

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**21-158**

**MICROBIOLOGY REVIEW**

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**MICROBIOLOGY REVIEW**  
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS  
(HFD-590)

**NDA #:** #21-158

**REVIEWER:** Peter A. Dionne  
**CORRESPONDENCE DATE:** 04-OCT-02  
**CDER DATE:** 07-OCT-02  
**REVIEW ASSIGN DATE:** 10-OCT-02  
**REVIEW COMPLETE DATE:** 31-JAN-03

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**SUBMISSION REVIEWED:** Resubmission: Response to FDA Action Letter

**DRUG CATEGORY:** Antimicrobial: Fluoroquinolone

**INDICATIONS:** Acute Exacerbations of Chronic Bronchitis (AECB) and Community-Acquired Pneumonia (CAP)

**DOSAGE FORM:** Tablet---320 mg/tablet

**DRUG PRODUCT NAME**

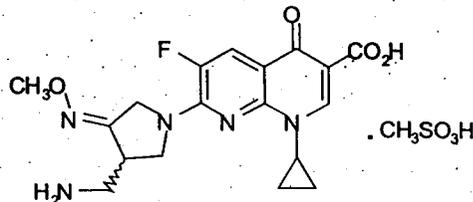
**PROPRIETARY:** FACTIVE™

**NONPROPRIETARY/USAN:** Gemifloxacin mesylate tablet

**CODE:** SB-265805-S; LB20304a

**CHEMICAL NAME:** (±)-7-[3-(aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 7<sup>4</sup>-(Z)-(O-methyloxime), monomethanesulfonate.

**STRUCTURAL FORMULA:**



**Molecular Formula:** C<sub>18</sub>H<sub>20</sub>FN<sub>5</sub>O<sub>4</sub>•CH<sub>4</sub>O<sub>3</sub>S  
**Molecular Weight:** 485.49.

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**SUPPORTING DOCUMENTS:**

**REMARKS/COMMENTS:**

This application is a response to the Agency's Action Letter dated December 15, 2000.

Only Community-Acquired Pneumonia (CAP) and Acute Exacerbations of Chronic Bronchitis (AECB) are being requested as indications.

The sponsor believes that the originally proposed gemifloxacin breakpoints for *Streptococcus pneumoniae* are correct and has submitted additional microbiology studies in this resubmission. Many of these new studies compare gemifloxacin to the newer fluoroquinolones, moxifloxacin and gatifloxacin.

A new controlled CAP study (Study 185) has been submitted along with a summary of a new open label CAP study (Study 287) designed to enrich the population with penicillin-resistant *Streptococcus pneumoniae*.

**CONCLUSIONS & RECOMMENDATIONS:**

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when changes are made to the MICROBIOLOGY subsection of the package insert. The changes needed should be sent to the sponsor at the time of labeling negotiations. Revisions needed in the Microbiology subsection of the label are listed as notification to the sponsor at the end of this review on pages 84-92.

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## EXECUTIVE SUMMARY

Gemifloxacin has a novel 3-aminomethyl-4-syn-methoxyimino-1-pyrrolidinyl substituent at the C7 position of the 6-fluoro-1, 8-naphyridone ring. This substituent appears to enhance the antipneumococcal activity of gemifloxacin compared to other fluoroquinolones.

Studies indicate that gemifloxacin has greater affinity for topoisomerase IV of *Streptococcus pneumoniae* than other fluoroquinolones. This difference is much greater when gemifloxacin is compared to levofloxacin or ciprofloxacin than when compared to moxifloxacin or gatifloxacin. Some studies suggest that gemifloxacin has almost equal affinity for topoisomerase IV and DNA gyrase in *S. pneumoniae*, but other studies indicate that like most other fluoroquinolones, gemifloxacin has a much greater affinity for topoisomerase IV.

Gemifloxacin's *in vitro* MIC values against *Streptococcus pneumoniae* are 4-8 times lower than those of trovafloxacin and moxifloxacin and over 32 times lower than the MIC values for ciprofloxacin and levofloxacin. Unfortunately, at the proposed human dose the AUC value for gemifloxacin is only about one-fourth that of most of the other fluoroquinolones. A 4-fold lower gemifloxacin MIC value for *Streptococcus pneumoniae*, therefore, is basically equivalent clinically to MICs of trovafloxacin or moxifloxacin. These lower MIC values for gemifloxacin are seen with most gram-positive bacteria. The difference between gemifloxacin and other fluoroquinolones against these gram-positive species is not as great as that seen with *Streptococcus pneumoniae*. The MIC values for gemifloxacin are usually equivalent or one dilution lower than those seen with trovafloxacin and 2- to 4-fold less than those seen with moxifloxacin. Gemifloxacin MICs are usually about 16 times less than those seen with ciprofloxacin.

Against most gram-negative bacteria, gemifloxacin MICs are usually 2-fold greater than those seen with ciprofloxacin and equivalent to those for most of the other comparator fluoroquinolones. Since gemifloxacin will have a susceptible breakpoint that is 4 to 8 times lower than that for most other fluoroquinolones, many of the gram-negative species will have MIC<sub>90</sub> values at or greater than the susceptible breakpoint. This means that during treatment there may be isolates that have MIC values above achievable serum or tissue levels of the drug.

Against anaerobes gemifloxacin MIC values are generally higher than those of trovafloxacin and 2 to 4 times less than those of ciprofloxacin or levofloxacin. It has borderline activity against *Peptostreptococcus* species and *Fusobacterium nucleatum* but poor activity against most other species. TABLE A shows MIC<sub>90</sub> values for gemifloxacin against some common pathogens.

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TABLE A  
Gemifloxacin *in vitro* Activity

PATHOGEN	MIC <sub>90</sub> (µg/mL)*
<i>Staphylococcus aureus</i> (methicillin-susceptible)	0.06
<i>Staphylococcus aureus</i> (methicillin-resistant)	≥8.0
<i>Staphylococcus epidermidis</i>	1.0
<i>Staphylococcus saprophyticus</i>	0.03
<i>Streptococcus pneumoniae</i>	0.03
<i>Streptococcus pyogenes</i>	0.03
Viridans Group <i>Streptococci</i>	0.06
<i>Streptococcus agalactiae</i>	0.06
<i>Enterococcus faecalis</i>	4.0
<i>Acinetobacter</i> species	≥8.0
<i>Escherichia coli</i>	0.25
<i>Klebsiella pneumoniae</i>	0.5
<i>Klebsiella oxytoca</i>	0.12
<i>Enterobacter cloacae</i>	0.25
<i>Enterobacter aerogenes</i>	≥8.0
<i>Proteus mirabilis</i>	4.0
<i>Proteus vulgaris</i>	0.25
<i>Citrobacter freundii</i>	2.0
<i>Morganella morganii</i>	0.25
<i>Serratia marcescens</i>	1-4
<i>Pseudomonas aeruginosa</i>	≥8.0
<i>Haemophilus influenzae</i>	0.03
<i>Haemophilus parainfluenzae</i>	0.06
<i>Moraxella catarrhalis</i>	0.015
<i>Bacteroides fragilis</i>	2-4
<i>Clostridium</i> species	0.06-16
<i>Prevotella</i> species	0.5-16
<i>Peptostreptococcus</i> species	0.03-4.0
<i>Fusobacterium nucleatum</i>	0.25-2.0
<i>Legionella pneumoniae</i>	0.015
<i>Mycoplasma pneumoniae</i>	0.12
<i>Chlamydia pneumoniae</i>	0.25
<i>Mycobacterium tuberculosis</i>	64.0

TABLE B gives a summary of gemifloxacin's *in vitro* activity compared to other fluoroquinolones. It must be remembered that gemifloxacin's susceptible breakpoint is 4-8 fold lower than that of most of the comparator quinolones.

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TABLE B

*In vitro* Activity of Gemifloxacin compared to other Fluoroquinolones (MIC<sub>90</sub>s µg/mL)

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

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When comparing these *in vitro* data it must be remembered that although gemifloxacin generally has much lower MIC values especially against gram-positive aerobes it must be remembered that gemifloxacin's susceptible breakpoint is 4-8 times lower than that for most other fluoroquinolones. Gemifloxacin has good activity against most gram-positive microorganisms but its activity against most gram-negative Enterobacteriaceae is borderline at best. Like most other fluoroquinolones it has poor activity against *Pseudomonas aeruginosa*, *Enterococcus* species, and anaerobes. It has good activity against *Haemophilus* species and *Moraxella catarrhalis*.

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As is the case with other fluoroquinolones, gemifloxacin MIC values against penicillin-resistant *Streptococcus pneumoniae* were the same as those for penicillin-susceptible strains. Macrolide-resistance also had no effect on gemifloxacin MIC against *S. pneumoniae*. Against ciprofloxacin-resistant *S. pneumoniae* strains gemifloxacin's MIC<sub>90</sub> value was 0.25 to 0.5 µg/mL in most studies. In these same studies moxifloxacin's MIC<sub>90</sub> was 2 to 4 µg/mL. Moxifloxacin's susceptible breakpoint is 1 µg/mL, so these isolates fall into the intermediate or resistant category. If a gemifloxacin susceptible breakpoint of 0.12 µg/mL is used then these isolates would be intermediate or resistant to gemifloxacin also. *Streptococcus pneumoniae* isolates that were intermediate or resistant to levofloxacin had gemifloxacin MIC<sub>90</sub> values of 0.5 to 1 µg/mL.

Overall, mutation frequencies are about equal for all of the tested fluoroquinolones. Mutation frequencies range from about  $2 \times 10^{-4}$  to  $<1 \times 10^{-10}$  when tested at 1 to 16 times the MIC of the isolate. As expected the frequencies were much higher at 1 x MIC than at 16 x MIC. Ciprofloxacin had slightly higher frequencies than did the other drugs.

Studies looking at mutations in the Quinolone-Resistant-Determining-Region (QRDR) show that single mutations in either *parC* or *gryA* increase the MIC of gemifloxacin 2- to 4-fold over the MIC of the parent strain. An 8- to 16-fold increase in gemifloxacin MIC was seen when mutations were present in both genes. A single mutation in *parC* increased ciprofloxacin MIC values, but not sparfloxacin MIC values. A single mutation in *gryA* increased sparfloxacin MICs but not ciprofloxacin MICs. These data seem to indicate that gemifloxacin targets both *parC* and *gryA* genes in *Streptococcus pneumoniae*. Some studies that measure the affinity for these enzymes, however, indicate that topoisomerase IV (*parC*) is the primary target. Studies in which gemifloxacin is used to select mutations indicate that *gryA* is the primary target. It appears that the primary gemifloxacin target in *S. pneumoniae* is still in doubt. This may be due to the different methods used to determine which gene is the primary target and the fact that gemifloxacin may target both genes.

Gemifloxacin, like ciprofloxacin, is a good substrate for the efflux pump in *Streptococcus pneumoniae*. Gatifloxacin is affected to some extent by efflux pumps, while moxifloxacin is a poor substrate for this pump.

In an *in vivo* model of pneumonia caused by *Streptococcus pneumoniae* in rats, strains with gemifloxacin MICs  $\leq 0.03$  µg/mL could be treated once a day and treatment started 24 hours post-infection. After treatment no bacteria could be detected in the lungs from these animals. When gemifloxacin MIC values were  $\geq 0.12$  µg/mL treatment had to be given twice a day and started 1 hour after infection. The bacterial count in the lungs of these animals never got below the level of detection, although in most cases the treatment was significantly better than no treatment and was better than treatment with levofloxacin. When gemifloxacin was compared to gatifloxacin and moxifloxacin in this experimental model, all three drugs were about equally effective.

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In the clinical studies submitted there were no *Streptococcus pneumoniae* isolates with gemifloxacin MICs greater than 0.06 µg/mL in the per protocol population. There is, therefore, no evidence that gemifloxacin can eradicate *S. pneumoniae* isolates with gemifloxacin MICs of  $\geq 0.125$  µg/mL from the respiratory tract of patients.

In an experimental *Legionella pneumophila* in guinea pigs pneumonia model gemifloxacin, azithromycin, and levofloxacin were all about equally effective. Gemifloxacin appears to have some activity in a rabbit meningitis model.

## PRECLINICAL EFFICACY (IN VITRO)

### MECHANISM OF ACTION

Quinolones act by inhibiting DNA synthesis through inhibition of the bacterial enzymes DNA gyrase and topoisomerase IV. These type II topoisomerases are essential for bacterial growth. DNA gyrase, which catalyzes negative supercoiling during DNA replication, is encoded by the *gyrA* and *gyrB* genes. Topoisomerase IV, encoded by the *parC* and *parE* genes, is important in separation of the daughter strands after replication. Quinolones form a tertiary complex with these topoisomerase enzymes and DNA causing an irreversible lethal lesion, perhaps a double stranded break, in the replication chromosome.

This submission contains several new studies that have been conducted to further investigate gemifloxacin's mechanism of action and compare its activity with that of other available fluoroquinolones (1,2,3,4,5). Most of these studies measured the inhibition of bacterial type II topoisomerases, isolated from respiratory pathogens, by gemifloxacin and comparator fluoroquinolones.

Morrissey and George (1) conducted a study to investigate the activity of gemifloxacin and comparator quinolones against topoisomerase IV and DNA gyrase in three *Streptococcus pneumoniae* isolates. The isolates studied were C3LN4, a ciprofloxacin-sensitive strain and two ciprofloxacin-resistant isolates, 502226 and 503244. Inhibition of DNA gyrase supercoiling and topoisomerase IV decatenation was analyzed and IC<sub>50</sub> (the concentration of drug required to inhibit enzyme activity by 50%) values calculated for each enzyme and drug combination. The results are summarized in TABLE 1.

