CENTER FOR DROG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-061 and 21-062

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

E. Atkins

Comments were conveyed to sponsor via facsimile dated 9-3-99. ______, RPM

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

AUG 12 1999

NDA number:	**21-061**
SUBMISSION DATE:	December 28, 1998; June 24, 1999; July 21, 1999
RECEIVED BY REVIEWER:	January 4, 1999
DRUG PRODUCT & DOSAGE FORMS:	Gatifloxacin tablets TEQUIN 200mg and 400mg oral tablets
SPONSOR:	Bristol –Myers Squibb Company 5 Research Parkway Wallingford, CT 06492
TYPE OF SUBMISSION:	NME
CATEGORY:	1S
OCPB REVIEWER:	Kathleen Uhl, MD

I. BACKGROUND

Gatifloxacin (BMS-206584) is a new synthetic fluoroquinolone antibacterial agent developed by Kyorin Pharmaceutical Co., Ltd. (Tokyo, Japan). Clinical pharmacology studies have been performed in Japan by Kyorin, in Germany by [redacted] and in the US by BMS. Gatifloxacin is a racemic mixture with no net optical rotation. The antibacterial activity of the S- and R- enantiomers are virtually identical. It is a sesquihydrate and is reported to have no other polymorphs.

Gatifloxacin is shown to possess a broad spectrum of antibacterial activity against Gram-positive and Gram-negative organisms, anaerobes, mycobacteria, *Mycoplasma* sp., and *Chlamydia* sp. The bactericidal activity is reported to be due to its inhibition of the bacterial topoisomerase II (DNA gyrase) and topoisomerase IV.

II. INDICATIONS AND DOSAGES

The applicant is seeking approval of gatifloxacin for the treatment of seven indications: community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute sinusitis, complicated urinary tract infections, uncomplicated urinary tract infections, uncomplicated skin and skin structure infections, and gonococcal urethritis and cervicitis.

A dosage of 400mg once daily is being proposed for all indications, with the exception of uncomplicated urinary tract infection where, in addition to a single 400mg dose, a dosage of 200mg daily for 3 days is being proposed. The proposed length of therapy for the majority of indications will be 7-14 days.

The drug will be marketed as a 200 and 400mg film-coated tablet for oral use and as 20mL (200mg) and 40mL (400mg) single-use sterile vials and 100mL (200mg) and 200mL (400mg) flexible bags.

III. CLINICAL PHARMACOLOGY/BIOPHARM SYNOPSIS

The sponsor has submitted 35 clinical pharmacology/biopharmaceutics study reports, including 3 population PK and PK/PD studies. The sponsor has also submitted 26 supportive clinical pharmacology/biopharmaceutics reports. The basic pharmacokinetic parameters, including bioavailability, are characterized in single and multiple dose pharmacokinetic studies in healthy volunteers, with both oral and IV formulations. Special populations studied included: renal impairment, hepatic impairment, and age and gender effects, Type II diabetics, population PK assessment of renal impairment, and population PK/PD in two Phase II/III studies. Food effects (high fat meal, continental breakfast, green tea and milk) and various drug-drug interactions (cimetidine, ferrous sulfate, calcium carbonate, aluminum hydroxide, digoxin, glyburide, theophylline, midazolam, warfarin, and probenecid) were studied. Pharmacodynamic assessments included: phototoxic potential, insulin/glucose homeostasis in healthy volunteers and patients with Type II diabetes, effect on QTc intervals, and crystalluria. These studies are summarized in Section X of this review, PK Summary, and full study reports are included

A. Dose Selection Criteria:

How was the dose in pivotal clinical studies decided?

Bactericidal activity in urine and plasma was determined in study AI420-061 (single oral dose, rising dose). The arbitrary bactericidal titer of 1:8 was used to suggest clinical response against a variety of pathogens. The appropriate bactericidal assay was performed (using 99.9% reduction in bacterial counts following at least 24hr incubation). These data suggest that 200mg should be appropriate for most urinary pathogens and that 400mg should treat most systemic infections. Additionally, *Streptococcus pneumoniae* demonstrated lower serum bactericidal titers than the other pathogens at any of the doses studied.

There did not appear to be a dose-related increase in the incidence of AEs in the Phase I studies. Following IV gatifloxacin, the incidence and severity of local reactions appeared to be dependent on dose and/or concentration of the infusion solution. One Phase II and two Phase III trials had some PK/PD assessment done. The population PK/PD assessment concluded no correlation between exposure (either AUC or Cmax) and the incidence of AEs. Cmax ranged from <3.0 to >8.0 μg/mL in 75% of subjects sampled and AUC ranged from <30 to >100μg•h/mL in 80% of subjects. AEs ranged from 0% to 100% across the spectrum of Cmax and AUCs with no correlation. There are no data to support whether there is a difference in the severity of AEs with exposure.

The population PK/PD assessment is suggestive, however this interpretation is weak due to two limitations. The two limitations of the PK/PD analysis are: (1) the total number of patients in the Phase II/III clinical studies that had PK and bacteriologic assessment is small and (2) the percentage of patients who fail the therapy is small. With respect to the number of patients, 21% of patients in the Phase II studies and approximately 25% of patients in the Phase III studies had both PK and bacteriologic data. Individual MIC data were not included, however, for most patients who had both PK and microbiologic sampling, the range for Cmax/MIC was 8 to 12 and the range for AUC/MIC was 75 to 175. There were 67-100% favorable clinical and bacteriologic responses noted and these do not correlate much with Cmax/MIC or AUC/MIC. These studies were not designed to be population PK/PD studies, but rather were analyzed using a population PK/PD approach after the fact.

B. Pharmacology:
What is known about the pharmacology of the drug?

1. Absorption: Gatifloxacin is extensively and almost completely absorbed after oral administration. Absolute bioavailability is approximately 95%.
2. Distribution: Gatifloxacin is approximately 20% bound to serum proteins. Tissue distribution studies demonstrate that gatifloxacin penetrates into lung tissue, bronchial mucosa, epithelial lining fluid, alveolar macrophages, blister fluid, and prostatic fluid very well but penetration into CSF and bone is poor. Extensive distribution into fat/adipose tissue and extensive total body distribution (as seen by the large volume of distribution, approximately 120L or 1.5-2.0L/kg) correlate with the observed half-life of this drug (7-11hrs).
3. Metabolism: No CYP450 mediated metabolism is apparent. Two minor metabolites have been detected.
4. Elimination: Gatifloxacin is eliminated almost exclusively by the kidney: approximately 70-80% recovered as unchanged drug in urine, 5% in feces, and two minor metabolites which represent less than 1% of total drug administered recovered in urine.
5. Mechanism of action: Gatifloxacin inhibits the activity of DNA gyrase which in turn inhibits bacterial DNA replication and transcription culminating in cell death. Gatifloxacin also inhibits topoisomerase IV, which plays a role in partitioning DNA during bacterial cell division.

C. Biopharmaceutics issues:
Are there any issues in comparing the clinical trial material with the to-be-marketed formulation? Are there any biopharmaceutics issues?

1. Food Effect: Studies looking at the effect of a high fat meal, continental breakfast, milk, and green tea showed no change in exposure of gatifloxacin as determined by CMAX and AUC when gatifloxacin was administered with these food/meals.
2. Pivotal Bioequivalence (BE) Study: The pivotal BE study (AI420-028) supports that the clinical formulation is bioequivalent to the to-be-marketed product.

of this study. No mass balance study in humans was included in this submission.

3. Assay: The validation and performance of the analytical methods is adequately documented.
4. Others: According to 21CFR320.22(a), the sponsor has submitted a to request for a waiver for not having to demonstrate bioequivalence for the 200mg tablets. The 200mg tablet is compositionally proportional to the 400mg tablet. The dissolution profiles for the 200mg and 400mg tablets are similar, therefore, the request for a waiver of need for in vivo bioequivalence for the 200mg tablet would be recommended.

D. Dose Adjustments:

Are there any variables that should be taken into account to adjust the dose?

The sponsor conducted a single oral dose renal impairment study (**AI420-017**). Drug elimination, as demonstrated by apparent oral clearance of gatifloxacin, is highly correlated with creatinine clearance (R^2=0.92). A 77% reduction in apparent oral clearance was seen in subjects with creatinine clearance <30mL/min and a 57% reduction in subjects with creatinine clearance of 30-50mL/min. The changes in gatifloxacin clearance are paralleled by complementary increases in AUC(INF), indicating more gatifloxacin exposure with declining renal function. Additionally, the half-life of gatifloxacin increases from 10hr in normal renal function to 31hrs with a creatinine clearance <30mL/min. A population PK analysis indicated that creatinine clearance was a major covariate for apparent oral drug clearance.

A population-based analysis was performed to simulate multiple different dosing regimens in renal impairment in order to propose dosing adjustment in renal impairment. The sponsor has proposed no dosage adjustment for patients with creatinine clearances of 30-50mL/min. The sponsor has proposed dosing adjustment for patients with creatinine clearance less than 30mL/min only as follows:

400mg on Days 1 and 2, followed by 400mg every other day.

