern you, call your healthcare provider.

General information about the safe and effective use of FACTIVE:
Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use FACTIVE for a condition for which it was not prescribed. Do not give FACTIVE to other people, even if they have the same symptoms that you have. It may harm them. **Keep FACTIVE and all medicines out of the reach of children.**

What are the ingredients in FACTIVE?
Active ingredient: gemifloxacin
Inactive ingredients: crospovidone, hydroxypropyl methycellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide.

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