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TABLE 1  
Quinolone inhibition of DNA gyrase and topoisomerase IV activity  
From three strains of *Streptococcus pneumoniae*

<i>S. pneumoniae</i> strain	Quinolone	MIC ( $\mu\text{g/mL}$ )	IC <sub>50</sub> ( $\mu\text{g/mL}$ ) <sup>a</sup>	
			Topoisomerase IV	DNA gyrase
C3LN4	Gemifloxacin	0.06	1.4 $\pm$ 0	47.5 $\pm$ 5.6
	Moxifloxacin	0.5	3.9 $\pm$ 0.26	44.0 $\pm$ 0
	Levofloxacin	1.0	4.0 $\pm$ 0	49.1 $\pm$ 0.5
	Ciprofloxacin	2.0	6.4 $\pm$ 0.15	59.2 $\pm$ 1.6
502226	Gemifloxacin	0.5	3.1 $\pm$ 0.15	88.0 $\pm$ 2.8
	Moxifloxacin	2.0	9.6 $\pm$ 0.4	95.5 $\pm$ 0.93
	Levofloxacin	16.0	15.8 $\pm$ 0.29	101.9 $\pm$ 5.1
	Ciprofloxacin	16.0	16.1 $\pm$ 0.23	142.9 $\pm$ 4.9
503244	Gemifloxacin	0.5	7.9 $\pm$ 0.35	92.8 $\pm$ 2.8
	Moxifloxacin	4.0	12.5 $\pm$ 0.5	104.5 $\pm$ 4.0
	Levofloxacin	16.0	17.8 $\pm$ 0.40	128.5 $\pm$ 3.2
	Ciprofloxacin	16.0	43.4 $\pm$ 0.52	160.3 $\pm$ 3.6

<sup>a</sup> Values shown are the mean  $\pm$  standard deviation of three determinations

The data in the above table show that gemifloxacin had the lowest IC<sub>50</sub> values and thus the highest affinity for topoisomerase IV against all three strains. With the exception of ciprofloxacin, all the quinolones exhibited similar IC<sub>50</sub> values against DNA gyrase from the ciprofloxacin-susceptible strain, C3LN4. Gemifloxacin was the most potent quinolone against DNA gyrase from the two ciprofloxacin-resistant strains. Overall, the IC<sub>50</sub> values for inhibition of DNA gyrase were higher than those for topoisomerase IV. This suggests that topoisomerase IV is the primary target in *S. pneumoniae*. This study does not take into account the pharmacokinetics of these compounds. Gemifloxacin's greater affinity for topoisomerase IV is counteracted by its much lower plasma concentrations when clinical doses are given.

George and Tse-Dinh conducted a similar study (2). In this study, wild-type and mutant topoisomerase IV and DNA gyrase subunits were extracted from *S. pneumoniae*. Enzymes were extracted from CP 397, a strain containing a single mutation in *parC*; and TPS-7, a double mutant strain with mutations in both *parC* and *gyrA* along with enzymes from a wild-type strain.

Results are shown in TABLE 2.

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TABLE 2  
Summary of the IC<sub>50</sub>s for DNA gyrase and topoisomerase IV

Strain	Compound	Topoisomerase IV IC <sub>50</sub> (µg/mL)	DNA gyrase IC <sub>50</sub> (µg/mL)
Wild type	Gemifloxacin	1.2	2
	Moxifloxacin	3.9	40
	Gatifloxacin	3.8	28
	Levofloxacin	6.3	48
	Ciprofloxacin	9	68
CP 397	Gemifloxacin	18	WT
	Moxifloxacin	21	WT
	Gatifloxacin	16	WT
	Levofloxacin	35	WT
	Ciprofloxacin	40	WT
TPS-3*	Gemifloxacin	18	92
	Moxifloxacin	21	103
	Gatifloxacin	16	135
	Levofloxacin	35	>200
	Ciprofloxacin	40	>200

WT = wild-type (inhibition of DNA gyrase from CP 397 was the same as that obtained from the wild-type enzyme)

\* Inhibition of topoisomerase IV from TPS-3 was the same as that obtained from strain CP 397. Both strains contain a S-79-Y mutation in *parC*.

Overall, gemifloxacin had the lowest IC<sub>50</sub>s against both the wild-type and mutant enzymes. Against the mutation in topoisomerase IV gemifloxacin was only slightly better than moxifloxacin and gatifloxacin was better than gemifloxacin. Gemifloxacin was only slightly better than moxifloxacin against the mutation in the DNA gyrase gene. Gemifloxacin's slightly better affinity for the enzymes is probably not clinically significant since clinical doses of gemifloxacin produce much lower plasma concentrations than are seen with the comparator quinolones.

Heaton et al. (3) conducted a study which looked at the ability of gemifloxacin and ciprofloxacin to stabilize complexes of recombinant *S. pneumoniae* gyrase or topoisomerase with DNA. The results are shown in TABLE 3. Gemifloxacin (MIC = 0.06 µg/mL) was 16-32-fold more active *in vitro* than ciprofloxacin (MIC = 1-2 µg/mL). Gemifloxacin was 25-fold more efficient than ciprofloxacin in promoting DNA cleavage by topoisomerase IV and 16-fold more efficient in promoting cleavage by DNA gyrase. Gemifloxacin's increased efficiency is somewhat lessened by the fact that its plasma concentrations are low at clinical doses.

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TABLE 3  
Growth inhibition of a strain of *S. pneumoniae* and drug-stimulated DNA  
Cleavage efficiencies of DNA gyrase and topoisomerase IV

Drug	MIC ( $\mu\text{g/mL}$ )	CC <sub>25</sub> ( $\mu\text{M}$ ) for DNA breakage <sup>a</sup>	
		Topoisomerase IV	Gyrase
Gemifloxacin	0.06	0.1	5
Ciprofloxacin	1-2	2.5	80

<sup>a</sup> CC<sub>25</sub> concentration of drug that converts 25% of the substrate DNA to linear form in the presence of gyrase or topoisomerase IV.

In a similar experiment, Fisher et al. (4) compared gemifloxacin against a broader range of quinolones. Wild-type and mutant topoisomerase IV and DNA gyrase subunits were purified. DNA supercoiling of relaxed plasma DNA was used to measure the inhibition of *S. pneumoniae* DNA gyrase. For topoisomerase IV, inhibition of enzymatic decatenation of DNA was determined. The results are shown in TABLE 4.

TABLE 4  
Inhibitory activity of fluoroquinolones against *S. pneumoniae*  
DNA gyrase and topoisomerase IV

Drug	MIC ( $\mu\text{g/mL}$ )	IC <sub>50</sub> ( $\mu\text{M}$ ) <sup>a</sup>	
		Topoisomerase IV	Gyrase
Gemifloxacin	0.03-0.06	2.5-5	5-10
Moxifloxacin	0.25	10	20
Gatifloxacin	0.25	10-20	20-40
Levofloxacin	1	40	80
Ciprofloxacin	1-2	20	40

<sup>a</sup> IC<sub>50</sub> concentration of drug that results in 50% inhibition of enzyme activity.

The data in the above table demonstrate that gemifloxacin is slightly better than moxifloxacin and gatifloxacin and considerably better than levofloxacin and ciprofloxacin at inhibiting topoisomerase IV and DNA gyrase. Activity against topoisomerase IV is about twice as good as against gyrase. Since topoisomerase IV is usually the primary target in *S. pneumoniae* (some studies suggest that gyrase is the primary target for gatifloxacin), the greater efficacy against topoisomerase IV is expected. Most studies suggest that the activity difference between the two enzymes should be greater for the levofloxacin and ciprofloxacin and should be almost equal for the newer drugs. The authors also examined the potency of each fluoroquinolone in stabilizing the cleavable complex of wild-type and mutant gyrase or topoisomerase IV. The results of these DNA cleavage assays are shown in TABLE 5. Once again gemifloxacin was the most effective drug tested. There was only a slight difference between gemifloxacin and moxifloxacin and gatifloxacin against DNA gyrase.

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TABLE 5  
Fluoroquinolone inhibition of recombinant *S. pneumoniae*  
DNA gyrase and topoisomerase IV

Quinolone	CC <sub>25</sub> (µM) for DNA breakage			
	Topoisomerase IV		DNA Gyrase	
	Wild-type	Phe-79ParC	Wild-type	Phe-81GyrA
Gemifloxacin	0.1-0.3	10-20	2.5	160
Moxifloxacin	2.5-5	160	10	160-320
Gatifloxacin	5-10	80-160	10-20	160-320
Levofloxacin	5-10	>320	20-40	>640
Ciprofloxacin	2.5-5	>160	40	>640

Morrissey et al. (5) investigated fluoroquinolone inhibition of DNA gyrase and topoisomerase IV in *Haemophilus influenzae*. DNA gyrase and topoisomerase IV were purified from five isolates of *H. influenzae* with raised fluoroquinolone MICs. The IC<sub>50</sub> values for ciprofloxacin, ofloxacin, grepafloxacin, and gemifloxacin were then determined. The results can be seen in TABLE 6. For most strains all four drugs gave similar results. Gemifloxacin and grepafloxacin appear to be slightly better against the DNA gyrase in strains with higher MICs.

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TABLE 6  
Fluoroquinolone inhibition of DNA gyrase and topoisomerase IV  
From five strains of *Haemophilus influenzae*

Isolate Number	Drug	MIC ( $\mu\text{g/mL}$ )	IC <sub>50</sub> $\mu\text{g/mL}$ ( $\pm$ SD)	
			Topoisomerase IV	DNA gyrase
ATCC 10211	Gemifloxacin	0.015	46.5 ( $\pm$ 3.5)	13.9 ( $\pm$ 1.2)
	Ciprofloxacin	0.015	51.6 ( $\pm$ 0.7)	20.2 ( $\pm$ 0)
	Ofloxacin	0.03	43.2 ( $\pm$ 1.1)	22.2 ( $\pm$ 0.3)
	Grepafloxacin	0.015	47.2 ( $\pm$ 1.4)	17.9 ( $\pm$ 5.7)
363036	Gemifloxacin	0.5	54.5 ( $\pm$ 5.0)	19.5 ( $\pm$ 1.5)
	Ciprofloxacin	1	69.1 ( $\pm$ 2.4)	42.5 ( $\pm$ 6.3)
	Ofloxacin	1	65.6 ( $\pm$ 1.4)	50.6 ( $\pm$ 1.7)
	Grepafloxacin	0.12	49.6 ( $\pm$ 2.4)	25.1 ( $\pm$ 0.2)
605068	Gemifloxacin	0.5	48.7 ( $\pm$ 1.6)	37.6 ( $\pm$ 3.9)
	Ciprofloxacin	2	63.6 ( $\pm$ 7.7)	36.9 ( $\pm$ 2.4)
	Ofloxacin	4	64.1 ( $\pm$ 1.6)	39.5 ( $\pm$ 1.7)
	Grepafloxacin	0.5	73.6 ( $\pm$ 3.7)	15.2 ( $\pm$ 0.7)
601099	Gemifloxacin	0.5	104.0 ( $\pm$ 1.6)	34.7 ( $\pm$ 4.6)
	Ciprofloxacin	4	105.1 ( $\pm$ 7.2)	51.7 ( $\pm$ 1.2)
	Ofloxacin	8	109.8 ( $\pm$ 7.2)	51.6 ( $\pm$ 0)
	Grepafloxacin	2	104.0 ( $\pm$ 1.6)	38.7 ( $\pm$ 6.5)
511334	Gemifloxacin	2	66.9 ( $\pm$ 1.8)	40.3 ( $\pm$ 3.2)
	Ciprofloxacin	16	117.1 ( $\pm$ 11.3)	110.9 ( $\pm$ 13.4)
	Ofloxacin	8	121.3 ( $\pm$ 2.0)	51.9 ( $\pm$ 4.3)
	Grepafloxacin	8	127.5 ( $\pm$ 6.0)	48.4 ( $\pm$ 3.0)

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### ANTIMICROBIAL SPECTRUM OF ACTIVITY

This section focuses on the activity of gemifloxacin and other quinolone comparators against clinically relevant respiratory tract pathogens recovered in the United States and Canada. Data from an anaerobic study, which compares gemifloxacin with newer fluoroquinolones, has been included. Most of the data presented is from a GlaxoSmithKline sponsored surveillance study.

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### *In Vitro* Activity against Respiratory Tract Pathogens

This section focuses on the activity of gemifloxacin against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in comparison with other agents, especially against other quinolones. It must always be remembered that just comparing MICs may not be clinically significant. The pharmacokinetics of the two drugs being compared is also important. Gemifloxacin usually has MICs that are lower than the comparator drug, but gemifloxacin's plasma concentration ( $C_{max}$ ) and its area under the concentration time curve (AUC) are lower than those of the comparators.

#### *Streptococcus pneumoniae*

Gemifloxacin demonstrates the lowest MICs against *Streptococcus pneumoniae*, compared with ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Most studies show that gemifloxacin MIC<sub>90</sub>s are 4-fold to 64-fold lower than those of comparator quinolones. Unfortunately, at the proposed human dose the AUC value for gemifloxacin is only about one-fourth that of most of the other fluoroquinolones. A 4-fold lower MIC value is, therefore, basically equivalent to that of trovafloxacin or moxifloxacin.

The GlaxoSmithKline sponsored surveillance study, known as the "Factive Targeted Surveillance (FACTS) Study", is a *Streptococcus pneumoniae in vitro* surveillance study conducted in the United States only (6). This on-going study, begun in 2000, was designed to target isolates, which have acquired quinolone resistance. This study has two phases. The first phase is a screening process designed to detect resistance to penicillin, macrolides, and the quinolones. Isolates having a levofloxacin E-test MIC of  $\geq 1.5 \mu\text{g/mL}$  and/or a gemifloxacin E-test MIC of  $\geq 0.25 \mu\text{g/mL}$  or gemifloxacin zone size  $\leq 15 \text{ mm}$ , are tested in the second phase against a panel of quinolones including gemifloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Some of these isolates are not resistant to levofloxacin (resistant MIC =  $8 \mu\text{g/mL}$ ) and may even be susceptible to levofloxacin (susceptible MIC =  $2 \mu\text{g/mL}$ ). Approximately 120 geographically distributed sites in the United States are participating in the study. The target number of isolates from each site is 75. In this study 6,257 isolates of *S. pneumoniae* were analyzed. Of these, 16.8% ( $n = 1,050$ ) and 16.2% ( $n = 1,016$ ) were penicillin-intermediate and -resistant, respectively. Twenty-four percent ( $n = 1,505$ ) were erythromycin-resistant. The MIC<sub>90</sub>s for gemifloxacin and levofloxacin from the first phase of testing were  $0.047 \mu\text{g/mL}$  and  $1.0 \mu\text{g/mL}$ , respectively (TABLE 7). The modal MICs for gemifloxacin ( $0.032 \mu\text{g/mL}$ ) and levofloxacin ( $0.75 \mu\text{g/mL}$ ) were the same as their MIC<sub>50</sub> values. The results of gemifloxacin and comparators against the resistant isolates will be discussed in a separate section on *in vitro* activity against resistant strains.