The sponsor concludes that this dosing adjustment will allow for exposures with AUC less than 100µg•h/mL and Cmax less than 9µg/mL. The sponsor concludes that the population PK/PD analysis in Phase II and III studies (although limited by the insufficient numbers) indicates that these levels of exposure correlate with good efficacy and no increase in the frequency of adverse events.

Simulations performed by [redacted] recommend different dosing adjustments than the sponsor has proposed (See Subsection F. Population PK/PD in Section X. PK SUMMARY). Since neither efficacy nor safety can be adequately correlated in the PK/PD relationship with Cmax or AUC, indices of exposure and altered pharmacokinetic parameters must be evaluated for dosing adjustment. In moderate renal insufficiency, the exposure is increased 2-fold and the clearance is decreased by 57%.

Simulations were performed using exposure information from subjects with renal function from normal to 50mL/min. The recommended dosage adjustment would be:

Creatinine Clearance	Initial Dose	Subsequent Dose*
> 50mL/min	400mg	400mg every day
30-50mL/min	400mg	400mg every other day
<30mL/min Hemodialysis Continuous peritoneal dialysis	400mg	200mg every day

*Start subsequent dose on Day 2 of drug administration

E. Drug-drug Interactions:

What evidence is there to support any drug-drug interactions?

1. *In vitro* metabolism: There is no evidence to support any metabolism of gatifloxacin by CYP450 enzymes.
2. *In vitro* DDI: Gatifloxacin can be classified as a non-inhibitor of CYP 1A2, 2C9, 2C19, 2D6, and 3A4.
3. *In vivo* DDI: Significant interactions occurred when gatifloxacin was administered with Digoxin **(AI420-035)**, Maalox® **(AI420-024)**, Ferrous sulphate **(AI420-057)**, and Probenecid **(AM1155-T101)**.

With digoxin, there was a 17% decrease in total clearance of digoxin. There was a corresponding 9% and 11% increase in mean digoxin Cmax and AUC(TAU), respectively. The 90% CI for Cmax was [1.00, 1.26] and for AUC(TAU) was [1.001.41]. The corresponding point estimates for Cmax and AUC(TAU) were 1.12 and 1.19. There were no changes in digoxin trough levels (Cmin) when gatifloxacin was administered concomitantly. Despite a statistically non-significant interaction with digoxin and gatifloxacin, there are serious potential interactions when individual data is evaluated. The changes in 3 individual subjects (25% of total subjects) were quite significant with digoxin Cmax increased by 18, 58, and 29%, digoxin AUC increased by 66, 79, and 104% and total clearance decreased by 40, 45, and 51% in these subjects. A narrow therapeutic index drug, such as digoxin, may not warrant dosing adjustment, but more intense therapeutic drug level monitoring is necessary when co-administered with gatifloxacin.

With Maalox®, mean CMAX and AUC(INF) of gatifloxacin were 47% and 40% lower when the antacid was administered 2 hours before gatifloxacin; 69% and 64% lower when the antacid was administered concomitantly with gatifloxacin; and 15% and 17% lower when the antacid was administered 2 hours after gatifloxacin. Minimal changes were seen when the antacid was administered 4 hours after gatifloxacin.

Co-administration of gatifloxacin with $FeSO_4$ decreased mean AUC(INF) by 35% and mean CMAX by 54%. TMAX was delayed when gatifloxacin was administered concomitantly with $FeSO_4$. Minimal changes were seen when $FeSO_4$ was administered either 2 hr before or 2 hr after gatifloxacin.

Probenecid administration resulted in a 42% increase in mean AUC(INF), 44% increase in mean T-HALF, 30% decrease in mean CL/F and 38% decrease in mean CL_T for gatifloxacin.

IV. COMMENTS FOR THE SPONSOR:

1. **Study AI420-018 (Hepatic Impairment):** This study report was received and reviewed prior to NDA submission and similar comments were relayed at that time.No data are available for patients with severe hepatic impairment. The number of subjects (n=1) in the severe hepatic impairment group (Child-Pugh C) is insufficient to support any labeling claims in this population. Further studies with patients with severe hepatic impairment will need to be performed to include this group of patients in the label. Furthermore, a multiple dose study was recommended after submission of this study report.

2. **Study AI420-035 (Digoxin interaction study):** Although there is no statistically significant interaction between gatifloxacin and digoxin, the severity of change in digoxin pharmacokinetics in three subjects would warrant therapeutic drug monitoring of digoxin during concomitant therapy with gatifloxacin. The extent of change in the pharmacokinetic parameters in these three subjects should be included in the label. Serum digoxin concentrations should be determined when gatifloxacin reaches steady state and whenever patients display signs and/or symptoms of digoxin intoxication.

3. **Study AI420-024 (Aluminum antacid interaction study):** The 90% confidence intervals for the "2 hours after" group, do not substantiate the conclusion of lack of effect. However, the 90% confidence intervals for the "4 hours after" group do fall within the accepted intervals. Aluminum containing antacids can be taken 4 hours after gatifloxacin, but not either 2 hours before, concomitantly, or 2 hours after.

4. **Study AI420-037/AI420-038 (Population PK/PD study reports):** The covariate conclusions of the PK/PD assessment are limited by the sample size (i.e., the small number per group) and the distribution within each group. No data for logistic regression analysis are available. Due to these inherent inadequacies it is difficult to determine the effect of race on the pharmacokinetics of gatifloxacin.

5. **Study AI420-017 (Renal impairment study and Population PK report):** The population PK/PD analysis demonstrates a weak relationship between Cmax/MIC and AUC/MIC with either efficacy or toxicity. The pre-defined set points of Cmax less than 9μg/mL and AUC less than 100μg•h/mL for dose adjustment are arbitrary. In this single dose study, the exposure (AUC) in the moderate renal impairment group (creatinine clearance 30-50mL/min) is double that of normal subjects. Additionally, the clearance of gatifloxacin is decreased by 57%. Based on this, dosage adjustment for both moderate and severe renal impairment is indicated. Simulations performed by at FDA indicate the following dose adjustment:

	Initial Dose	**Subsequent doses***
Moderate renal impairment (creatinine clearance 30-50mL/min)	400mg	400mg every other day
Severe renal impairment (creatinine clearance <30mL/min)	400mg	200mg every day

*Start subsequent dose on Day 2 on drug administration

V. GENERAL COMMENTS

1. Study AI420-017 (Renal impairment)

Based on this Phase I study, a single 400mg dose of gatifloxacin was well tolerated in this small study of patients with varying degrees of renal insufficiency. The small study size is not large enough to support the conclusion that gatifloxacin is safe in patients with renal impairment. This study however does give good predictions for the pharmacokinetic changes of gatifloxacin in patients with renal insufficiency and on dialysis. A population PK approach was used to provide dosing rationale for patients with renal impairment. The model is acceptable and the proposal for reducing the dosing frequency appears adequate with respect to targeting AUCs less than 100μg•h/mL should be modified. The sponsor has arbitrarily defined the target Cmax and AUC should be less than 9μg/mL and AUC less than 100μg•h/mL This target AUC level comes about via Population PK/PD studies in Phase II and III studies, which depicted no relationship between the incidence of adverse events and efficacy with increasing AUC or Cmax. In moderate renal insufficiency (creatinine clearance 30-50mL/min) there is a 2 fold increase in AUC and greater than 2-fold reduction in clearance of gatifloxacin. This information, in conjunction with data from subjects with normal renal function, led to simulations performed by Dr. He Sun (Pharmacometrics node). These simulations suggest that a different dosage adjustment than what the sponsor has proposed may be warranted, for both severe and moderate renal insufficiency.

2. Study AI420-035 (Digoxin interaction study)

Even though the results of this Phase I drug-drug interaction study concludes statistically non-significant interaction with digoxin and gatifloxacin, there are substantial pharmacokinetic alterations when individual data are evaluated. Three subjects which represent 25% of the subjects in the study had significant changes in Cmax, AUC and total clearance. This may not produce any clinically significant problem with a healthy subject, however, the effect on patients requiring digoxin therapy for cardiac indications may be substantially different. A narrow therapeutic index drug, such as digoxin, may not warrant dosing adjustment, but might warrant more intense therapeutic drug level monitoring when co-administered with gatifloxacin.

3. Study AI420-021(Age and gender effects)

The results of this study indicate that dose adjustment is not necessary based on age or gender alone. Elderly females had the most substantial changes in pharmacokinetic parameters. Cmax and AUC were increased by approximately 20% and 30%, respectively, when compared either vs. young or vs. males. Creatinine clearance naturally decreases with advancing age, but additionally, the creatinine clearance for women is 85% of that for a similarly aged male (with the same serum creatinine). Additionally, elderly females had the most treatment emergent AEs in this small Phase I study.