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TABLE 7  
*In vitro* activity of gemifloxacin, levofloxacin, and penicillin against 6,257  
*S. pneumoniae* isolates (FACTS Study)

Compound	MIC range ( $\mu\text{g/mL}$ )	MIC <sub>50</sub> ( $\mu\text{g/mL}$ )	MIC <sub>90</sub> ( $\mu\text{g/mL}$ )
Gemifloxacin	0.004-2	0.032	0.047
Levofloxacin	0.002->32	0.75	1
Penicillin	0.004->32	0.032	2

In another study, 550 *Streptococcus pneumoniae* isolates collected in 1999-2000 from 16 geographically distributed U.S. hospitals, were tested against gemifloxacin and other comparator compounds (7,8). Gemifloxacin had the lowest MIC<sub>90</sub> of all the quinolones tested with an MIC<sub>90</sub> of 0.03  $\mu\text{g/mL}$ . Gemifloxacin's MIC<sub>90</sub> against *S. pneumoniae* was 8-fold lower than that of moxifloxacin, 16-fold lower than that of gatifloxacin, 32-fold lower than that of levofloxacin, and 64-fold lower than that of ciprofloxacin (TABLE 8). Gemifloxacin's AUC value, however, is about 4-fold lower than most of the comparator quinolones at clinical doses. Since there is a one-dilution (2-fold) error rate when doing susceptibility testing, this makes gemifloxacin equivalent to moxifloxacin and only slightly better than gatifloxacin when pharmacokinetic parameters are considered.

TABLE 8  
*In vitro* activity of gemifloxacin and comparators against 550  
*S. pneumoniae* isolates (reference 7 and 8)

Compound	MIC range ( $\mu\text{g/mL}$ )	MIC <sub>50</sub> ( $\mu\text{g/mL}$ )	MIC <sub>90</sub> ( $\mu\text{g/mL}$ )
Gemifloxacin	0.008-0.5	0.015	0.03
Ciprofloxacin	$\leq 0.25$ ->8	1	2
Levofloxacin	$\leq 0.12$ ->2	1	1
Gatifloxacin	$\leq 0.03$ ->1	0.25	0.5
Moxifloxacin	$\leq 0.03$ ->1	0.12	0.25

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One thousand four hundred fifty (1450) *S. pneumoniae* isolates collected in 1999-2000 from 23 sites in Canada, were tested against gemifloxacin and other comparator compounds (9). Gemifloxacin had the lowest MIC<sub>90</sub> value at 0.06 µg/mL. The MIC<sub>90</sub> of gemifloxacin was 4-fold lower than that of gatifloxacin and 16-fold lower than ciprofloxacin and levofloxacin. The 4-fold difference between gatifloxacin and gemifloxacin would make them clinically equivalent when pharmacokinetic parameters are considered. Moxifloxacin was not tested in this study (TABLE 9).

TABLE 9  
*In vitro* activity of gemifloxacin and comparators against 1,450  
*S. pneumoniae* isolates from Canada (reference 9)

Compound	MIC range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)
Gemifloxacin	≤0.015-0.5	≤0.015	0.06
Ciprofloxacin	≤0.12->16	1	1
Levofloxacin	≤0.12->16	1	1
Gatifloxacin	≤0.06->8	0.25	0.25

*Haemophilus influenzae*

Two hundred and ninety *Haemophilus influenzae* isolates collected in 1999-2000 from sixteen geographically distributed U.S. hospitals, were tested against gemifloxacin and other comparator compounds (7). Gemifloxacin's had an MIC<sub>90</sub> value of 0.008 µg/mL. Gemifloxacin's activity was similar to that of ciprofloxacin, levofloxacin, and gatifloxacin (MIC<sub>90</sub>s of 0.015 µg/mL). Moxifloxacin had a slightly higher MIC<sub>90</sub> value of 0.03 µg/mL. All these fluoroquinolones had low MIC values against *H. influenzae*. Gemifloxacin's MIC values were slightly lower but it must be remembered that its pharmacokinetic parameters are 4-fold lower than most of the comparators. The data from this study are shown in TABLE 10.

TABLE 10  
*In vitro* activity of gemifloxacin and comparators against 290  
*H. influenzae* isolates from U.S. hospitals (reference 7)

Compound	MIC range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (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

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TABLE 13  
*In vitro* activity of gemifloxacin and comparators against isolates of  
Macrolide-resistant *S. pneumoniae*

# of isolates	Macrolide resistance criteria (µg/mL)	MIC <sub>90</sub> (µg/mL)				Reference
		Gemi	Cipro	Levo	Gati	
1,505	Erythromycin MIC ≥ 1	0.047	NT	1	NT	6
115	Clarithromycin MIC ≥ 1	0.06	2	2	0.25	9

Gemi = gemifloxacin; Cipro = ciprofloxacin; Levo = levofloxacin; Gati = gatifloxacin;  
NT = not tested

**Ciprofloxacin non-susceptible *S. pneumoniae***

In a study of 167 isolates from Canada with reduced susceptibility to ciprofloxacin (MIC ≥ 4 µg/mL) (11), the MIC<sub>90</sub> for gemifloxacin was 0.5 µg/mL. The MIC<sub>90</sub> values were 4 µg/mL, 4 µg/mL, 16 µg/mL, and 32 µg/mL for moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin, respectively. The MIC<sub>90</sub> values for moxifloxacin and gatifloxacin are at the resistant breakpoint for these antimicrobials. The MIC<sub>90</sub> for gemifloxacin was 8-fold lower than that for moxifloxacin or gatifloxacin but gemifloxacin's pharmacokinetic parameters are about 4-fold lower than the parameters for these two antimicrobials. This study is summarized in TABLE 14.

In another Canadian study, 90 isolates with reduced susceptibility to ciprofloxacin (MIC ≥ 2 µg/mL) were tested (12). The MIC<sub>90</sub> for gemifloxacin was 0.25 µg/mL, compared with 2 µg/mL, 4 µg/mL, 16 µg/mL, and 32 µg/mL for moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin, respectively. Moxifloxacin's MIC<sub>90</sub> value is in the intermediate range for *S. pneumoniae*.

TABLE 14  
*In vitro* activity of gemifloxacin and comparators against isolates of  
Ciprofloxacin non-susceptible *S. pneumoniae*

# of isolates	Cipro MIC (µg/mL)	MIC <sub>90</sub> (µg/mL)					Reference
		Gemi	Cipro	Levo	Gati	Moxi	
167	≥ 4	0.5	32	16	4	4	11
90	≥ 2	0.25	32	16	4	2	12

Gemi = gemifloxacin; Cipro = ciprofloxacin; Levo = levofloxacin; Gati = gatifloxacin; Moxi = moxifloxacin

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**Levofloxacin non-susceptible *S. pneumoniae***

A collection of 57 isolates with levofloxacin MICs  $\geq 8$   $\mu\text{g/mL}$  was tested against levofloxacin, gatifloxacin and gemifloxacin (13). The gemifloxacin MIC<sub>90</sub> was 1  $\mu\text{g/mL}$ , compared to 8  $\mu\text{g/mL}$  for gatifloxacin and  $>16$   $\mu\text{g/mL}$  for levofloxacin. In another study, 32 isolates with levofloxacin MICs  $\geq 4$   $\mu\text{g/mL}$  (intermediate susceptibility) were tested against gemifloxacin and other comparators (14). The gemifloxacin MIC<sub>90</sub> was 0.5  $\mu\text{g/mL}$  compared to 2  $\mu\text{g/mL}$ , 4  $\mu\text{g/mL}$ , and 8  $\mu\text{g/mL}$  for moxifloxacin, gatifloxacin, and levofloxacin, respectively (TABLE 15).

Of the 6,257 *S. pneumoniae* isolates analyzed in the FACTS study, 56 (0.9%) were non-susceptible to levofloxacin (MIC  $\geq 3$   $\mu\text{g/mL}$ ) (6). Gemifloxacin had a MIC<sub>90</sub> value of 1.5  $\mu\text{g/mL}$ . Levofloxacin, gatifloxacin, and moxifloxacin had MIC<sub>90</sub> values of  $>32$   $\mu\text{g/mL}$ ,  $\geq 32$   $\mu\text{g/mL}$ , and 12  $\mu\text{g/mL}$ , respectively (TABLE 15).

TABLE 15  
*In vitro* activity of gemifloxacin and comparators against isolates of  
Levofloxacin non-susceptible *S. pneumoniae*

# of isolates	Levo MIC ( $\mu\text{g/mL}$ )	MIC <sub>90</sub> ( $\mu\text{g/mL}$ )				Reference
		Gemi	Levo	Gati	Moxi	
56	$\geq 3$	1.5	$>32$	4	4	6
57	$\geq 8$	1	$>16$	8	NT	13
32	$\geq 4$	0.5	8	4	2	14

Gemi = gemifloxacin; Cipro = ciprofloxacin; Levo = levofloxacin; Gati = gatifloxacin; Moxi = moxifloxacin  
NT = not tested

***Haemophilus influenzae* with elevated fluoroquinolone MICs**

A total of 27 strains of *Haemophilus influenzae* collected by four investigators between 1994-2001 had elevated ciprofloxacin or ofloxacin MIC values at  $\geq 4$ -fold the usual MIC<sub>90</sub> value of 0.06  $\mu\text{g/mL}$  (15). These strains had 2-4 mutations within the quinolone resistance determining region (QRDR) and all had elevated gemifloxacin MICs that ranged from 0.016-2  $\mu\text{g/mL}$  (TABLE 16).

TABLE 16  
Gemifloxacin activity against 27 fluoroquinolone resistant strains\* of  
*H. influenzae*

	MIC Range ( $\mu\text{g/mL}$ )	MIC <sub>50</sub> ( $\mu\text{g/mL}$ )	MIC <sub>90</sub> ( $\mu\text{g/mL}$ )	% $\leq 0.25$ $\mu\text{g/mL}$
Gemifloxacin	0.016-2	0.25	1	57.1

\* Screening reproducible MICs of  $>0.06$   $\mu\text{g/mL}$  for ciprofloxacin and/or ofloxacin

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The activities of gemifloxacin and four other quinolones were tested against fifteen *H. influenzae* isolates with well characterized QRDR mutations (15). The results can be seen in TABLE 17. Unfortunately the highest concentration of moxifloxacin tested was 4 µg/mL or it is difficult to compare moxifloxacin MIC<sub>90</sub> values with the other drugs which were tested at concentration up to 32 µg/mL. It appears that except for ciprofloxacin all the other drugs are basically equivalent against strains with 1 or 2 mutations. Gemifloxacin has lower MICs against strains with 3 or 4 mutations, but is basically equivalent to gatifloxacin and moxifloxacin when pharmacokinetic parameters are considered.

TABLE 17  
Activity of five quinolones against 15 *H. influenzae* strains with well characterized QRDR mutations

No. of QRDR Mutations (no. tested)	MIC Parameter	Quinolone MIC (µg/mL)				
		Gemi	Cipro	Levo	Gati	Moxi
1 or 2 (12)	Range	0.016-1	0.12->32	0.06-2	0.06-1	0.12-2
	MIC <sub>50</sub>	0.06	0.5	0.25	0.12	0.25
	MIC <sub>90</sub>	1	>32	2	1	2
3 or 4 (3)	Range	1-2	>32	>32	4->32	>4
	MIC <sub>50</sub>	1	>32	>32	4	>4
1 to 4 (15)	Range	0.016-2	0.12->32	0.06->32	0.06->32	0.12->4
	MIC <sub>50</sub>	0.12	1	1	0.5	0.5
	MIC <sub>90</sub>	1	>32	>32	4	>4

Gemi = gemifloxacin; Cipro = ciprofloxacin; Levo = levofloxacin; Gati = gatifloxacin; Moxi = moxifloxacin

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**In Vitro Activity against Atypical Organisms**

This section contains data for gemifloxacin and comparators against *Legionella* species and *Mycoplasma pneumoniae*.

***Legionella pneumophila***

In a study (16) testing *Legionella pneumophila* and other *Legionella* species, trovafloxacin was found to have the lowest MIC<sub>90</sub> values (0.008 µg/mL). Gemifloxacin, levofloxacin, ciprofloxacin, and moxifloxacin all had MIC<sub>90</sub> values of 0.03 to 0.06 µg/mL (see TABLE 18).

TABLE 18  
Activity of gemifloxacin and comparators against *Legionella* strains

Organism	Antimicrobial Agent	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)
<i>L. pneumophila</i> Serogroup I (n = 68)	Trovafloxacin	0.004	0.008	0.004-0.015
	Gemifloxacin	0.015	0.03	0.008-0.06
	Levofloxacin	0.015	0.03	0.015-0.03
	Ciprofloxacin	0.03	0.03	0.015-0.06
	Moxifloxacin	0.03	0.06	0.015-0.06
<i>L. pneumophila</i> serogroups other than Serogroup 1 <sup>a</sup> (n =38)	Trovafloxacin	0.004	0.008	≤0.002-0.008
	Gemifloxacin	0.015	0.03	0.008-0.06
	Levofloxacin	0.015	0.03	0.008-0.03
	Ciprofloxacin	0.03	0.03	0.008-0.03
	Moxifloxacin	0.03	0.06	0.015-0.06
<i>Legionella</i> species other than <i>pneumophila</i> <sup>b</sup> (n = 10)	Trovafloxacin	0.004	0.008	0.004-0.015
	Gemifloxacin	0.015	0.03	0.015-0.06
	Levofloxacin	0.03	0.06	0.008-0.06
	Ciprofloxacin	0.008	0.03	0.008-0.03
	Moxifloxacin	0.03	0.06	0.015-0.06

<sup>a</sup> Serogroups 2,3,4,5,6,7,15

<sup>b</sup> *L. micdadei* (n = 5); *L. dumofii* (n = 1); *L. longbeachae* (n = 2); *L. feeleii* (n = 1); *L. bozemanii* (n = 1)

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*Mycoplasma pneumoniae*

*Mycoplasma pneumoniae* isolates were collected from six different countries, including the United States, over a ten year period (17). There were 103 isolates tested. Gemifloxacin, gatifloxacin, and moxifloxacin had comparable activity with an MIC<sub>90</sub> value of 0.125 µg/mL. Ciprofloxacin and levofloxacin had higher MIC<sub>90</sub> values of 4 µg/mL and 2 µg/mL, respectively (see TABLE 19).

TABLE 19  
Activity of gemifloxacin and comparators against 103 isolates  
Of *Mycoplasma pneumoniae*

Compound	MIC range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)
Gemifloxacin	≤0.001-0.25	0.06	0.125
Ciprofloxacin	0.5-4	2	4
Levofloxacin	0.06-2	0.5	2
Gatifloxacin	0.016-0.25	0.06	0.125
Moxifloxacin	0.016-0.25	0.06	0.125

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*In Vitro* Activity against Anaerobic Organisms

In a study of anaerobic isolates collected from patients with sinusitis, gemifloxacin had an MIC of ≤0.25 µg/mL for 127/162 (78%) of the anaerobes tested (18). Gemifloxacin had borderline activity (MIC<sub>90s</sub> ≤0.25 µg/mL) against *Fusobacterium* species, *Peptostreptococcus* species, and *Veillonella* species. The MIC<sub>90s</sub> were 0.5 µg/mL for gemifloxacin and levofloxacin and 0.25 µg/mL for gatifloxacin and moxifloxacin against *Propionibacterium* species. Gemifloxacin had poor activity against *Prevotella* species with an MIC<sub>90</sub> of 2 µg/mL (see TABLE 20).

Not enough additional isolates have been tested to allow *Peptostreptococcus* species into the *in vitro* activity list (list #2) in the label. The MIC<sub>90</sub> value is close to the susceptible breakpoint of ≤0.25 µg/mL and many studies have higher MIC<sub>90</sub> values.

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TABLE 20  
Comparative *in vitro* activity of gemifloxacin against  
Anaerobic bacteria

Organism	Number of Isolates	Agent	MIC Range (µg/mL)	MIC <sub>50</sub> /MIC <sub>90</sub> (µg/mL)
<i>Fusobacterium</i> species <sup>1</sup>	20	<b>Gemifloxacin</b>	≤0.03-0.25	<b>0.125/0.125</b>
		Levofloxacin	≤0.03-2	1/1
		Gatifloxacin	0.125-0.5	0.25/0.5
		Moxifloxacin	≤0.03-0.5	0.125/0.25
<i>Prevotella</i> species <sup>2</sup>	10	<b>Gemifloxacin</b>	<b>0.5-8</b>	<b>1/2</b>
		Levofloxacin	0.5-4	1/1
		Gatifloxacin	0.25-1	0.25/0.5
		Moxifloxacin	0.25-1	0.5/1
<i>Prevotella melaninogenica</i>	13	<b>Gemifloxacin</b>	<b>0.5-2</b>	<b>1/1</b>
		Levofloxacin	0.5->8	1/1
		Gatifloxacin	0.25->8	0.25/0.5
		Moxifloxacin	0.5-8	0.5/1
<i>Propionibacterium</i> species <sup>3</sup>	28	<b>Gemifloxacin</b>	<b>0.06-0.5</b>	<b>0.25/0.5</b>
		Levofloxacin	0.125-0.5	0.25/0.5
		Gatifloxacin	0.06-0.5	0.125/0.25
		Moxifloxacin	0.06-0.5	0.25/0.25
<i>Peptostreptococcus magnus</i>	40	<b>Gemifloxacin</b>	≤0.03-8	<b>0.06/0.06</b>
		Levofloxacin	0.125->8	0.25/0.5
		Gatifloxacin	≤0.03-8	0.125/0.25
		Moxifloxacin	0.06-8	0.125/0.125
<i>Peptostreptococcus micros</i>	16	<b>Gemifloxacin</b>	<b>0.06-1</b>	<b>0.125/0.125</b>
		Levofloxacin	0.06-1	0.5/0.5
		Gatifloxacin	0.06-2	0.25/0.25
		Moxifloxacin	0.125-1	0.25/0.5
<i>Peptostreptococcus</i> species <sup>4</sup>	12	<b>Gemifloxacin</b>	≤0.03-0.5	<b>0.125/0.25</b>
		Levofloxacin	0.25-8	4/4
		Gatifloxacin	0.06-1	0.5/1
		Moxifloxacin	0.06-1	0.5/1
<i>Veillonella</i> species	13	<b>Gemifloxacin</b>	≤0.03-4	<b>0.06/0.125</b>
		Levofloxacin	0.25-8	0.25/0.5
		Gatifloxacin	0.06-2	0.125/0.25
		Moxifloxacin	0.06-4	0.125/0.25
Other anaerobes	10	<b>Gemifloxacin</b>	≤0.03->4	<b>0.5/2</b>
		Levofloxacin	≤0.03->8	1/8
		Gatifloxacin	≤0.03->8	0.25/4
		Moxifloxacin	≤0.03->8	0.25/4

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<sup>1</sup> includes *Fusobacterium nucleatum*, 16; *F. necrophorum*, 1; *F. naviforme*, 2; *F. varium*, 1.

<sup>2</sup> includes *Prevotella bivia*, 1; *P. buccae*, 6; *P. intermedia*, 1; *P. oris* 2.

<sup>3</sup> includes *Propionibacterium acnes*, 12; *P. avidium*, 8; *P. granulosum*, 8.

<sup>4</sup> includes *Peptostreptococcus anaerobius*, 1; *P. asaccharolyticus*, 5; *P. prevotii*, 2; others 4.

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## DEVELOPMENT OF RESISTANCE

Fluoroquinolone resistance can arise either through mutations in defined regions of DNA gyrase and topoisomerase IV, termed the Quinolone-Resistance Determining regions (QRDRs), or through altered efflux. Studies on the mechanisms and development of resistance to gemifloxacin were presented in the original NDA 21-158. Recent studies have been conducted to further characterize and assess development of resistance to gemifloxacin in comparison with other quinolones.

### Resistance Selection

The ability of sequential subcultures to select for resistant mutants when exposed to sub-inhibitory concentrations of gemifloxacin, moxifloxacin, gatifloxacin, ciprofloxacin, and trovafloxacin was studied in *Streptococcus pneumoniae* (19). Selection of resistant mutants and single-step mutation rates were determined for 16 *S. pneumoniae* isolates (8 with ciprofloxacin MICs = 0.25-1 µg/mL, 4 with ciprofloxacin MICs = 8-16 µg/mL, and 4 with ciprofloxacin MICs = 16-32 µg/mL). Subculturing was performed 50 times, or until mutants resistant to the selecting drug emerged. Emergence of resistance was classified as isolates with gemifloxacin MICs  $\geq 2$  µg/mL; moxifloxacin, gatifloxacin, and trovafloxacin MICs  $\geq 4$  µg/mL (for parent strains with initial MICs of 0.06-2 µg/mL) or 4 times the initial MIC (for parent strains with initial MICs of 4 µg/mL); ciprofloxacin MICs  $\geq 8$  µg/mL (for parent strains with initial MICs 0.5-1 µg/mL) or 4 times the initial MIC (for parent strains with initial MICs 8-32 µg/mL). The results of the multi-step resistance selection are summarized in TABLE 21.

TABLE 21  
Multi-step resistance selection of gemifloxacin and comparators  
In 16 *Streptococcus pneumoniae* isolates

Selecting Agent	MIC of Selected Mutants (µg/mL)	Resistant Mutants Selected	Number of Passages
Gemifloxacin	2	6	5-26
Moxifloxacin	4-16	12	5-41
Gatifloxacin	4-16	12	5-29
Ciprofloxacin	8-128	11	4-16
Trovafloxacin	4	4	4-33

It appears that the number of passages required to select a resistant mutant is about equal for all the tested quinolones. Gemifloxacin and trovafloxacin appear to have less resistant mutants selected. The small number of selected mutants for gemifloxacin is probably, however, due to the fact that an MIC of  $\geq 2$  µg/mL was selected as the resistant breakpoint for gemifloxacin. If the correct MIC of  $\geq 0.125$  µg/mL were chosen there probably would have been many more resistant mutants selected.

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Single-step mutation frequencies for gemifloxacin and comparator quinolones were also investigated against the 16 pneumococcal isolates (20). Mutation frequency was calculated as the number of resistant colonies per inoculum at 1x, 2x, 4x, 8x, and 16x the MIC of each drug tested. The frequencies of single-step mutations with gemifloxacin ranged from  $2.0 \times 10^{-4}$  to  $<1.0 \times 10^{-10}$ . This range was equivalent to that seen with gatifloxacin ( $2.8 \times 10^{-4}$  to  $<1.0 \times 10^{-10}$ ) and slightly lower than that seen with moxifloxacin ( $3.0 \times 10^{-4}$  to  $<2.0 \times 10^{-9}$ ). Ciprofloxacin showed slightly higher frequencies with a range of  $>3.0 \times 10^{-1}$  to  $<5.0 \times 10^{-9}$ . Overall, the mutation frequencies were about equal for all the fluoroquinolones tested. As expected the frequencies were much higher at 1 x MIC than at 16 x MIC.

The frequency of selecting gemifloxacin-resistant *S. pneumoniae* compared with moxifloxacin, gatifloxacin, and levofloxacin was investigated by Pidcock (21). One wild-type strain and nine other strains were studied to determine the frequency of selection of mutants after exposure to multiples (2x and 4x) of the MIC either in the presence or absence of reserpine. The frequencies of mutant selection are shown in TABLE 22. None of the quinolones selected any mutants from the wild-type strain (M3), strain M26 (ParC Ala79), strain M126 (ParC Tyr79, GyrA Lys85), or strain M129 (Par C Asn83, GyrA Phe81). For those strains from which mutants were selected, the frequency of mutation ranged from  $2 \times 10^{-5}$  to  $2 \times 10^{-11}$ .

Gemifloxacin selected mutants from one double mutant strain (M34, ParC Ala79, GyrA Ala85) and three single mutant strains (M122, GyrA Lys85; M123, GyrA Phe81; M130, ParC Asn83). Susceptibility testing found that the mutants selected from M34 and M122 had the same susceptibility as their respective parent strains.

The highest gemifloxacin MIC was  $\leq 2 \mu\text{g/mL}$ . The highest MIC seen for moxifloxacin and gatifloxacin was  $16 \mu\text{g/mL}$ ,  $64 \mu\text{g/mL}$  for levofloxacin, and  $128 \mu\text{g/mL}$  for ciprofloxacin. It must be remembered, however, that gemifloxacin has pharmacokinetic parameters that are 4-8 times lower than those of most other fluoroquinolones. A gemifloxacin MIC of  $2 \mu\text{g/mL}$  is, therefore, clinically equivalent to moxifloxacin MIC of 8 to  $16 \mu\text{g/mL}$ .

Reserpine inhibits an efflux pump mechanism present in *S. pneumoniae*. The presence of reserpine affected the number of mutants selected after exposure to each of the four agents. This can be seen in TABLE 22 by either a decrease in the frequency of resistance or inhibition of the selection of mutants in the presence of reserpine. These results suggest that a reserpine-susceptible efflux pump may be a step in fluoroquinolone resistance development. Moxifloxacin was affected to a much lesser extent than the other drug tested. Many studies show that moxifloxacin is a poor substrate for the efflux pump in *S. pneumoniae*. The role of efflux will be discussed in greater detail in the next section of this review.

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TABLE 22  
 Frequency of Mutant Selection

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

R = reserpine, Gemi = gemifloxacin, Gati = gatifloxacin, Moxi = moxifloxacin, Levo = levofloxacin

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In a study conducted by Gillespie, mutation rates of ciprofloxacin and gemifloxacin were calculated using the median mutation method (24). This method measures the risk of mutation per cell division as opposed to mutation frequencies which measure the number of mutant colonies as a proportion of the total number of organisms plated. *Streptococcus pneumoniae* isolates were exposed to concentrations 2x and 4x the MIC of a clinically isolated wild-type strain, for both gemifloxacin (0.03 µg/mL) and ciprofloxacin (1 µg/mL). At 2 x MIC, ciprofloxacin had a mutation rate of  $7.8 \times 10^{-10}$ . The mutation rate for gemifloxacin at 2 x MIC was  $1.66 \times 10^{-9}$ , which was higher than that for ciprofloxacin. Only one of 39 gemifloxacin selected colonies, however, had a mutation in the QRDR region (single *gyrA*). No mutations were selected by either drug at 4 x MIC. The overall rate of mutation in any of the four QRDR genes, *parC*, *parE*, *gyrA*, and *gyrB*, was determined to be  $7.7 \times 10^{-10}$  mutations per cell division. The overall mutation rate for a single *gyrA* mutation was  $1.6 \times 10^{-11}$ . Strains in which a *gyrA* mutation was already present were subjected to a second round of resistance induction with gemifloxacin as the selecting agent. This mutation rate was determined to be  $5.26 \times 10^{-9}$  mutations per cell division. It appears that once one mutation is present it is easier to get a second mutation.

Gillespie also compared the spectrum of mutations in the QRDR of *Streptococcus pneumoniae* seen when either gemifloxacin or ciprofloxacin was the selecting agent (21). A subset of resistant colonies obtained during the mutation rate experiments was selected for QRDR sequencing. Thirty-four mutants selected by ciprofloxacin were sequenced. Of these, 23 were found to be single *parC* mutants and two were double mutants, one with a *parC* and *gyrA* mutation and the other with mutations in *parC* and *gyrB*. Only one mutation, a single *gyrA* mutation, was seen in the 39 gemifloxacin selected colonies subjected to QRDR sequencing. In order to investigate the lack of *parC* mutants seen when gemifloxacin was the selecting agent, the MICs of ciprofloxacin selected mutants were measured. These results are shown in TABLE 23. These data show that a single *parC* mutation does not produce a significant increase in the gemifloxacin MIC. Only a *gyrA parC* double mutant cause a significant rise in gemifloxacin MIC. This was also seen with moxifloxacin. It appears that gemifloxacin and moxifloxacin need a double mutation to lead to significant increases in MIC values, while levofloxacin and ciprofloxacin only need a single mutation in *parC* to have a significant rise in MIC values.

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TABLE 23  
MICs ( $\mu\text{g/mL}$ ) of ciprofloxacin selected *S. pneumoniae* mutants

Mutation	MIC ( $\mu\text{g/mL}$ )			
	Gemi	Moxi	Levo	Cipro
WT	0.016	0.064	0.038	0.5
<i>parC</i> S79Y	0.064	0.125	1.5	4.0
<i>parC</i> S79F	0.032	0.125	1.0	2.0
<i>parC</i> S79Y, <i>gyrA</i> S81Y	0.25	2.0	>32	>32
<i>gyrA</i> S81Y*	0.023	0.125	0.75	1.0
<i>parC</i> S79Y	0.064	0.125	1.0	6.0
<i>parC</i> S79Y	0.047	0.064	1.0	4.0

WT = wild-type, Gemi = gemifloxacin, Moxi = moxifloxacin, Levo = levofloxacin, Cipro = ciprofloxacin

\* Selected by gemifloxacin

Data represents the mean of three E-test results

Two routes to resistance were seen in this study: (1) *parC* followed by mutation in *gyrA* or (2) a single mutation in *gyrA*. While mutation rates for gemifloxacin and ciprofloxacin were similar, in order to acquire high level resistance to gemifloxacin, a second mutation appears to be necessary. A single *parC* mutation is enough to elevate ciprofloxacin's MIC value into the resistant category, but does not elevate gemifloxacin's or moxifloxacin's MIC into their resistant category. A double-mutation also appears to be needed to get isolates resistant to levofloxacin.