VI. COMMENTS FOR DRAFT LABELING (Sponsor's version 28-DEC-98):

The following changes to the label are proposed:

1. In the "Clinical Pharmacology" Section:

***5* pages of revised draft labeling have been redacted from this portion of the document.**

[redacted]

VI. RECOMMENDATIONS:

The information for Section 6: Human Pharmacokinetics and Bioavailability of NDA 21-061 for gatifloxacin has been reviewed and was found to be acceptable and adequate to support approval of the oral gatifloxacin formulation. The dissolution method [redacted] with Q of [redacted] at 20 minutes is acceptable. The request for waiving bioequivalence for the 200mg tablet is approved. Please pass the following sections to the sponsor: Section IV - COMMENTS FOR THE SPONSOR and Section VI – COMMENTS FOR DRAFT LABELING.

/S/

Kathleen Uhl, MD
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

OCPB Briefing July 6, 1999 (F. Ajayi, Z. Akl, D. Bashaw, M. Chen, P. Hepp, P. Honig, S. Huang, J. Korvick, J. Lazor, P. Lee, L. Lesko, M. Mehta, F. Pelsor, R. Roca, A. Selen, J. Smith, H. Sun).

RD/FT initialed by F. Ajayi, Ph.D, Team Leader /S/ 8/12/99
cc: HFD-590 (NDA 21-061, J. Korvick, B Atkins)
HFD-205 (FOI)
HFD-880 (F. Pelsor, F. Ajayi, K. Uhl)

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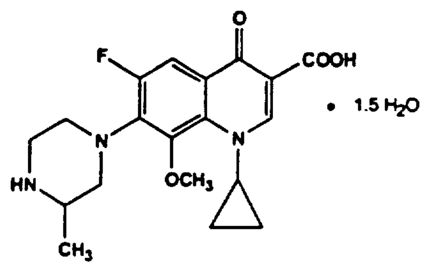
VIII. DRUG CHARACTERISTICS AND FORMULATIONS

1. Physical/Chemical Properties:

Gatifloxacin: a synthetic broad-spectrum 8-methoxyfluoroquinolone antibacterial agent for oral or intravenous administration.

Chemical name: (±) -1-cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

Structure:



Molecular weight: 402.42

Dissociation/Ionization: Gatifloxacin contains two ionizable moieties, a carboxylic acid and an amine. The following dissociation constants were calculated for these two groups:

2. Formulations and Dissolution:

Gatifloxacin Tablets: film coated, immediate release, in 200mg and 400mg strengths. Both tablet strengths are manufactured from a common tablet blend. The proposed commercial formulations are given below.

Composition	Quantity per tablet (gm) 200 mg tablet	400 mg tablet	Function
Gatifloxacin	0.2^	0.4^	Active
Microcrystalline cellulose			
Sodium Starch Glycolate			
Magnesium Stearate			
TOTAL tablet weight	0.30600	0.61200	

Two 400mg film-coated formulations were used in the PK, Phase II and pivotal Phase III studies. The bioequivalence of the proposed commercial 400mg tablet [redacted] and the Phase III pivotal clinical trials tablets [redacted] was established in the pivotal BE study (**AI420-028**) at doses of 400mg (1 X 400mg tablets) i.e., AUC(INF) ratio 97.4% (90%CI, 89.6-105.9%); Cmax ratio 99.1% (90%CI, 83.7-117.3%).

A bioequivalence study between the 400mg proposed commercial tablet and the 200mg Phase III tablet or 200mg proposed commercial tablet was not deemed necessary by the sponsor. Both proposed commercial tablet strengths are manufactured from a single stock common granulation using the same manufacturing equipment, and the tablet ingredients are compositionally proportional. Thus, the 200mg tablet would also be considered bioequivalent to the 400mg proposed commercial tablet.

The proposed dissolution methods and specification for the 200mg and 400mg gatifloxacin film-coated tablets are outlined below.

Proposed Dissolution Method and Specification

Dosage Form	Film-coated Tablet
Strength	400mg
Apparatus	[redacted]
Dissolution Medium	
Volume	
Paddle Speed	
Sampling Time	
Analytical Method	
Specification	

Gatifloxacin Intravenous Solution: sterile, aqueous concentrated solution intended for IV administration following dilutions in a suitable vehicle to a final concentration of 2mg/mL. The composition of the proposed commercial formulations is provided below.

Ingredient	**Quantity per**			**Function**
	1 mL	**One Vial (200mg)**	**One Vial (400mg)**	
Gatifloxacin	10 mg	200 mg	400 mg	Active ingredient
Dextrose Anhydrous	[redacted]			
Hydrochloric Acid				
Sodium Hydroxide				
Water for Injection				
[redacted]				

[redacted]

The pH range for the proposed commercial product will be 3.5 to 5.5, adjusted with HCl or NaOH. It will be supplied in 20mL (200mg) and 40mL (400mg) single dose vials and in 100mL (200mg) and 200mL (400mg) pre-mix flexible bags. The concentration of gatifloxacin in the pre-mix flexible bags is 2mg/mL. The 2 Phase III studies (AI420-037 and AI420-038) and the Phase I BA study (AI420-046) used the proposed commercial formulation. The formulation for the Phase I study AI420-025 (single dose, multiple dose, dose escalation study) [redacted] and the supportive study AM1155-I101 used water.

IX. ANALYTICAL METHODS SUMMARY

X. PHARMACOKINETIC STUDIES SUMMARY:

The following is a summary of the results of the relevant pharmacokinetics and biopharmaceutics studies of gatifloxacin.

A. *IN VITRO* STUDIES

1. Human serum protein binding (Reports 910070387, 910072083):

2. Metabolism (Reports: 910058992, 910058991, 910058993, 910068926, 910068927)

cDNA-derived cytochrome P450s were incubated with model substrates specific for that isoform. The paired isoform:substrate pairs used were: CYP3A4:testosterone; CYP2D6:bufuralol; CYP1A2:phenacetin; CYP2C9:diclofenac; CYP2C19:S-mephenytoin. A single concentration of each substrate was used (approximately twice the apparent Km) with eleven gatifloxacin concentrations from 0-300μM (0 to 120μg/mL). Mean Cmax from clinical studies is approximately 4-5μg/mL or 10μM. Microsomes were incubated at 37°C and metabolism was determined by the production of metabolite.

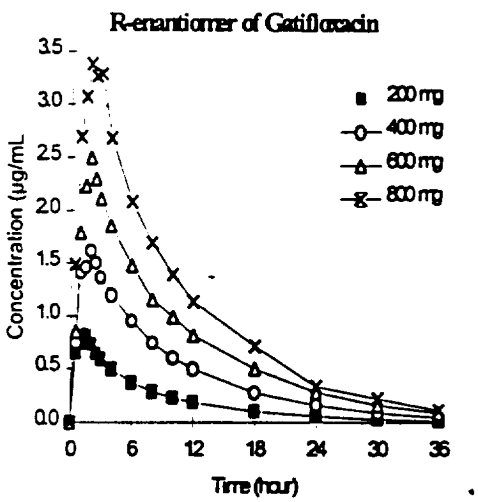
Gatifloxacin did not substantially inhibit CYP3A4, CYP2D6, CYP1A2, CYP2C9, and CYP2C19. Neither the IC50, nor Ki could be determined, since gatifloxacin was not inhibitory.

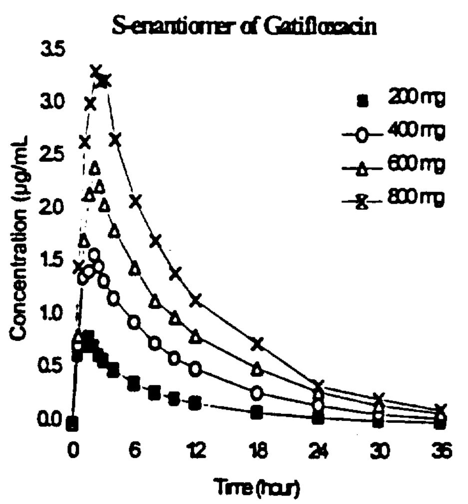
There are no reports of *in vitro* metabolism studies using liver slices or other hepatic tissues. The quantification of urinary metabolites was performed in *in vivo* studies.

B. BASIC PHARMACOKINETICS

1. Single Dose PK – Gatifloxacin PO

Protocol AI420-039: Dose Escalation, 200, 400, 600, 800mg, n= 15 healthy males (200, 400, 600mg: 12 gatifloxacin, 3 placebo) or n=8 (800mg: 6 gatifloxacin, 2 placebo), dosage formulation was 200 or 400mg tablets. Mean (SD) PK for racemic gatifloxacin are summarized below.





Oral Dose	200mg	400mg	600mg	800mg
CMAX (μg/mL)	1.976 (0.395)	3.802 (0.498)	5.272 (1.073)	7.039 (1.790)
AUC(INF) (μg•h/mL)	14.196 (2.399)	33.789 (3.110)	53.912 (8.906)	76.184 (15.230)
UR (%)	73.794 (10.898)	90.220 (13.474)	80.250 (8.185)	83.036 (4.686)
CL/F (L/h)	14.45 (2.38)	11.92 (1.04)	11.40 (1.89)	10.85 (2.12)
Vd /F (L)	105.2 (20.06)	111.99 (14.89)	100.15 (15.80)	95.40 (15.20)

Mean (SD) PK for each stereoisomer of gatifloxacin is summarized below.