Heaton *et al.* have also supported the idea that in order for resistance to gemifloxacin to arise, *S. pneumoniae* requires two mutation (3). In this study, mutant *S. pneumoniae* were selected by exposure to ciprofloxacin, sparfloxacin, or gemifloxacin. A few of the selected mutants were subjected to sequencing in order to define QRDR mutations and their susceptibilities to gemifloxacin, ciprofloxacin, and sparfloxacin determined (see TABLE 24):

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TABLE 24  
QRDR mutations and MICs of *S. pneumoniae* mutants  
Selected with gemifloxacin, sparfloxacin, and ciprofloxacin

Strain	MIC (µg/mL)			QRDR Mutations	
	GEMI	SPAR	CIPRO	GyrA	ParC
7785	0.06	0.5	1-2	----	----
1C1	0.06	0.5	4	----	----
2C6	0.12-0.25	0.5	8	----	S79Y
2C7	0.12-0.25	0.5	8	----	S79F
1S1	0.12-0.25	2	2	S81F	----
1S4	0.12-0.25	2	2	S81Y	----
3C4	1	16	64	S81Y	S79Y
2S1	0.5	16	64	S81F	S79Y
2S4	0.5	16	16	S81F	D83N
1GM4*	0.12-0.25	1	2-4	----	----
1GM5*	0.25	2	2	S81F	----
1GM7*	0.25	4-8	2	E85K	----
1GM9*	0.25	2	2	E85K	----
1GM10*	0.25	2	2	S81Y	----
1GM11*	0.25	2	2	S81F	----
2GM1**	1	32	64	S81F	S79F
2GM2**	1	32	64	S81F	S79Y
2GM17**	1	32	64	S81F	S79Y
2GM18**	1	32	64	S81F	S79Y

\* Mutants obtained from first step selection by gemifloxacin using strain 7785

\*\* Mutants obtained from second step selection by gemifloxacin using strain 1GM5

GEMI = gemifloxacin, SPAR = sparfloxacin, CIPRO = ciprofloxacin

Single mutations in either *parC* or *gyrA* increased the MIC of gemifloxacin 2- to 4-fold over the MIC of the parent strain, 7785. An 8- to 16-fold increase in gemifloxacin MIC was seen when mutations were present in both *parC* and *gyrA*. A *parC* only mutation increased the MIC of ciprofloxacin 4- to 8-fold, but did not increase the MIC of sparfloxacin. A *gyrA* mutation increased the MIC of sparfloxacin 4- to 8-fold, but did not increase the MIC of ciprofloxacin. Double mutations increased the MICs of sparfloxacin and ciprofloxacin 32- to 64-fold. Double mutants appeared to be resistant to all three drugs tested. These results support the theory that gemifloxacin is a dual targeting fluoroquinolone. Single mutations in either the *parC* or *gyrA* gene can increase gemifloxacin MICs enough to put the isolate at or just above the susceptible breakpoint. Sparfloxacin primary targets the *gyrA* gene in *S. pneumoniae* and ciprofloxacin has as its primary target. Single mutations in *gyrA* will increase sparfloxacin MICs into the intermediate category. Ciprofloxacin is not a very good drug against *S. pneumoniae* and most strains have MIC values at or close to the susceptible breakpoint even without mutations in the QRDR. A single mutation in the *parC* gene, therefore, can cause an isolate to become resistant.

The type and frequency of first and second step mutants selected by gemifloxacin at 1x and 1.5x the MIC were also examined. During the first round of selection, only single *gyrA* mutants were selected by gemifloxacin suggesting that *gyrA*

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is the preferred target in *S. pneumoniae*. An additional *parC* mutation was acquired during second-step selection. The mutation frequency of both first- and second-step mutants for both drug concentrations was approximately  $10^{-9}$ .

**Efflux**

One of the mechanisms of resistance described for fluoroquinolones is efflux. The possibility that an efflux mechanism may be contributing to the elevated MICs of mutant *S. pneumoniae* isolates was investigated by Nagai *et al.* (19). The MICs of sixteen parent *S. pneumoniae* strains and eighty quinolone selected mutants were determined in the presence and absence of 10 µg/mL of reserpine (an inhibitor of efflux pumps). An efflux mechanism (PmrA) was believed to be present when the MIC in the presence of reserpine was at least fourfold less than the MIC in the absence of reserpine. In the presence of reserpine, mutants had MICs that were 4-8x lower for gatifloxacin (13/80 mutants) and 4-32x lower for ciprofloxacin (53/80 mutants) and gemifloxacin (39/80 mutants). This suggests the presence of an efflux mechanism. No mutants had lower trovafloxacin or moxifloxacin MICs in the presence of reserpine. It appears that trovafloxacin and moxifloxacin are poor substrates for efflux pumps in *S. pneumoniae*. Gatifloxacin is affected to some extent by efflux pumps and gemifloxacin and ciprofloxacin are good substrates for the efflux pump in *S. pneumoniae*.

Piddock examined the effect of reserpine on the selection of mutants from *Streptococcus pneumoniae* strains exhibiting either single or double mutations (20). These results were shown earlier in TABLE 22. Reserpine markedly affected the numbers of mutants selected after exposure to each of the four agents (gemifloxacin, moxifloxacin, gatifloxacin, and levofloxacin). This is demonstrated in TABLE 22 by either a decrease in the frequency of resistance or inhibition of the selection of mutants in the presence of reserpine. These results suggest that a reserpine-susceptible efflux pump may be a step in fluoroquinolone resistance. Moxifloxacin was affected to a much lesser extent than the other drug tested. Many studies show that moxifloxacin is a poor substrate for the efflux pump in *S. pneumoniae*.

Brenwald and Gill conducted a study to characterize three isolates of *Streptococcus pneumoniae* demonstrating efflux-mediated fluoroquinolone resistance (22). Susceptibility studies with the efflux inhibitors reserpine and rescinnamine, indicated that all three isolates had an efflux phenotype as demonstrated by both inhibitors causing a four- to eight-fold reduction in the MIC of norfloxacin (TABLE 25). Ciprofloxacin exhibited a four- to eight-fold reduction in MIC in the presence of reserpine for all three strains. Moxifloxacin, sparfloxacin, and grepafloxacin were either unaffected or showed a two-fold reduction in the presence of reserpine. In the presence of reserpine, gemifloxacin showed a four-fold reduction in MIC for one strain and a two-fold or less reduction for the other two strains. The *pmrA* gene was found in all three strains but not in multiple copies.

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TABLE 25  
Susceptibilities of *S. pneumoniae* strains with and Efflux Pump

Strain	Antimicrobial	MIC ( $\mu\text{g/mL}$ )
L11259	Norfloxacin	64
	Norfloxacin + Reserpine	8
	Norfloxacin + Rescinnamine	16
	Gemifloxacin	0.25
	Gemifloxacin + Reserpine	0.06
	Ciprofloxacin	16
	Ciprofloxacin + Reserpine	2
	Moxifloxacin	0.5
	Moxifloxacin + Reserpine	0.25
	Sparfloxacin	0.5
	Sparfloxacin + Reserpine	0.5
	Grepafoxacin	0.5
	Grepafoxacin + Reserpine	0.5
	209165	Norfloxacin
Norfloxacin + Reserpine		16
Norfloxacin + Rescinnamine		16
Gemifloxacin		0.25
Gemifloxacin + Reserpine		0.12
Ciprofloxacin		16
Ciprofloxacin + Reserpine		4
Moxifloxacin		0.5
Moxifloxacin + Reserpine		0.5
Sparfloxacin		1
Sparfloxacin + Reserpine		1
Grepafoxacin		1
Grepafoxacin + Reserpine		0.5
507103		Norfloxacin
	Norfloxacin + Reserpine	16
	Norfloxacin + Rescinnamine	16
	Gemifloxacin	0.12
	Gemifloxacin + Reserpine	0.12
	Ciprofloxacin	16
	Ciprofloxacin + Reserpine	8
	Moxifloxacin	>2
	Moxifloxacin + Reserpine	>2
	Sparfloxacin	>4
	Sparfloxacin + Reserpine	>4
	Grepafoxacin	>2
	Grepafoxacin + Reserpine	>2

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Mutant Prevention Concentration

Mutant prevention concentration (MPC) is a new method of evaluation the activity of fluoroquinolones and their potential for development of resistance. MPC testing is similar to the methodology used to determine MIC values. Plates containing antimicrobials are inoculated with a suspension of organisms containing a specific concentration of cells (CFU/mL). The MPC is recorded as the lowest antimicrobial concentration that prevents growth of the organism. MIC testing uses an inoculum concentration of  $10^5$  CFU/mL while MPC testing uses a higher inoculum concentration of around  $10^{10}$  CFU/mL. With a high concentration of organisms present, first step mutants are more likely to be seen within the organism population. If no growth occurs in this high concentration of organisms then the antimicrobial concentration was able to inhibit growth of both wild type organisms and first step mutants. Any organisms still able to grow at this antimicrobial concentration or higher concentrations would require two mutations. To this reviewer this is just another method to make a drug with lower MIC values appear to be better than one with higher MIC values. It would be expected that no matter what inoculum was used a drug with a lower MIC would always have a lower MPC also.

Blondeau *et al.* investigated the MPC of gemifloxacin, moxifloxacin, gatifloxacin, and levofloxacin against 150 clinical isolates of *S. pneumoniae* (25). The MIC and MPC of each isolate was determined by agar dilution. TABLE 26 summarizes the results obtained. As expected the MPC values were lower for the drugs with lower MIC values.

TABLE 26  
Comparative activity of quinolones by mutant prevention concentration  
Against 150 clinical isolates of *S. pneumoniae*

Antimicrobial Agent	MPC <sub>50</sub> (µg/mL)	MPC <sub>90</sub> (µg/mL)
Gemifloxacin	0.12	0.5
Moxifloxacin	0.5	1
Gatifloxacin	0.5	2
Levofloxacin	1	4

Two other studies investigated the MPC of gemifloxacin and other fluoroquinolones against strains of *S. pneumoniae*. Smith *et al.* examined the MPC of five quinolones against two single step *S. pneumoniae* mutants created from two different wild-type strains (24). Allen and Rybak measured the MPC of gemifloxacin and four comparators against two clinical isolates of *S. pneumoniae* (25). The MIC and MPC values determined in these two studies are shown in TABLE 27. As expected the MPC values pretty much followed the MIC values, although the MPC for moxifloxacin was somewhat higher than expected for strain 2670. In all cases the MPCs for ciprofloxacin and levofloxacin appear to be higher than those for gemifloxacin, moxifloxacin, and gatifloxacin.

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TABLE 27  
MPC values for gemifloxacin and comparators  
against four *S. pneumoniae* strains

	<i>S. pneumoniae</i> 2670		<i>S. pneumoniae</i> 2587		<i>S. pneumoniae</i> 68		<i>S. pneumoniae</i> 79	
	MIC ( $\mu\text{g/mL}$ )	MPC ( $\mu\text{g/mL}$ )	MIC ( $\mu\text{g/mL}$ )	MPC ( $\mu\text{g/mL}$ )	MIC ( $\mu\text{g/mL}$ )	MPC ( $\mu\text{g/mL}$ )	MIC ( $\mu\text{g/mL}$ )	MPC ( $\mu\text{g/mL}$ )
Gemi	0.016	0.06	0.016	0.13	0.03	0.5	0.03	0.125
Moxi	0.06	1	0.06	0.5	0.125	0.5	0.125	0.5
Gati	0.25	0.5	0.25	0.5	0.125	0.5	0.25	1
Levo	0.5	2	0.5	2	1	2	1	4
Cipro	1	8	1	16	0.5	8	0.5	8

Gemi = gemifloxacin, Moxi = moxifloxacin, Gati = gatifloxacin, Levo = levofloxacin,  
Cipro = ciprofloxacin

*S. pneumoniae* 2670 and 2587 are from Smith *et al.* (27)

*S. pneumoniae* 68 and 79 are from Allen and Rybak (26)

Smith *et al.* also measured the mutant prevention MIC ( $MP_{MIC}$ ) which they defined as the multiple of the MIC corresponding to the MPC. The  $MP_{MIC}$ s determined for gemifloxacin, moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin against two first step mutants of *S. pneumoniae* created from two different wild-type strains are shown in TABLE 28.

TABLE 28  
 $MP_{MIC}$ s obtained from single-step mutants of *S. pneumoniae*

Isolate	$MP_{MIC}$				
	Gemi	Moxi	Gati	Levo	Cipro
2670	4x	16x	2x	4x	8x
2587	8x	8x	2x	4x	16x

Gemi = gemifloxacin, Moxi = moxifloxacin, Gati = gatifloxacin, Levo = levofloxacin,  
Cipro = ciprofloxacin

Evaluating the MPC as a function of the fold MIC increase ( $MP_{MIC}$ ) may allow the comparison of multiple antimicrobials' intrinsic ability to prevent the selection of resistant mutants. It can be seen from the above table that gatifloxacin appears to be the best drug at doing this. Levofloxacin appears to be slightly better than gemifloxacin with moxifloxacin and ciprofloxacin bringing up the rear. There probably, however, is not that much of a difference between any of the tested drugs. The clinical significance of this is also unknown.

Blondeau investigated the MPCs of *Streptococcus pneumoniae* isolates exhibiting elevated levofloxacin MPCs of 4 to  $>512 \mu\text{g/mL}$  (26). The MPCs for gemifloxacin, moxifloxacin, and gatifloxacin were measured against nineteen of these isolates. The isolates were also characterized to determine the mutations within the QRDR. These results are shown in TABLE 29.

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TABLE 29  
MPCs and QRDR mutations associated with 19 strains of  
*S. pneumoniae* exhibiting high levofloxacin MPCs

Isolate	MPC (µg/mL)				Changes in QRDR	
	Gemi	Moxi	Gati	Levo	<i>parC</i>	<i>gyrA</i>
10	0.5	4	4	32	D83N	S81F
12	0.5	4	8	32	S79F	S81Y
13	≥2	32	32	128	S79F S52G N19D	S114G
15	0.25	1	8	32	S79F	None
18	0.25	2	8	64	S79F	None
27	8	>128	8	16	S52G N91D	S114G
33	0.063	1	2	8	K137N	None
36	0.25	8	NT	4	K137N	None
37	0.125	4	1	>512	K137N	None
42	0.5	1	1	32	K137N	None
43	0.5	2	0.5	8	None	None
48	0.5	1	1	8	K137N	None
51	0.25	0.5	1	8	K137N	None
64	0.25	2	1	8	K137N	None
74	32	16	8	8	S62G	None
78	0.125	0.5	0.5	8	None	None
87	0.25	0.5	1	8	None	None
89	1	1	4	8	S52G	S114G
103	0.125	2	4	8	None	None

Gemi = gemifloxacin, Moxi = moxifloxacin, Gati = gatifloxacin, Levo = levofloxacin, NT = not tested, QRDR, quinolone-resistance-determining region. Amino acid in wild-type protein is indicated before its number in the protein, followed by the amino acid change. D = aspartic acid, F = phenylalanine, G = glycine, K = lysine, N = asparagines, S = serine, Y = tyrosine

Although gemifloxacin MPCs were lower than those for the other tested drugs, it must be remembered that it will have a lower breakpoint. A gemifloxacin MPC of 0.12 µg/mL is probably equivalent to a moxifloxacin or gatifloxacin MPC of 1 µg/mL and a levofloxacin MPC of 2 µg/mL. Gemifloxacin, therefore, is probably better than levofloxacin but only equivalent to or slightly inferior to moxifloxacin and gatifloxacin in this experiment.