Dose (mg)	Enantiomer	CMAX (μg/mL)	TMAX* (h)	AUC(INF) (μg•h/mL)	T-HALF (h)	MRT (h)	CLR (L/h)	UR (%)
200 (n=12)	R	0.995 (0.200)	1.00 (0.50, 2.50)	6.999 (1.201)	6.86 (1.21)	9.59 (1.92)	10.89 (2.59)	36.936 (5.279)
	S	0.981 (0.196)	1.00 (0.50, 2.50)	7.197 (1.207)	7.06 (1.17)	9.97 (1.93)	10.53 (2.39)	36.858 (5.623)
400 (n=12)	R	1.922 (0.254)	1.25 (0.50, 3.00)	16.711 (1.533)	7.15 (0.55)	10.51 (0.65)	10.83 (1.70)	44.986 (6.541)
	S	1.880 (0.244)	1.25 (0.50, 3.00)	17.078 (1.579)	7.41 (0.63)	10.95 (0.69)	10.65 (1.69)	45.235 (6.943)
600 (n=11)	R	2.676 (0.541)	2.00 (1.00, 3.00)	26.734 (4.389)	7.46 (0.73)	11.24 (0.96)	9.20 (1.89)	40.007 (4.120)
	S	2.596 (0.533)	2.00 (1.00, 3.00)	27.178 (4.527)	7.87 (0.77)	11.80 (1.01)	9.12 (1.91)	40.243 (4.068)
800 (n=6)	R	3.539 (0.897)	2.00 (2.00, 3.00)	37.612 (7.665)	7.25 (0.68)	10.79 (0.72)	9.09 (1.70)	41.420 (2.346)
	S	3.500 (0.893)	2.25 (2.00, 3.00)	38.572 (7.566)	7.58 (0.81)	11.25 (0.81)	8.88 (1.59)	41.615 (2.343)

* median value (minimum, maximum)

Increases in Cmax and AUC(0-INF) were observed as the dose increased with no overlap in the individual values between the dose groups. Although the magnitude of these increases were not strictly dose proportional, the relationships of dose vs. Cmax and vs. AUC(INF) showed linear trends. The data suggest dose-proportional pharmacokinetics over the range of doses from 200mg to 800mg. Mean Tmax was 1.0hr after 200mg, 1.25hr after 400mg, 2.0hr after 600mg, and 2.125hr after 800mg dose.

Mean plasma T½ ranged from 6.86 to 7.87, including all doses and both R- and S-enantiomers. The mean amount of gatifloxacin excreted in the urine from 0 to 36 hrs post-dose was relatively high, accounting for 73.8 to 90.2% of the administered dose. Mean CLr were 10.71, 10.74, 9.16, and 8.99 L/hr for 200, 400, 600, and 800mg doses, respectively. These results suggest that renal excretion is a major route of gatifloxacin elimination. Total clearance (CL/F) decreases with increasing dose, i.e., 14.45 L/hr for 200mg dose and 10.85 L/hr for 800mg dose, which may indicate that gatifloxacin kinetics are not strictly linear.

No difference in clinical tolerance was noted between the four dose levels of gatifloxacin, i.e., there was no tendency to have more AEs at high doses. Urine and serum bactericidal titres (PD assessment) of various urinary and systemic pathogens demonstrated that as the dose was increased there was a general increase in the titers obtained. Using a bactericidal titres cut-off of 1:8 as a stringent test for potential efficacy, this data indicated that 200mg dose would treat most urinary pathogens and that 400mg dose would treat most systemic pathogens.

2. Multiple Dose PK – Gatifloxacin PO

Protocol AI420-040: Multiple dose, 400mg and 600mg (1 x 400mg and 1 x 200mg) qD x 10days, n=42 healthy males, 21/dose group(18 gatifloxacin, 3 placebo). Steady-state plasma gatifloxacin concentrations were reached following the 3rd daily dose for both the 400 and 600mg groups. The PK results are shown below.

Dose (mg)	Day	CMAX (µg/mL)	TMAX* (h)	AUC‡ (µg•h/mL)	T-HALF (h)	UR (%)	VDBETA/F (L)	CLT/F (mL/min)
400 (n=18)	1	3.682 (0.751)	1.50 (0.50, 3.00)	30.871 (4.390)	6.74 (0.68)	83.053 (11.664)	127.66 (16.39)	220.09 (31.19)
	15	4.226 (1.283)	1.50 (0.50, 4.00)	34.409 (5.740)	7.06 (0.58)	80.171 (12.054)	-	198.52 (30.71)
Point estimate**		1.13	-	1.11	-		-	-
90% CI		1.01-1.26	-	1.07-1.15	-		-	-
600 (n=18)	1	5.266 (1.237)	1.50 (1.00, 3.00)	51.728 (7.625)	7.34 (0.92)	80.339 (8.714)	125.03 (22.22)	197.49 (30.30)
	15	5.811 (1.043)	1.50 (1.00, 4.00)	61.763 (10.198)	7.71 (0.98)	77.077 (8.319)	-	166.33 (28.85)
Point estimate**		1.12	-	1.19	-		-	-
90% CI		1.01-1.23	-	1.15-1.23	-		-	-

- median value (minimum, maximum)
- ** calculation based on the ratio of the geometric means

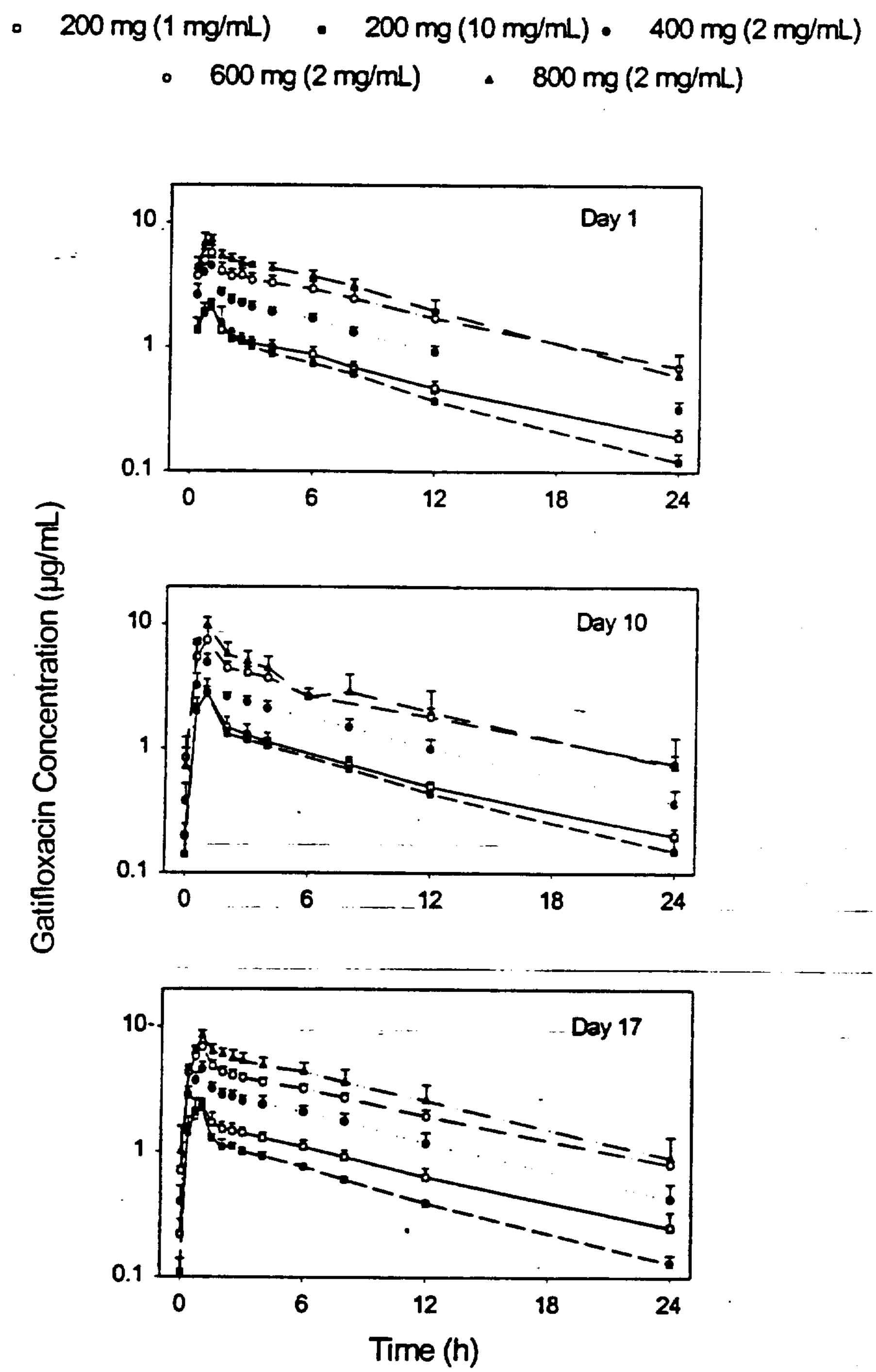
‡ AUC(INF) day 1 and AUC(TAU) day 15

After 10 days of repeated dosing with 400mg, mean AUC(tau) was increased by 22% compared to Day 1. Similarly, with repeated dosing of 600mg, mean AUC(tau) after 10 days of dosing was increased by 34% compared to Day 1. These results suggested accumulation of gatifloxacin in plasma of approximately 30% at steady-state.

The mean T½ estimates appeared to be minimally prolonged with repeated dosing. Mean total clearance (CLT/F) was 10% lower after repeated administration of 400mg and 16% lower after repeated administration of 600mg. Thus, multiple dose PK can be predicted from single dose PK. Mean renal clearance (CLR) was 13% lower after repeated administration of 400mg and 19% lower after repeated administration of 600mg. The mean total amount of gatifloxacin excreted (Ae) was 4% lower following multiple dosing compared with single dosing, and this was comparable with both the 400 and 600mg doses. The percentage of gatifloxacin excreted in the urine after either single or multiple 400 and 600mg doses was relatively high and ranged between 77-83%, and more than 88% overall recovery was accounted by feces and urine.

3. Single Dose PK & Multiple Dose PK – Gatifloxacin IV

Protocol AI420-025: Single dose, multiple dose escalation 200, 400, 600 or 800 mg gatifloxacin, 60 min infusions, n=40 (3:1 ~~ratio in~~ each dose group, gati:placebo). Mean (SD) PK for gatifloxacin are summarized below for both single dose (Day 1), and multiple dose (Day 10 below is the 7th day of dosing, and Day 17 is the 14th day of dosing).



Variable	Dose, mg (mg/mL)	Mean (SD) Gatifloxacin Pharmacokinetic Variables		
		Day 1	Day 10	Day 17
T-HALF (h)	200 (10)	9.1(3.3), N=6	N/A	12.0(7.7), N=3
	200 (1)	13.0(4.1), N=6	N/A	12.5(2.5), N=5
	400 (2)	9.4(1.7), N=6		13.9(3.9), N=5
	600 (2)	11.1(1.4), N=6		12.0(1.5), N=5
	800 (2)	8.4(2.1), N=4		12.4(2.4), N=3
%UR	200 (10)	73.6(7.8), N=6	81.2(7.3), N=6	76.7(22.9), N=3
	200 (1)	69.8(5.8), N=6	74.8(10.3), N=5	69.2(12.5), N=4
	400 (2)	82.5(7.2), N=6	86.3(7.5), N=5	83.5(13.9), N=5
	600 (2)	78.8(10.2), N=6	78.0(13.0), N=6	85.5(7.7), N=4
	800 (2)	75.6(14.1), N=4	77.0(9.9), N=4	71.9(23.7), N=2
CLT (mL/min)	200 (10)	238(34), N=6	225(34), N=6	255(11), N=3
	200 (1)	191(22), N=6	204(30), N=5	178(24), N=5
	400 (2)	206(14), N=6	216(24), N=6	191(24), N=5
	600 (2)	174(25), N=6	184(20), N=6	181(15), N=5
	800 (2)	207(39), N=4	231(69), N=4	190(40), N=3
CLR (mL/min)	200 (10)	175(31), N=6	183(34), N=6	195(60), N=3
	200 (1)	134(17), N=6	152(26), N=5	124(29), N=4
	400 (2)	170(14), N=6	185(16), N=5	161(43), N=5
	600 (2)	137(18), N=6	143(23), N=6	150(18), N=4
	800 (2)	157(47), N=4	179(68), N=4	143(43), N=3
VSS (L)	200 (10)	139(18), N=6	121(12), N=6	163(43), N=3
	200 (1)	140(20), N=6	138(34), N=5	138(26), N=5
	400 (2)	129(10), N=6	134(10), N=6	148(39), N=5
	600 (2)	129(14), N=6	130(19), N=6	146(12), N=5
	800 (2)	117(6), N=4	127(9), N=4	140(17), N=3
VSS (L/kg)	200 (10)	1.9 (0.2), N=6	1.6 (0.2), N=6	2.1 (0.4), N=3
	200 (1)	2.0 (0.1), N=6	1.9 (0.2), N=5	1.9 (0.3), N=5
	400 (2)	1.5 (0.2), N=6	1.9 (0.1), N=6	1.6 (0.5), N=5
	600 (2)	1.7 (0.2), N=6	1.7 (0.1), N=6	1.9 (0.3), N=5
	800 (2)	1.5 (0.1), N=4	1.6 (0.2), N=4	1.7 (0.2), N=3
MRT (h)	200 (10)	9.8(1.1), N=6	9.0(0.8), N=6	10.8(3.2), N=3
	200 (1)	12.2(2.1), N=6	11.0(1.7), N=5	13.0(2.3), N=5
	400 (2)	10.5(0.8), N=6	10.4(1.5), N=6	12.9(2.4), N=5
	600 (2)	12.4(1.1), N=6	11.8(1.1), N=6	13.5(0.6), N=5
	800 (2)	9.7(1.9), N=4	9.8(2.7), N=4	12.4(1.4), N=3

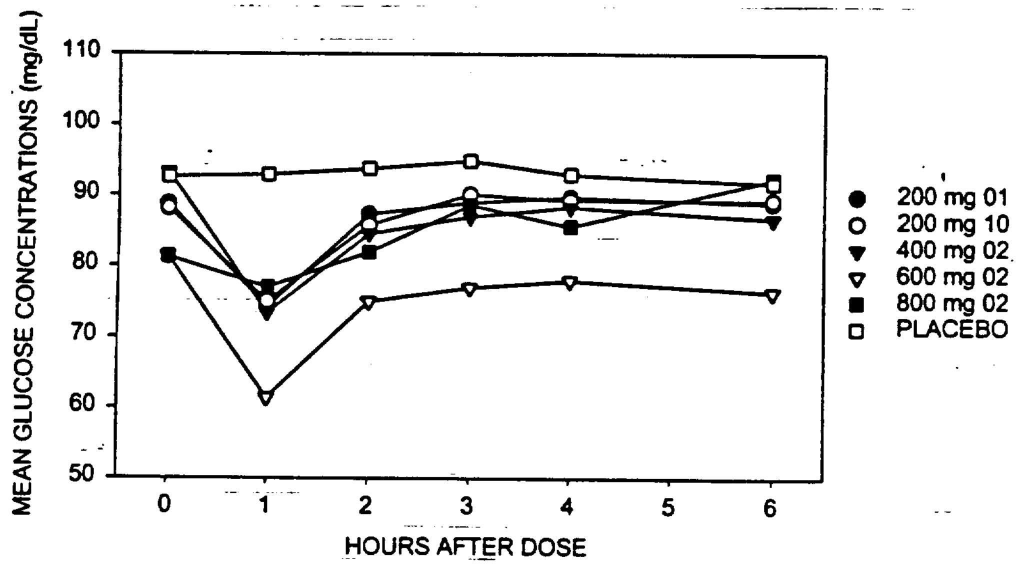
CLT, CLR, T-HALF, MRT and VSS appeared to be unchanged with ~~respect to dose and time~~. The mean (SD) PK values for AUC and Cmax are summarized below for both single dose (Day 1), and multiple dose (Day 10 below is the 7th day of dosing, and Day 17 is the 14th day of dosing). Steady state gatifloxacin concentrations were achieved following the 3rd dose in a multiple dosing regimen. Total variability in these parameters (as %RSD) was ~30% or less (except for CLR for 800mg on Day 10). The PK results indicate dose proportional increases in systemic exposure to gatifloxacin in plasma suggesting that the pharmacokinetics of gatifloxacin were linear and stationary across the clinical range of 200 to 800mg.

At the end of the infusion, a mild to moderate, transient decrease in fasting serum glucose without a corresponding change in insulin and c-peptide was noted. No changes were seen with fasting glucose or the glucose tolerance test. No clinically meaningful changes were apparent in ECG results or spirometry.