In another part of this study Blondeau (26) conducted time kill experiments using the MPC drug concentration instead of multiples of the MIC which are normally used in standard time kill experiments. Gemifloxacin, moxifloxacin, and levofloxacin all exhibited a 3 log reduction (bactericidal effect) in viable count after 24 hours of exposure. After one hour of exposure, gemifloxacin reduced viable cells by 15-57%. A decrease of 52-99% in viable cells was seen after four hours of exposure to gemifloxacin. Moxifloxacin and levofloxacin gave equivalent or slightly better results compared to gemifloxacin at times less than 24 hours.

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BACTERICIDAL STUDIES

*Streptococcus pneumoniae* and *Haemophilus influenzae*

Kays evaluated the bactericidal activity of gemifloxacin against four clinical isolates of levofloxacin-resistant *S. pneumoniae* (51). All these isolates were resistant to levofloxacin with MICs  $\geq 8$   $\mu\text{g/mL}$ . Gemifloxacin concentrations of 0.5, 1, 2, 4, and 8 x MIC were tested by time-kill methodology. The results are shown in TABLE 30.

TABLE 30  
Change in bacterial counts from 0-12 hours for four levofloxacin-resistant *S. pneumoniae* isolates at different gemifloxacin concentrations

Strain	MICs		Gemifloxacin Concentration				
	( $\mu\text{g/mL}$ )		0.5 x MIC	1 x MIC	2 x MIC	4 x MIC	8 x MIC
	GEM	LEV					
M3	0.03	8	+0.46	+1.10	+0.18	-2.12	-3.29
M32	0.25	8	-0.14	-1.58	-3.55	-3.94	-3.91
M205	0.5	16	+0.33	-2.18	-2.58	-2.55	-2.69
W34	1	32	-0.55	-2.25	-3.62	-3.61	-3.69

Gemifloxacin was bactericidal at 12 hours for isolate M3 at a gemifloxacin concentration of 8 x MIC. Gemifloxacin was also bactericidal at 2x, 4x, and 8 x MIC for isolated M32 and W34. Gemifloxacin was not bactericidal for isolate M205 with a gemifloxacin MIC of 0.5  $\mu\text{g/mL}$ . These data seem to indicate that the total gemifloxacin concentration used is more important than the multiple of the MIC. It took 8 x MIC (0.25  $\mu\text{g/mL}$ ) to get a bactericidal effect with isolate M3 (MIC = 0.03  $\mu\text{g/mL}$ ), but only 2 x MIC (0.5  $\mu\text{g/mL}$ ) for isolate M32.

Morrissey *et al.* (28) investigated the bactericidal activity of gemifloxacin, ciprofloxacin, ofloxacin, and grepafloxacin against ten isolates of *H. influenzae*, some exhibiting elevated quinolone MICs. Broths containing fluoroquinolones at concentrations between 0.003 and 200  $\mu\text{g/mL}$  were inoculated with exponentially growing *H. influenzae* and incubated. Viable counts were performed. The average  $\log_{10}$  change in viable count was plotted against  $\log_{10}$  fluoroquinolone concentration. The area-under-the curve of the bactericidal portion of a plot of  $\log_{10}$  reduction in viable count against  $\log_{10}$  fluoroquinolone concentration was measured and from this a bactericidal index (BI) was calculated. BIs greater zero indicate bactericidal activity and higher BIs are associated with increased bactericidal activity. The BIs and MICs of the four quinolones against the 10 *Haemophilus influenzae* isolates are shown in TABLE 31.

All the fluoroquinolones were bactericidal against *H. influenzae* ATCC 10211 (ciprofloxacin MIC of 0.015  $\mu\text{g/mL}$ ) and the other strains with ciprofloxacin MICs less than 1  $\mu\text{g/mL}$ . Against *H. influenzae* 511334 (ciprofloxacin MIC of 16  $\mu\text{g/mL}$ ) only gemifloxacin and grepafloxacin were bactericidal. Levofloxacin, moxifloxacin and gatifloxacin were not tested in this study. It appears that all fluoroquinolones are bactericidal against most strains of *H. influenzae*. Ofloxacin appears to be somewhat less active compared to other drugs tested.

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TABLE 31  
Bactericidal index and minimum inhibitory concentration (MIC) of fluoroquinolones  
Against 10 isolates of *Haemophilus influenzae*

Isolate Number	Antimicrobial	MIC (µg/mL)	Bactericidal Index*
ATCC 10211	<b>Gemifloxacin</b>	<b>0.015</b>	<b>8.5</b>
	Ciprofloxacin	0.015	8.1
	Ofloxacin	0.03	6.6
	Grepafoxacin	0.015	6.6
511334	<b>Gemifloxacin</b>	<b>2</b>	<b>2.1</b>
	Ciprofloxacin	16	0
	Ofloxacin	8	0
	Grepafoxacin	8	0.4
601099	<b>Gemifloxacin</b>	<b>0.5</b>	<b>1.9</b>
	Ciprofloxacin	4	1.5
	Ofloxacin	8	0.2
	Grepafoxacin	2	1.4
605068	<b>Gemifloxacin</b>	<b>0.5</b>	<b>6.7</b>
	Ciprofloxacin	2	3.0
	Ofloxacin	4	1.3
	Grepafoxacin	0.5	2.6
1998363036	<b>Gemifloxacin</b>	<b>0.5</b>	<b>7.4</b>
	Ciprofloxacin	1	5.6
	Ofloxacin	1	4.6
	Grepafoxacin	0.12	3.2
501162	<b>Gemifloxacin</b>	<b>0.25</b>	<b>3.6</b>
	Ciprofloxacin	0.5	2.5
	Ofloxacin	0.5	2.0
	Grepafoxacin	1	1.8
7111143	<b>Gemifloxacin</b>	<b>0.03</b>	<b>8.6</b>
	Ciprofloxacin	0.12	7.5
	Ofloxacin	0.12	6.3
	Grepafoxacin	1	10.8
1998322139	<b>Gemifloxacin</b>	<b>0.25</b>	<b>9.2</b>
	Ciprofloxacin	0.5	6.4
	Ofloxacin	0.25	6.4
	Grepafoxacin	0.12	5.7
1998331290	<b>Gemifloxacin</b>	<b>0.25</b>	<b>16.0</b>
	Ciprofloxacin	0.12	11.6
	Ofloxacin	0.25	10.2
	Grepafoxacin	0.03	12.7
1998331259	<b>Gemifloxacin</b>	<b>0.03</b>	<b>9.8</b>
	Ciprofloxacin	0.03	6.9
	Ofloxacin	0.12	6.2
	Grepafoxacin	0.015	6.6

\* BI calculations are made by plotting log<sub>10</sub> reduction in viable count against log<sub>10</sub> drug concentration and measuring the area-under-the-curve of the bactericidal section of the graph.

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Intracellular Pathogens

Several studies have investigated the bactericidal activity of gemifloxacin and comparators against intracellular pathogens such as *Legionella* species, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

In one study (29), the intracellular activity of gemifloxacin, levofloxacin, gatifloxacin, moxifloxacin, and erythromycin was assessed and compared against intracellular *Legionella pneumophila* and *Legionella micdadei* at 0.1, 0.25, 0.5, 1.0, 5.0, and 10 x MIC. Increasing concentrations of gemifloxacin resulted in increased killing. Even at 0.1 x MIC, gemifloxacin had activity against both species of *Legionella*. The activities of all the fluoroquinolones were similar and in all cases, greater than that of erythromycin. Removal of gemifloxacin or erythromycin (10 x MIC) at 24 hours resulted in decreased intracellular activity. Activity continued even at 72 hours after drug removal. Re-growth to control levels did not occur.

Ye *et al.* (16) compared the *in vitro* susceptibility of *Legionella* species to gemifloxacin, moxifloxacin, levofloxacin, ciprofloxacin, grepafloxacin, trovafloxacin, and other non-quinolone comparators. Testing was carried out at 1x and 8 x MIC for each drug and the results were expressed as percent inhibition defined as

$$\frac{\text{Total Legionella at 48 hours with agent}}{\text{Total Legionella at 48 hours without agent}} \times 100$$

Values less than 100% were indicative of an inhibitory effect. These results are shown in TABLE 32. All the quinolones were superior to erythromycin and azithromycin in inhibiting intracellular *Legionella* species at 8 x MIC. Overall, the quinolones appeared to have similar activity.

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TABLE 32  
Effects of antimicrobial agents on intracellular multiplication of  
*Legionella* species expressed as percent inhibition ratio

Antimicrobial Agent	MIC <sub>90</sub> (µg/mL)	<i>L. pneumophila</i>		<i>L. micdadei</i>		<i>L. longbeachea</i>	
		1 x MIC	8 x MIC	1 x MIC	8 x MIC	1 x MIC	8 x MIC
Gemifloxacin	0.015	24.9	10.5	0.56	0.18	0.84	0.008
Moxifloxacin	0.03	17.0	1.1	0.75	0.29	0.71	0.04
Levofloxacin	0.03	34.2	9.3	0.58	0.19	0.1	0.02
Ciprofloxacin	0.03	20.5	10.5	8.6	0.17	0.627	0.003
Trovafloxacin	0.008	21.7	11.9	10.7	0.44	9.7	0.04
Grepafloxacin	0.06	23.8	15.1	0.52	0.28	0.11	0.02
Clarithromycin	0.06	12.7	15.7	3.7	1.4	30.2	6.3
Azithromycin	0.25	39.1	25.3	16.9	1.1	52.8	6.5
Erythromycin	0.5	50.3	40.0	12.6	1.5	26.7	5.7
Telithromycin	0.125	7.3	3.5	5.6	1.0	9.2	1.2

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Hammerschlag *et al.* (30) investigated the effect of prolonged treatment of gemifloxacin compared with azithromycin on viability of *Chlamydia pneumoniae* in an *in vitro* infection model. This model mimics *in vivo* conditions. Continuously infected Hep-2 cells were seeded into 24-well plates the day before the experiment. The medium was then replaced with medium containing either gemifloxacin or azithromycin at final concentrations of 0.25 µg/mL (the MIC for both drugs) and 2.5 µg/mL and incubated at 35°C for 30 days. The media was changed every third day. Infected cells and supernatants were collected at 0, 6, 12, 18, 24, and 30 days and frozen. The inclusion-forming units per milliliter (IFU/ML) were calculated for every time point. Cultures with no antimicrobial added were used as controls. In this model, gemifloxacin at the MIC (0.25 µg/mL) and at 2.5 µg/mL reduced the concentration of *C. pneumoniae* by 5 log<sub>10</sub>. This was similar to the activity of azithromycin. However, neither antimicrobial completely eliminated *C. pneumoniae* from continuously infected cells, even after 30 days of treatment.

Waites *et al.* (17) examined the bactericidal activity of gemifloxacin and comparators against *Mycoplasma pneumoniae*. Minimal bactericidal concentration (MBC) testing was performed on 13 *M. pneumoniae* isolates. The results of this testing are presented in TABLE 33. Among fluoroquinolones, moxifloxacin had the greatest number of MBCs for *M. pneumoniae* isolates which were 0-2 x the MIC (7/13) followed by gatifloxacin (6/12), gemifloxacin (4/12), levofloxacin (4/13), and sparfloxacin (1/13). Azithromycin had the greatest number of MBCs which were 0-2 x MIC (11/12). Clarithromycin, erythromycin, and doxycycline showed primarily a bacteriostatic effect against *M. pneumoniae*, with most MBCs being >8 x MIC.

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TABLE 33  
Minimal bactericidal results for *M. pneumoniae* (n=13)

Drug	No. isolates with Minimal Bactericidal Concentrations			
	MIC	2 x MIC	4 x MIC	8 x MIC
Gemifloxacin*	0	4	4	4
Ciprofloxacin	0	3	4	6
Levofloxacin	0	4	6	3
Sparfloxacin	0	1	2	10
Gatifloxacin*	2	4	3	3
Moxifloxacin	0	7	4	2
Azithromycin*	8	3	0	1
Clarithromycin	0	0	1	12
Erythromycin	0	2	0	11
Doxycycline	0	0	0	12

\* One isolate had bacterial contamination and could not be evaluated

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In order to characterize the dynamics of the antimicrobial effect of gemifloxacin against *Mycoplasma pneumoniae* over time, time kill studies were performed on a single clinical isolate and compared with levofloxacin (17). The isolate chosen had an MIC of 0.063 µg/mL for gemifloxacin and 0.5 µg/mL for levofloxacin. Dilutions of gemifloxacin and levofloxacin corresponding to 0.5x, 1x, 2x, 4x, and 8 x the MIC of the strain were prepared in broth and actively growing 4-day cultures of *M. pneumoniae* were added to achieve concentrations of approximately  $10^5$ – $10^6$  CFU/mL. A control tube containing no antimicrobial was also inoculated. An aliquot of each dilution and control was removed immediately (time 0) and serially diluted in fresh media. Aliquots of each serial dilution were incubated onto agar plates after 24, 48, 72, 96, 120, and 144 hours of incubation.

Levofloxacin was bactericidal, as demonstrated by a reduction in viable count from approximately  $10^5$  to  $10^2$  CFU/mL (3 logs), after 24 hours at 8 x MIC (4 µg/mL). The drug was bactericidal after 72-96 hours for concentrations 1 to 4 x MIC. A single time point at 120 hours showed bactericidal effect for the concentration of 0.5 x MIC. Concentrations <8 x MIC showed a bacteriostatic effect at 24 and 48 hours time points with decreased CFU counts of 1-2 logs.

Gemifloxacin was also bactericidal against this isolate. The gemifloxacin concentration tested at 8 x MIC (0.5 µg/mL) showed bactericidal activity after 48 hours. The 4 x MIC concentration was bactericidal at 72 hours. Lower concentrations of 2 x MIC and the MIC were bactericidal at 120 and 144 hours. The 0.5 x MIC concentration was not bactericidal at any time point.

The above data seem to show that levofloxacin had better bactericidal activity against this isolate of *Mycoplasma pneumoniae* than did gemifloxacin.