Variable	Study Day	Dose(mg)	Arithmetic Mean (SD)	Geo. Mean (%CV)
CMAX (μg/mL)	Day 1	200	1.21 (0.23)	2.20(11)
		400	4.53 (0.62)	4.49(14)
		600	5.95 (0.79)	5.91(13)
		800	7.64 (1.03)	7.59(13)
	Day 10	200	2.81 (0.80)	2.70(28)
		400	4.93 (0.79)	4.88(16)
		600	7.39 (1.81)	7.17(24)
		800	9.62 (1.58)	9.51(16)
	Day 17	200	2.42 (0.37)	2.39(15)
		400	4.56 (0.61)	4.53(13)
		600	6.86 (0.63)	6.84(9)
		800	8.44 (0.80)	8.41(9)
AUC(TAU) (μg•h/mL)	Day 1	200	14.8 (1.5)	14.76 (10)
		400	28.6 (2.1)	28.50 (7)
		600	49.2 (7.0)	48.79 (14)
		800	59.2 (9.4)	58.66 (16)
	Day 10	200	16.6 (2.5)	16.48(15)
		400	31.2 (3.4)	31.00(11)
		600	54.8 (6.7)	54.52(12)
		800	62.5 (21.4)	60.03(34)
	Day 17	200	19.0 (2.4)	18.82(13)
		400	35.4 (4.6)	35.22(13)
		600	55.6 (4.6)	55.45(8)
		800	72.3 (15.8)	71.13(22)

CMAX and AUC(TAU) increased approximately proportionally to dose on Days 1, 10, and 17. The R^2 values for the regression of dose on mean CMAX are 0.989, 0.999, and 0.994 for Days 1, 10 and 17, respectively. The R^2 values for the regression of dose on mean AUC(TAU) are 0.984, 0.968, and 0.998 for Days 1, 10 and 17, respectively. Total variability in these parameters (as %RSD) was ~30% or less (with the exception of AUC(TAU), Day 10, 800mg). Within each dose group, mean CMAX was 1-18% greater on Day 17 compared to Day 1. Across dose levels, mean CMAX was -3-22% greater on Day 17 compared to Day 1. Within each dose group, mean AUC(TAU) was 19-26% greater on Day 17 compared to Day 1. Across dose levels, mean AUC(TAU) was 14-27% greater on Day 17 compared to Day 1. These results suggested accumulation of gatifloxacin in plasma of less than 30% at steady-state. Multiple-dose pharmacokinetics can be based on single-dose data, and no time-dependent changes in gatifloxacin pharmacokinetics were seen.

Mean serum glucose concentrations over the 6-hour period following the start of the 1- hour gatifloxacin infusion on Study Day 1 are illustrated below. A mild to moderate, transient decrease in fasting serum glucose values at the 1 hour (end of infusion) time point can be seen. A corresponding change in insulin and c-peptide was not noted.



4. Distribution – Gatifloxacin

As indicated in the results of the above studies, the volume of distribution of gatifloxacin after IV administration (Vd_{ss}) was relatively large and ranged from 1.5-2.1 L/kg. The serum protein binding determined from *in vitro* and *in vivo* clinical studies at clinically relevant serum concentrations was 16-25% bound. In light of the minimal extent of protein binding and the large volume of distribution, this data would suggest that gatifloxacin penetrates extensively into tissues. The sponsor conducted 19 clinical studies with varying doses and dose regiments to evaluate the penetration of gatifloxacin into various tissues. Following oral administration to adults, gatifloxacin levels were determined in skin; CSF; ocular, middle ear, sinus and oropharyngeal tissues; dental and oral surgical tissues; saliva; sputum, bronchial macrophases, and epithelial cells; bile; urine; prostate, epididymis and prostatic fluid; and gynecological tissues. No tissue penetration studies were performed using IV gatifloxacin. No determination of the extent of gatifloxacin secretion in breast milk was performed. The full reviews of these studies can be found in Appendix 2.

Briefly, gatifloxacin penetrated well into and persisted for a substantial amount of time following dosing for most of the tissues/fluids studied. This is evidenced by the ratios of tissue/serum that approached or exceeded 1.0. Notably gatifloxacin penetration into lung tissues/fluid was very extensive, especially into alveolar macrophages, with mean macrophage/serum ratios as high as 37 after 400mg single dose (Study AI420-030). The lowest penetration of gatifloxacin was for CSF and bone. The mean CSF/serum ratio was 0.36 following 200mg BID for 3 days (Study T-111). The range for penetration in various jaw bones following 100 or 150mg single doses ranged from 0.116-1.95 (Study T-211 & T313).

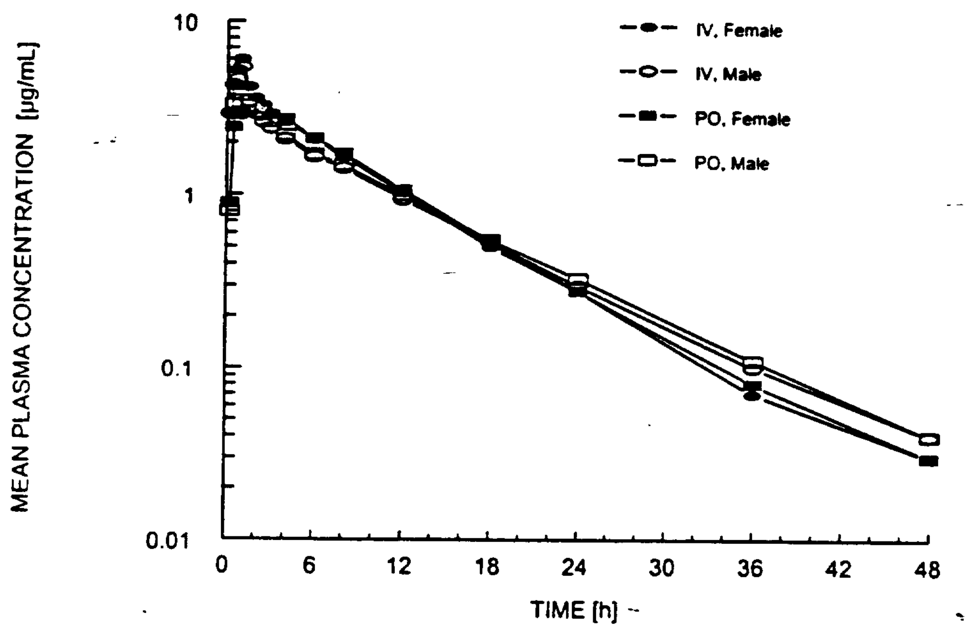
C. BIOAVAILABILITY /BIOEQUIVALENCE

1. Bioavailability

Study AI420-046: Absolute Bioavailability of Gatifloxacin tablets, 400mg dose for tablet and IV infused over 1hr, n=24 healthy young, males (12) and females (12), crossover design. Mean (SD) PK values are provided below.

	IV	Oral
Cmax (µg/mL)	5.77 (0.88)	4.21 (1.4)
AUC (µg•hr/mL)	35.73 (6.8)	34.59 (8.52)
T-half (hr)	6.95 (0.84)	7.42 (0.98)*
CLR (mL/min)	112.16 (31.24)	110.48 (33.02)
UR(%)	57.27 (13.26)	55.55 (18.12)
MRT (hr)	8.76 (1.31)	10.16 (1.42)*

P≤0.001



The absolute bioavailability, [F], of oral gatifloxacin was 96%, with overall 90% confidence limits of (88%, 104%), indicating nearly complete oral absorption of gatifloxacin from the 400mg tablet formulation. Mean peak plasma gatifloxacin concentrations (Cmax) following the 1 hr infusion was 44% higher than that for oral gatifloxacin, 5.70µg/mL vs. 3.96µg/mL, respectively. Total variability (as %RSD) in AUC(INF) was 19% and 25% and for Cmax was 15% and 33%, for the IV and oral formulations, respectively. T-half, CLR, and Vd were 15%, 27%, and 30% lower in females compared to males, respectively, explained partially by differences in creatinine clearance and lean body weight.

Study AI420-021: Food Effect, 400mg (1 x 400mg); n=18 healthy young males, European continental breakfast, crossover design. Formulation used was bioequivalent to the proposed commercial 400mg formulation. Mean (SD) PK and statistical results are provided below.

Conditions	CMAX (µg/mL)	TMAX* (h)	AUC(0-T) (µg•h/mL)	AUC(INF) (µg•h/mL)	T-HALF (h)	MRT (h)
Fasting	3.524 (0.634)	2.00 (1.00, 3.00)	32.44 (4.66)	32.81 (4.75)	7.09 (0.61)	10.37 (0.89)
Fed	3.208 (0.508)	2.00 (0.50, 3.00)	30.13 (4.34)	30.50 (4.44)	7.11 (0.53)	10.70 (1.07)
Point Estimate	0.91	-	0.93	0.93	-	-
90% Confidence Interval	0.85 - 0.98	-	0.90 - 0.96	0.90 - 0.96	-	-

median value (minimum, maximum)

Administration of a single 400mg dose of gatifloxacin to healthy subjects under fed conditions resulted in similar estimates of AUC(INF) and Cmax. The 90% confidence intervals and ratios for both AUC(INF) and Cmax demonstrated that the systemic availability was equivalent under fed and fasted conditions. These results indicated that food (European continental breakfast) does not significantly alter the oral absorption of gatifloxacin from a formulation equivalent to the proposed commercial tablet formulation.

Study AI420-014: Food Effect, 400mg (1 x 400mg), n=18 healthy young males, standard high-fat breakfast, crossover design. Formulation used was bioequivalent to the proposed commercial 400mg formulation. Mean (SD) PK and statistical results are provided below.

PHARMACOKINETIC VARIABLE	FASTED MEAN[B]	FED MEAN[B]	2 SIDED P-VALUE	RATIO OF MEANS (FED:FASTED)	90% CONFIDENCE INTERVAL FOR RATIO OF MEANS
CMAX (µg/mL)	3.44	3.10	0.12	0.90	(0.81, 1.01)
AUC(INF) (µg•h/mL)	32.19	29.83	0.005	0.93	(0.89, 0.96)
T-HALF (h)	7.25	7.19	0.80	0.99	(0.93, 1.05)
MRT (h)	10.68	10.44	0.43	0.98	(0.93, 1.03)
CLR (mL/min)	173.68	192.45	0.04	1.11	(1.03, 1.20)
UR (%)	78.50	81.45	0.58	1.04	(0.92, 1.18)
TMAX (h)	0.75	2.0	0.06	NA	(-1.125, -0.25)

[B] Means are ajusted based on ANOVA model.

Administration of a single 400mg dose of gatifloxacin to healthy subjects under fed conditions resulted in similar estimates of AUC(INF) and Cmax. The 90% confidence intervals and ratios for both AUC(INF) and Cmax demonstrated that the systemic availability was equivalent under fed and fasted conditions. These results indicated that food (standard high-fat breakfast) causes a statistically significant change in the kinetics of gatifloxacin (p=005 for AUC) but these are not clinically relevant.

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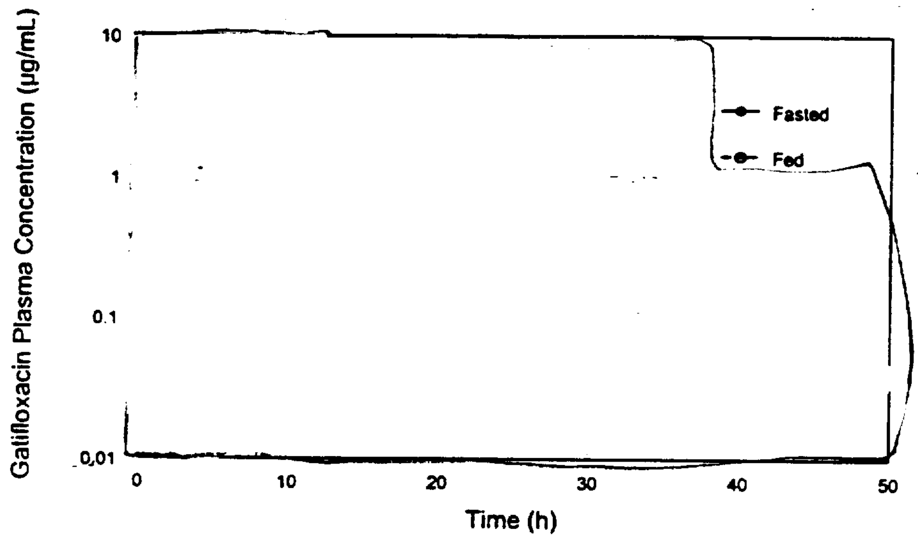


Study AI420-028: Pivotal Bioequivalence – Proposed commercial 400mg tablet vs. Clinical Trials 400mg vs. new wet granulation (not used in any clinical studies), 400mg dose, n=18 healthy male subjects, 3 way crossover. The proposed commercial batch was prepared at 60kg, 91,000 units, approximately 10% of commercial scale. Mean (SD) PK and statistical results are provided below.

Pharmacokinetic Variable	Test 1[a] Means	Test 2[b] Means	Reference[c] Means	Ratio of Geometric Means (T/R)	90% Confidence Interval for Ratio of Means	2-sided P-value
CMAX (µg/mL)	3.20	1.50	3.23	Test 1 0.991 Test 2 0.464	(0.837, 1.173) (0.392, 0.549)	
AUC(INF) (µg•h/mL)	27.42	20.2	28.2	Test 1 0.974 Test 2 0.717	(0.896, 1.059) (0.659, 0.779	
TMAX (h)[e]	0.88	3.00	1.00			Test 1 p=0.91 Test 2 p<0.001
T-HALF (h)[f]	8.07	9.19	8.08			Test 1 p=0.98 Test 2 p<0.001

[a] Test 1: Proposed Commercial formulation
[b] Test 2: Wet formulation (not used in ANY clinical studies)
[c] Reference: Clinical trials formulation

Following a single 400mg dose the AUC(INF) and CMAX estimates for the proposed commercial tablet was comparable to those of the clinical tablet formulation. The 90% confidence limits on the ratio of the mean AUC(INF) and CMAX estimates for the proposed commercial and clinical tablets were within the accepted boundaries of 80%-125% for establishing bioequivalence. The difference in Tmax was only seen with the formulation not used in clinical studies. The sponsor concluded that the clinical trials and the proposed commercial (i.e., biobatch) tablet formulations were bioequivalent. This conclusion was acceptable.

D. SPECIAL POPULATIONS

Study AI420-018: Hepatic Impairment. 400mg single dose in chronic, stable hepatic impaired subjects, n=8(Child-Pugh Class B, n=7; Child-Pugh Class C, n=1) compared to matched control subjects with normal hepatic function (n=8). Full results can be found in **Appendix 2**. Mean PK results are listed below.

Pharmacokinetic Variable	Hepatic subjects	Normal Controls	Ratio of Means (Hepatic subjects:Controls)	90% Confidence Interval for Ratio of Means
CMAX (µg/mL)[a]	5.14	3.91	1.32	(1.04, 1.67)
AUC(INF) (µg•h/mL)[a]	45.2	36.9	1.23	(1.07, 1.40)

[a] for CMAX and AUC(INF), the means, ratios, and confidence intervals are based on geometric means because the data were analyzed on a log scale

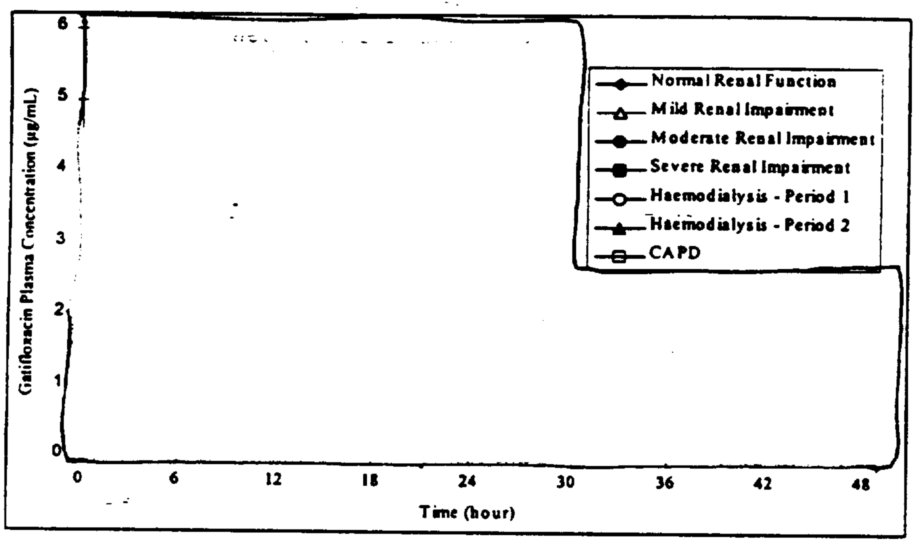
Mean systemic exposure (AUC(INF)) to gatifloxacin was 24% higher in hepatic impaired subjects compared to controls. Mean Cmax values were 34% higher in hepatic impaired subjects. Mean T-half was 0.33hrs shorter in hepatic impaired subjects. Mean CLR and CLT/F were decreased by 15% and 18% respectively in hepatic impairment. These differences in pharmacokinetic parameters between controls and hepatic impaired subjects are relatively minimal with a single dose.

The sponsor had been told that this study was inadequate due to the number or patients with severe hepatic impairment (i.e., Child-Pugh Class C). It was suggested that additional studies be performed using more patients with Class C and also using a multiple dose design.

Study AI420-017: Renal impairment. 400mg single dose in 6 groups (n=8/group): (1) CL_{CR}>90mL/min ("normal"), (2) mild renal impairment, CL_{CR} 50-90 mL/min, (3) moderate renal impairment, CL_{CR} 30-50 mL/min, (4) severe renal impairment, CL_{CR} <30mL/min and not requiring dialysis, (5) hemodialysis, (6) CAPD. For subjects on dialysis, 400mg of gatifloxacin 400mg was given 3 hr prior to a dialysis session in Period 1 and immediately after the dialysis session in Period 2. The results of this study are illustrated below.