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## **PRECLINICAL EFFICACY (IN VIVO)**

### **PHARMACOKINETICS AND PHARMACODYNAMICS**

#### **AUC/MIC and C<sub>max</sub>/MIC ratios**

Pharmacokinetics/pharmacodynamic (PK/PD) parameters can be useful in predicting the potential for efficacy, bacterial eradication, and development of resistance with antimicrobial therapy. Fluoroquinolones and aminoglycosides have been shown to exhibit concentration dependent killing (i.e. the amount of drug, not the frequency of dosing influences efficacy with these drugs). This can be measured by the ratio of the area under the time-concentration curve to the MIC (AUC/MIC) or the ratio of the peak serum concentration to the MIC (C<sub>max</sub>/MIC). Assessment of the pharmacodynamics of fluoroquinolones in animal models and in humans has indicated that the primary determinant of efficacy is the AUC/MIC ratio. It has also been determined that the target AUC/MIC ratio needed to achieve maximal bacteriological efficacy in *S. pneumoniae* infections is 25-30 (31). In fluoroquinolones, the C<sub>max</sub>/MIC ratio has also been shown to predict efficacy and is being accepted to also correlate with a low potential for development of resistance. A target C<sub>max</sub>/MIC ratio of approximately 10 is thought to be

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needed for a high probability of efficacy and a low potential for development of resistance (31, 32, 33, 34, 35).

Comparative PK/PD data for gemifloxacin, moxifloxacin, gatifloxacin, and levofloxacin are shown in TABLE 34. All the fluoroquinolones demonstrate a AUC/MIC<sub>90</sub> ratio (for *S. pneumoniae*) above the required 25-30. When protein binding is taken into account and the free drug AUC/MIC<sub>90</sub> ratio is calculated all of the tested fluoroquinolones still have the needed 25-30 ratio for *S. pneumoniae*. Although levofloxacin has a ratio somewhat lower than the other drugs it still meets the required ratio. When C<sub>max</sub>/MIC<sub>90</sub> ratios are compared only gemifloxacin and moxifloxacin are above the ratio of 10. Only gemifloxacin is above this ratio of 10 when protein binding is taken into account. Levofloxacin has the lowest C<sub>max</sub>/MIC ratio. This should indicate that resistance would develop, but after about 15 years of use levofloxacin-resistant *Streptococcus pneumoniae* still only make up about 1-2% of the *S. pneumoniae* isolates in most surveillance studies. The C<sub>max</sub>/MIC ratio, therefore, may help predict the rate in which resistance will develop, but even a low ratio does not necessarily mean that resistance will be a major problem.

TABLE 34  
Comparative PK/PD parameters for *Streptococcus pneumoniae*

Antimicrobial (dose)	24 h AUC/MIC <sub>90</sub>		24 h C <sub>max</sub> /MIC <sub>90</sub>	
	Total Drug	Free Drug	Total Drug	Free Drug
Gemifloxacin (320 mg)	8.4/0.03 = 280	2.9-3.8/0.03 = 97-127	1.6/0.03 = 53.3	0.56-0.72/0.03 = 18.7-24
Moxifloxacin (400 mg)	48.0/0.25 = 192	24.0 /0.25 = 96	4.5/0.25 = 18.0	2.3/0.25 = 9.2
Gatifloxacin (400 mg)	51.3/0.5 = 103	41.0/0.5 = 82	4.2/0.5 = 8.4	3.4/0.5 = 6.8
Levofloxacin (500 mg)	47.5/1.0 = 48	29.5-36.1/1.0 = 30-36	5.7/1.0 = 5.7	3.5-4.3/1.0 = 3.5-4.3

TABLE 35 contains data obtained when these PK/PD parameters are examined in a population of *Streptococcus pneumoniae* isolates with ciprofloxacin MICs ≥ 4 µg/mL. Gemifloxacin is the only tested fluoroquinolones with the required AUC/MIC ratio of 25-30 when considering total drug level. None of the tested drugs, however, has the needed AUC/MIC ratio of 25-30 when free drug is considered. None of the drugs has the targeted C<sub>max</sub>/MIC ratio of 10 for either total drug or free drug.

TABLE 35  
Comparative PK/PD parameters for *S. pneumoniae* (ciprofloxacin MIC ≥ 4 µg/mL)

Antimicrobial (dose)	24 h AUC/MIC <sub>90</sub>		24 h C <sub>max</sub> /MIC <sub>90</sub>	
	Total Drug	Free Drug	Total Drug	Free Drug
Gemifloxacin (320 mg)	8.4/0.25 = 33.6	2.9-3.8/0.25 = 11.6-15.2	1.6/0.25 = 6.4	0.56-0.72/0.25 = 2.2-2.9
Moxifloxacin (400 mg)	48.0/4.0 = 12.0	24.0 /4.0 = 6.0	4.5/4.0 = 1.1	2.3/4.0 = 0.6
Gatifloxacin (400 mg)	51.3/4.0 = 12.8	41.0/4.0 = 10.3	4.2/4.0 = 1.1	3.4/4.0 = 0.9
Levofloxacin (500 mg)	47.5/16 = 3.0	29.5-36.1/16.0 = 1.8-2.3	5.7/16.0 = 0.4	3.5-4.3/16.0 = 0.2-0.3

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***In vitro* Pharmacodynamic Models**

The activity of gemifloxacin and comparator quinolones was studied in numerous *in vitro* pharmacodynamic models. Zhanel *et al.* examined the bacterial killing of gemifloxacin, moxifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin against one ciprofloxacin-intermediate and six ciprofloxacin-resistant *S. pneumoniae* isolates obtained from a Canadian surveillance study (36, 37). Experiments were performed simulating fluoroquinolone peak serum concentrations and AUCs achieved in human serum after standard oral doses. Both low-level (ciprofloxacin MIC = 4 µg/mL) and high-level (ciprofloxacin MIC = 16 µg/mL) ciprofloxacin-resistant *S. pneumoniae* isolates representing four different resistant phenotypes (ParC mutant, efflux only mutant, ParC and efflux, and ParC and GyrA mutant) were studied (TABLE 36).

TABLE 36  
Susceptibility of ciprofloxacin-intermediate and -resistant  
*S. pneumoniae* to fluoroquinolones

Strain	MIC (µg/mL)						ParC Change	GyrA Change	Efflux
	Cipro	Levo	Gati	Moxi	Gemi				
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	

Cipro = ciprofloxacin, Levo = levofloxacin, Gati = gatifloxacin, Moxi = moxifloxacin, Gemi = gemifloxacin

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The activity of the fluoroquinolones against these *S. pneumoniae* strains using simulated serum concentrations is shown in TABLE 37.

TABLE 37  
Fluoroquinolone killing of ciprofloxacin-intermediate and -resistant  
*S. pneumoniae* simulating free serum concentrations

Strain	Log <sub>10</sub> killing at 6, 24, and 48 hours, respectively <sup>a</sup>				
	Cipro	Levo	Gati	Moxi	Gemi
2680	0.4/0/0	3.4/≥4.5/≥4.5	3.3/≥4.5/≥4.5	3.4/≥4.5/≥4.5	3.9/≥4.5/≥4.5
4610	0/0/0	3.0/≥4.5/≥4.5	3.2/≥4.5/≥4.5	3.4/≥4.5/≥4.5	3.6/≥4.5/≥4.5
16072	0/0/0	3.3/≥4.5/≥4.5	3.5/≥4.5/≥4.5	3.5/≥4.5/≥4.5	3.6/≥4.5/≥4.5
18705	0/0/0	2.0/3.5/2.0	3.2/≥4.5/≥4.5	3.3/≥4.5/≥4.5	3.9/≥4.5/≥4.5
16701	0/0/0	0.2/0/0	0.4/0/0	0.5/0.5/0	1.8/3.5/2.0
17012	0/0/0	0.2/0/0	0.3/0/0	0.7/0.5/0	3.0/≥4.5/≥4.5
18410	0/0/0	0.1/0/0	0.1/0/0	0.4/0.4/0	3.0/≥4.5/≥4.5

<sup>a</sup> = growth reduction relative to initial inoculum

Cipro = ciprofloxacin, Levo = levofloxacin, Gati = gatifloxacin, Moxi = moxifloxacin, Gemi = gemifloxacin

The data in the above table demonstrate that ciprofloxacin produced no reduction of growth at 6, 24, or 48 hours against all seven strains. This indicates that ciprofloxacin is not a very good drug against *S. pneumoniae*. Levofloxacin was bactericidal (≥3 log killing) at 6, 24, and 48 hours for the ParC as well as the efflux mutants, but only bactericidal at 24 hours for the ParC with efflux strain. Levofloxacin demonstrated no reduction of growth against the ParC and GyrA double mutants. Gatifloxacin and moxifloxacin were bactericidal at 6, 24, and 48 hours against the ParC, efflux, and ParC with efflux mutants, but demonstrated little or no growth reduction against ParC and GyrA mutants. Gemifloxacin was bactericidal at 6, 24, and 48 hours against the ParC, efflux, and ParC with efflux mutants. Against two of the ParC and GyrA double mutants gemifloxacin was bactericidal at 6, 24, and 48 hours but against one ParC and GyrA double mutant gemifloxacin showed reduced activity with bactericidal killing at 24 hours but with subsequent growth at 48 hours. The strain producing the reduced gemifloxacin activity had a gemifloxacin MIC of 0.25 µg/mL while the other two double mutant strains had gemifloxacin MICs of 0.12 µg/mL. There appears to be some difference in activity around the breakpoint of 0.12 µg/mL.

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**Effect of Serum Binding**

The efficacy of quinolone antimicrobial has been demonstrated to correlate with the AUC/MIC ratio. It has been suggested that the critical value predicting good efficacy in animal models of *Streptococcus pneumoniae* infection is 25-30. Recent studies have discussed the need to use the free fraction of compound in these analyses. Studies have been performed to examine the correlation between efficacy of gemifloxacin and AUC<sub>total</sub>/MIC or AUC<sub>free</sub>/MIC for strains of *S. pneumoniae* with differing susceptibility to gemifloxacin. The data compare gemifloxacin with moxifloxacin and gatifloxacin, both of which have lower serum binding values in human serum compared with gemifloxacin (50, 20, and 55-65%, respectively) (38).

Rats were infected intrabronchially with one of thirteen strains of *S. pneumoniae* (gemifloxacin MICs of 0.03-1.0 µg/mL). Doses administered were chosen to approximate in the rat the serum or tissue AUCs achieved in man following therapeutic dosing (see TABLE 38). Therapy began 24 hours later and continued for 3 days. Approximately 14 hours after cessation of therapy, the animals were killed and the lungs excised for enumeration of viable bacterial numbers. Percentage binding to rat serum proteins was determined.

TABLE 38  
Doses administered to rats to approximate AUC<sub>total/free</sub> achieved in man  
Following therapeutic dosing

Group	Rat				Man			
	Dose (mg/kg/d)	AUC <sub>total</sub> (mg.h/L)	% bound	AUC <sub>free</sub> (mg.h/L)	Dose (mg/kg/d)	AUC <sub>total</sub> (mg.h/L)	% bound	AUC <sub>free</sub> (mg.h/L)
GEMI	240	6.9	43	3.7	320	8.4	55-65	2.9-3.8
MOXI	300	27.6	24	21.0	400	30	50	15
GATI	200	33.2	23.5	25.0	400	31.4	20	25.1

Efficacy studies were done on thirteen strains of *Streptococcus pneumoniae* having various susceptibility to gemifloxacin (MIC 0.03-1.0 µg/mL), moxifloxacin (0.125-4µg/mL), and gatifloxacin (0.25-8 µg/mL). A ≥2.5 log<sub>10</sub> reduction in bacterial count was used to define clinical efficacy. This value seems to be picked arbitrarily and does not even represent a bactericidal effect. It may have been picked so that all the strains with gemifloxacin MICs of 0.25 µg/mL would show satisfactory results. The AUC<sub>total</sub>/MIC for the strains with a gemifloxacin MIC of 0.25 µg/mL were all approximately 25. The AUC/MIC value for these strains is close to the limit found to represent clinical efficacy. Strains with a gemifloxacin MIC of ≤0.125 µg/mL had much higher AUC/MIC values of 56 or higher. The AUC<sub>free</sub>/MIC for the strains with gemifloxacin MICs of 0.25 µg/mL were approximately 14.9. Against strains of *S. pneumoniae* with gemifloxacin MIC of 0.5 µg/mL the AUC<sub>total</sub>/MIC was 13.8 and the AUC<sub>free</sub>/MIC was 7.4. These values are below the 25-30 limit for clinical efficacy. Gemifloxacin produced a ≥2.5 log reduction in bacterial count for all seven strains with a gemifloxacin MIC of 0.25 µg/mL and for one of five strains with a gemifloxacin MIC of 0.5 µg/mL.

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There were three strains with moxifloxacin MICs of 1 µg/mL. These strains had an AUC<sub>total</sub>/MIC of 27.6 and an AUC<sub>free</sub>/MIC of 21. Moxifloxacin produced a ≥ 2.5 log reduction in bacterial count for these three strains with a moxifloxacin MIC of 1 µg/mL and for two of five strains with a moxifloxacin MIC of 2 µg/mL.

There were three strains with gatifloxacin MICs of 2 µg/mL. These strains had an AUC<sub>total</sub>/MIC of 16.6 and an AUC<sub>free</sub>/MIC of 12.5. The AUC<sub>total</sub>/MIC value is below the 25-30 limit needed for clinical efficacy. Gatifloxacin produced a ≥2.5 log reduction in bacterial count for all three of these strains with a gatifloxacin MIC of 2 µg/mL and for two of six strains with a gatifloxacin MIC of 4 µg/mL.

## ANIMAL PROPHYLATIC AND THERAPEUTIC STUDIES

The efficacy of gemifloxacin was examined in the original NDA in respiratory tract (RTI) and urinary tract infection (UTI). Additional studies have been performed since the original NDA submission. Most of these studies examined the efficacy of gemifloxacin against experimental pneumococcal infections.

### *In vivo* models of *S. pneumoniae* respiratory tract infection

Additional studies were performed using strains of *S. pneumoniae* with gemifloxacin MICs ≥0.125 µg/mL that were highly resistant to ciprofloxacin and levofloxacin. Six of these isolates were genetically-defined second step mutants (TABLE 39). In this study (39) once again a reduction in bacterial count in the lungs was the measurement of clinical efficacy. The bacteria were not eradicated from the lungs and a significant difference from untreated control (p≤0.01) was taken to be a success. Data not shown in TABLE 39 (see TABLE 41) demonstrate that isolates with gemifloxacin MICs of ≤0.03 µg/mL had a reduction in bacterial counts to the level of detection. As the gemifloxacin MIC value increases the reduction in bacterial count becomes less. The amount of reduction in bacterial count that indicates clinical efficacy has not been determined. In fact one isolate with a levofloxacin MIC of 16 µg/mL (levofloxacin-resistant) had a significant difference from untreated control. Another fact not shown in this table is that dosing for isolates with gemifloxacin MIC of ≥0.125 µg/mL had to be increased to twice a day. Isolates with gemifloxacin MICs of ≤0.03 µg/mL showed good results with bacterial count reduction to the limit of detection with once a day dosing.

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TABLE 39  
Efficacy of gemifloxacin against respiratory tract infections in rats  
Caused by *S. pneumoniae*

<i>S. pneumoniae</i> Strain	Resistance profile	MIC ( $\mu\text{g/mL}$ )		Log <sub>10</sub> CFU/Lungs		
		GEMI	LEVO	NTC	GEMI	LEVO
305313	CIP-R	0.125	1	7.9 ± 0.4	3.3 ± 1.3 <sup>a,b</sup>	5.7 ± 1.3 <sup>a</sup>
622286	CIP-R/MAC-R	0.125	4	6.4 ± 1.3	2.5 ± 1.1 <sup>a,b</sup>	5.1 ± 1.3
PT94254123	CIP-R	0.25	16	8.1 ± 0.8	4.4 ± 0.7 <sup>a,b</sup>	6.8 ± 0.6 <sup>a</sup>
402123 <sup>+</sup>	CIP-R	0.25	8	8.3 ± 0.8	5.7 ± 0.9 <sup>a,b</sup>	7.3 ± 1.2
509063 <sup>+</sup>	CIP-R	0.25	8	6.2 ± 1.6	3.5 ± 1.1 <sup>a,b</sup>	6.2 ± 0.7
214152 <sup>+</sup>	CIP-R	0.5	16	6.6 ± 1.6	3.8 ± 1.4 <sup>a</sup>	5.0 ± 1.4
TPS 3 <sup>+</sup>	CIP-R	0.5	16	6.7 ± 0.4	5.5 ± 1.8	5.9 ± 1.3
TPS 5 <sup>+</sup>	CIP-R	0.5	32	6.2 ± 0.5	4.5 ± 1.2 <sup>a,b</sup>	5.7 ± 0.5
703316 <sup>+</sup>	CIP-R	0.5	>16	6.6 ± 0.4	6.2 ± 0.9	6.5 ± 0.3
42064	CIP-R	0.5	16	6.7 ± 0.3	5.4 ± 1.9	5.2 ± 1.1

MAC-R = macrolide-resistant; CIP-R = ciprofloxacin-resistant

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

<sup>a</sup> Significant difference compared with untreated controls ( $p \leq 0.01$ )

<sup>b</sup> Significant difference compared with levofloxacin ( $p \leq 0.01$ )

<sup>+</sup> Genetically-defined second step mutants

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**Efficacy in comparison with moxifloxacin and gatifloxacin  
Against *S. pneumoniae* respiratory tract infections**

The efficacy of gemifloxacin in comparison with moxifloxacin and gatifloxacin in experimental models of RTI caused by *S. pneumoniae* was also examined (40). The susceptibility of the strains tested to the agents is shown in TABLE 40.

TABLE 40  
MICs of gemifloxacin, moxifloxacin, and gatifloxacin against  
*S. pneumoniae*

<i>S. pneumoniae</i> strain	MIC ( $\mu\text{g/mL}$ )		
	GEMI	MOXI	GATI
404053	≤0.03	0.06	0.125
406081	≤0.03	0.125	0.25
205118	≤0.03	0.25	1.0
305313	0.125	2.0	4.0
509063 <sup>+</sup>	0.25	2.0	4.0
PT9424123	0.25	2.0	4.0
622286	0.125	1.0	1.0
402123 <sup>+</sup>	0.25	2.0	4.0

<sup>+</sup> Genetically-defined second step mutants

GEMI = gemifloxacin, MOXI = moxifloxacin, GATI = gatifloxacin

With the exception of gatifloxacin against *S. pneumoniae* 509063, all therapies were significantly effective compared with untreated controls ( $p \leq 0.01$ ) (TABLE 41). Gemifloxacin showed significant improvement ( $p \leq 0.05$ ) in effect against two of the strains when compared to moxifloxacin and gatifloxacin. The two strains for which gemifloxacin appeared to be better than moxifloxacin was a strain with gemifloxacin MIC of  $\leq 0.03 \mu\text{g/mL}$  and another with gemifloxacin MIC of  $0.125 \mu\text{g/mL}$ , the two strains with gemifloxacin MICs of  $0.25 \mu\text{g/mL}$  gave basically equivalent results with gemifloxacin and moxifloxacin. The p value was also increased to show that gemifloxacin results were significantly better. Overall it appears that except for gatifloxacin against strain 509063, that all three drugs were basically equivalent.

TABLE 41  
Efficacy of gemifloxacin, moxifloxacin, and gatifloxacin against  
*S. pneumoniae*

<i>S. pneumoniae</i> strain	Log <sub>10</sub> CFU/lungs			
	GEMI	MOXI	GATI	NTC
404053	$\leq 1.7$	$\leq 1.7$	$\leq 1.7$	$6.5 \pm 1.5$
406081	$\leq 1.7$	$\leq 1.7$	$\leq 1.7$	$6.8 \pm 1.0$
205118	$1.9 \pm 0.6^{*,**}$	$2.9 \pm 1.6$	$3.7 \pm 1.1$	$6.3 \pm 1.1$
305313	$4.0 \pm 0.8$	$3.5 \pm 1.4$	$4.1 \pm 1.4$	$6.1 \pm 1.5$
509063*	$3.8 \pm 1.6^*$	$4.6 \pm 1.3$	$6.1 \pm 1.2^c$	$7.0 \pm 0.4$
PT 9424123	$3.1 \pm 0.7$	$3.6 \pm 1.9$	$4.0 \pm 1.4$	$6.8 \pm 1.4$
622286	$2.6 \pm 1.2^{**}$	$4.6 \pm 2.0$	$3.6 \pm 2.3$	$7.4 \pm 1.4$
402123*	$3.6 \pm 1.1$	$3.9 \pm 1.3$	$3.1 \pm 1.1$	$6.1 \pm 2.2$

\* significantly different compared with GATI  $p < 0.05$

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

<sup>c</sup> Not significantly different compared to non-treated controls (NTC)  $p > 0.05$

\* Genetically-defined second step mutants

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### Miscellaneous In Vivo Studies

#### Efficacy of gemifloxacin in an experimental bacterial/viral co-infection

Viruses can predispose the host to secondary bacterial infections. Studies have demonstrated that viral infections predispose the host lung to bacterial pneumonia. It has been shown that cells stimulated with virus show enhanced bacterial adherence. This bacterial adherence to host tissue is an essential step in bacterial colonization and infection (41,42,43).

Studies have been performed to demonstrate the efficacy of gemifloxacin in comparison to levofloxacin, moxifloxacin, or gatifloxacin in mice predisposed with influenza and co-infected with *Streptococcus pneumoniae*. Mice were infected intranasally with a dose of influenza virus that leads to a non-lethal self-limiting infection. On day 9 post-influenzae challenge, the mice were given a second challenge with *S. pneumoniae*. Mice that had recently cleared a primary viral challenge required 4 log<sub>10</sub> less pneumococci to produce mortality than saline inoculated controls. To examine the effect of gemifloxacin, mice were infected as stated above with *S. pneumoniae* strain

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#1629. Oral therapy with gemifloxacin, levofloxacin, moxifloxacin, or gatifloxacin commenced up to 40 hours post-bacterial co-infection and was given twice daily for 3 days.

In initial studies gemifloxacin was evaluated when treatment was initiated 6, 24, or 40 hours post-bacterial co-infection. When treatment started 40 hours post-infection, no mice survived in the control group. Mice given gemifloxacin at a dose of 25 mg/kg twice daily for 3 days had a 20% survival rate, mice treated with 50 mg/kg had a 50% survival rate, and mice treated with 100 mg/kg had a 80% survival rate.

In another part of the experiment a comparison of gemifloxacin, levofloxacin, moxifloxacin, and gatifloxacin was made. Mice were treated as stated above and followed for survival. Mice treated with saline control had a survival rate of 11%, Mice treated with levofloxacin (50, 100, or 200 mg/kg) showed about the same survival rate as control at the lower two doses. At 200 mg/kg the survival rate was about 55%. Mice treated with gemifloxacin, moxifloxacin, or gatifloxacin (50, 100, or 200 mg/kg) showed significant improvement in survival over controls with survival rates as high as 90%.

#### *Legionella pneumophila* in guinea pigs

The effect of treatment of guinea pigs infected with *L. pneumophila* pneumonia along with gemifloxacin's intracellular activity against *Legionella pneumophila* was studied (44). Gemifloxacin, azithromycin, and levofloxacin reduced bacterial counts of two *L. pneumophila* strains grown in guinea pig alveolar macrophages by 2 to 3 log<sub>10</sub> CFU. Gemifloxacin and levofloxacin had approximately equivalent intracellular activity.

Therapy studies of gemifloxacin, azithromycin, and levofloxacin performed using a guinea pig model of *L. pneumophila* pneumonia were performed. All 15 guinea pigs treated with gemifloxacin (10 mg/kg/dose given once daily for 2 days) survived for 9 days, as did 13 of 14 guinea pigs treated with the same dose of gemifloxacin for 5 days. All 12 azithromycin treated (15 mg/kg/dose given once daily for 2 days) animals survived, as did 11 or 12 animals treated with levofloxacin (10 mg/kg/dose for 5 days). None of the control animals saw the sun come up on the ninth day.

#### Experimental meningitis

The activity of gemifloxacin in the rabbit meningitis model was studied (45). The standard regimen consisted of Ceftriaxone combined with vancomycin. Gemifloxacin penetrated into inflamed meninges (22-36%) and produced some killing that was slightly better than that seen with controls (-0.68 ± 0.30 log<sub>10</sub> CFU/mL.h compared to +0.07 ± 0.09 log<sub>10</sub> CFU/mL.h). This was slightly better than the regimen of ceftriaxone and vancomycin (-0.49 ± 0.09 log<sub>10</sub> CFU/mL.h). This strain had a penicillin MIC of 4 µg/mL and a gemifloxacin MIC of 0.015 µg/mL. When tested against a penicillin- and ciprofloxacin-resistant strain (penicillin MIC 4 µg/mL; ciprofloxacin MIC 32 µg/mL), gemifloxacin showed some activity (-0.48 ± 0.16 log<sub>10</sub> CFU/mL.h) which was better than control (+0.29 ± 0.22 log<sub>10</sub> CFU/mL.h).

Gemifloxacin appears to have some activity in this model, but it is hard to tell how significant the small drops in bacterial CFUs are clinically.

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## CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

Two new community-acquired pneumonia studies have been submitted. Study 185 is an open label multicenter study comparing the efficacy and safety of gemifloxacin versus intravenous ceftriaxone (with or without a macrolide) followed by cefuroxime (with or without a macrolide). Study 287 was an open label, non-comparative study to assess the efficacy and safety of gemifloxacin once daily for 7 days, for the treatment of community-acquired pneumonia (CAP) of suspected pneumococcal origin in countries with a high prevalence of drug-resistant respiratory pathogens.

### STUDY 185

This study compared gemifloxacin to intravenous ceftriaxone followed by cefuroxime in the treatment of CAP. The study was conducted in 15 countries. The study was a randomized, open label, multicenter study. Four visits were performed over a maximum duration of six weeks to evaluate clinical and bacteriological response to treatment. Patients received either oral gemifloxacin 320 mg once daily for a minimum of 7 days up to a maximum of 14 days or ceftriaxone 2 grams iv once daily (minimum of 1 day up to a maximum of 7 days) and then switched to oral cefuroxime 500 mg twice a day (minimum of 1 day up to a maximum of 13 days, such that the total iv/oral treatment was  $\leq 14$  days).

Samples of sputum or other respiratory secretions were obtained prior to the first dose of study medication (screening, Day 0), at the end of therapy, and at follow-up. All respiratory pathogens isolated were sent to the central laboratory for confirmation of identification, antimicrobial susceptibility testing, and storage. Blood samples for bacteriological evaluations were taken at screening. Patients with a positive blood culture had repeat samples taken at the next visit. Samples of blood for serological evaluation were collected prior to the first dose of study medication and at follow-up in all patients. The central laboratory conducted acute and convalescent phase serological assays for *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Chlamydia psittaci*. In addition, a urine sample was collected prior to the first dose of medication and an assay for *Legionella pneumophila* sero-group 1 antigen was conducted on the sample.

The primary efficacy parameter was clinical response at follow-up (21-28 days post-therapy) in the clinical per protocol (PP) population. Secondary efficacy parameters were clinical response at end of therapy (2-4 days post-therapy), radiological response at follow-up, clinical and radiological response at follow-up, bacteriological response at end of therapy and at follow-up and the time of discharge from hospital.

In total, 341 patients received study medication (gemifloxacin: 169 patients, ceftriaxone/cefuroxime: 172 patients). Overall, 18.6% (32) of gemifloxacin and 16.2% (28) of ceftriaxone/cefuroxime patients were withdrawn from the study, most due to adverse reactions. The numbers of patients who were randomized, received study medication and completed the study, together with the numbers of patients eligible for the various intent-to-treat (ITT) and per protocol (PP) populations are tabulated by treatment group in TABLE 42.

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TABLE 42  
Patient Disposition (All Randomized Patients)

Population	Treatment Group	
	Gemifloxacin 320 mg od N	Ceftriaxone 2g iv od/ Cefuroxime 500 mg bid N
Randomized (Clinical ITT)	172	173
Received Study Medication (ITT)	169	172
Completed Study	140	145
Number of Patients Withdrawn	32	28
Clinical PP End of Therapy	123	129
Clinical PP Follow-UP	116	121
Bacteriological ITT	88	82
Bacteriological PP End of Therapy	67	65
Bacteriological PP Follow-Up	64	63

TABLE 43 shows the number of patients with key pathogens associated with CAP at screening in the bacteriology ITT population. TABLE 44 shows the same data for the bacteriology PP population.

TABLE 43  
Number of Patients with Key Pathogens (Bacteriology ITT Population)

Pre-Therapy Pathogen	Treatment Group			
	Gemifloxacin 320 mg od N = 88		Ceftriaxone 2g iv od/ Cefuroxime 500 mg bid N = 82	
	n	(%)*	n	(%)*
<i>S. pneumoniae</i>	26	(29.5)	25	(30.5)
<i>M. pneumoniae</i>	26	(29.5)	16	(19.5)
<i>C. pneumoniae</i>	19	(21.6)	18	(22.0)
<i>H. influenzae</i>	10	(11.4)	15	(18.3)
<i>H. parainfluenzae</i>	10	(11.4)	4	(4.9)
<i>L. pneumoniae</i>	6	(6.8)	4	(4.9)

\* Percentages are based on the total number of patients; some patients may have more than one pathogen

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