Group	CLcr (mL/min)[1]	CMAX (µg/mL)	TMAX* (h)	T-HALF (h)	CLT/F (mL/min)	AUC(INF) (µg.h/mL)	CLR (mL/min)	UR %
Normal Renal Function	>90 (113)	3.963 (0.86)	0.75 (0.50-1.50)	10.22 (2.41)	212 (33)	32.13 (5.01)	149 (43)	71 (20)
Mild Renal Impairment	50-90 (72)	4.447 (1.11)	1.13 (0.75-2.00)	11.19 (2.79)	148 (41)	47.98 (12.68)	124 (38)	84 (8)
Moderate Renal Impairment	30-50 (44.3)	5.112 (1.77)	0.75 (0.50-6.00)	17.16 (8.46)	92 (17)	74.91 (12.63)	67 (24)	71 (17)
Severe Renal Impairment	<30 (17.6)	4.491 (1.22)	1.50 (0.50-6.0)	30.68 (8.42)	48 (16)	149.31 (35.59)	23 (13)	45 (13)
Haemodialysis - Period 1-	N/A	3.764 (1.07)	2.00 (0.75-3.00)	35.84 (9.17)	46 (12)	151.19 (35.11)	-	-
Haemodialysis - Period 2-	N/A	4.668 (0.95)	1.50 (1.00-3.00)	35.65 (7.04)	38 (8)	180.27 (34.38)	-	-
CAPD	N/A	4.674 (1.33)	1.75 (0.50-3.00)	40.26 (8.33)	31 (8)	226.95 (59.99)	-	-

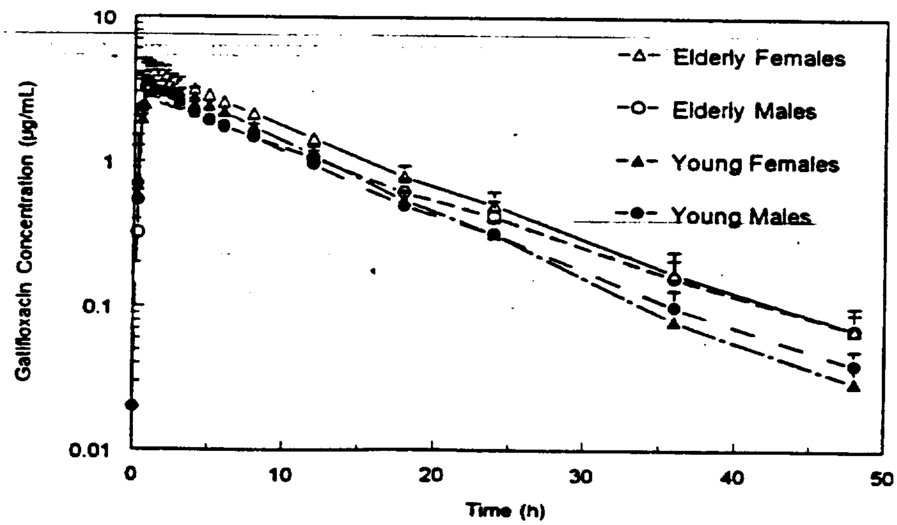
[1] Values in parentheses indicate mean creatinine clearance for each group.



The systemic exposure of gatifloxacin was increased in subjects with renal impairment, evident from the hyperbolic relationship between AUC(INF) or T-HALF and CL_{CR}. Mean AUC(INF) and T-HALF increased from 31.90 to 149.31 µg•h/mL and 10.22 hrs to 30.68hr in groups 1 (normal) and 4 (severe), respectively. The TMAX or CMAX of gatifloxacin remained comparable across renal function groups. A direct linear relationship existed between CL_{CR} and CLT/F (R^2=0.92) or CLR (R^2=0.78). An 77% reduction in CLT/F and corresponding 4 fold increase in gatifloxacin exposure was noted in subjects with severe renal impairment compared to that in subjects with normal renal function. This finding suggests dose modification in renal impairment. A population PK approach was used to describe the dosing modification suggestions.

The T-HALF following dialysis was 35 and 40 hours following hemodialysis and CAPD. The mean amount of drug removed by a 4-hour haemodialysis session was 13.6% when the dialysis session was performed 3 hours after drug administration, and 6.6% when the dialysis session was performed 44 hours after dosing. The mean amount of drug removed by peritoneal dialysis over 8 days was 11%.

Study AI420-021: Effect of Age and Gender. Single 400mg dose, 24 young (n=12 males, n=12 females), 24 elderly (n=12 males, n=12 females). Statistical results for age effects are summarized below.



Pharmacokinetic Variable	Geo. Mean for Elderly	Geo. Mean for Young	Ratio of Geo. Means (E/Y)	90% C.I. for Ratio
CMAX (µg/mL)				
Males	3.68	4.14	0.89	(0.76, 1.03)
Females	4.46	3.68	1.21	(1.04, 1.41)
Both genders	4.05	3.91	1.04	(0.93, 1.15)
AUC(INF) (µg•h/mL)				
Males	35.6	32.5	1.10	(0.99, 1.21)
Females	47.2	35.7	1.32	(1.19, 1.46)
Both genders	41.0	34.1	1.20	(1.12, 1.29)

Variable	Mean for Elderly	Mean for Young	2-sided p-value	Difference: Elderly-Young	90% C.I. for Difference
T-HALF (h)	10.49	7.45	*<0.001*	3.04	(2.29, 3.78)
MRT (h)	12.47	10.38	*<0.001*	2.09	(1.50, 2.67)
%UR (% dose)	76.4	78.2	0.64	-1.74	(-7.87, 4.39)
CLT/F (mL/min)					
males	189.8	207.8	0.12	-18.07	(-37.18, 1.04)
females	142.1	188.2	*<0.001*	-46.04	(-65.15, -26.93)
overall	166.0	198.0	*<0.001*	-32.06	(-45.57, -18.54)
CLR (mL/min)	125.6	151.9	*0.01*	-26.37	(-42.74, -10.00)

Elderly females had 21% higher mean CMAX and 32% higher AUC(INF) compared to young females. There was no age effect for males. Mean T-HALF was 3.04 hrs longer in elderly than young subjects, which was partially accounted for by decreased creatinine clearance. Mean CLT/F was significantly lower in elderly females, which was also accounted for by declining renal function with age. Age effects are mainly due to changes in renal function.

The effects of gender are summarized in the two tables below.

Pharmacokinetic Variable	Geo. Mean for Females	Geo. Mean for Males	Ratio of Geo. Means (F/M)	90% C.I. for Ratio
CMAX (µg/mL)				
in young	3.68	4.14	0.89	(0.76, 1.03)
in elderly	4.46	3.68	1.21	(1.04, 1.41)
in both age groups	4.05	3.90	1.04	(0.93, 1.16)
AUC(INF) (µg•h/mL)				
in young	35.7	32.5	1.10	(0.99, 1.22)
in elderly	47.2	35.6	1.33	(1.20, 1.47)
in both age groups	41.1	34.0	1.21	(1.12, 1.30)

Variable	Mean for Females	Mean for Males	2-sided p-value	Difference: Females-Males	90% C.I. for Difference
T-HALF (h)	8.42	9.52	0.02	-1.10	(-1.84, -0.35)
MRT (h)	11.04	11.81	0.03	-0.77	(-1.36, -0.19)
%UR (% dose)	79.6	74.9	0.20	4.7	(-1.42, 10.84)
CLT/F (mL/min)					
young	188.2	207.8	0.09	-19.6	(-38.76, -0.54)
elderly	142.1	189.8	<0.001	-47.6	(-66.73, -28.51)
overall	165.2	198.8	<0.001	-33.6	(-47.15, -20.13)
CLR (mL/min)	129.9	147.6	0.08	-17.7	(-34.06, -1.32)

Mean Cmax and AUC(INF) were 21% and 33% higher for females compared to males. Adjustments for body weight partially reduced the gender differences. CLT/F was lower among females, but more so for elderly females; adjustments for both creatinine clearance and body weight corrected these differences.

Age and gender effects were only done using SINGLE dose study design.

Study AI420-032: Glucose homeostasis in Type II Diabetics on Diet/Exercise, single and multiple dose (10days), n=16/group: gatifloxacin (400mg), ciprofloxacin (500mg), or placebo. Statistical summary of this study is shown below. The pharmacokinetic parameters for gatifloxacin were similar in this patient group to normal, healthy volunteers. Following oral glucose tolerance test, there was a lack of effect of gatifloxacin on glucose tolerance and pancreatic β-cell function.

Variable	Study Day	Drug*	Geometric Mean	Ratio (90% C.I.) Study Drug:Placebo	Ratio (90% C.I.) GATI:CIPRO
Glucose AUC (mg•h/dL)	Day 1	Placebo	860	-	-
		GATI	629	0.73 (0.70, 0.76)	0.84 (0.81, 0.87)
		CIPRO	751	0.87 (0.84, 0.91)	-
	Day 10	Placebo	821	-	-
		GATI	698	0.85 (0.82, 0.89)	0.95 (0.92, 0.99)
		CIPRO	732	0.89 (0.86, 0.93)	-
Insulin AUC (μU•h/mL)	Day 1	Placebo	47.91	-	-
		GATI	68.66	1.43 (1.29, 1.59)	1.12 (1.01, 1.25)
		CIPRO	61.12	1.28 (1.15, 1.42)	-
	Day 10	Placebo	42.10	-	-
		GATI	44.78	1.06 (0.95, 1.19)	0.69 (0.62, 0.78)
		CIPRO	64.54	1.53 (1.38, 1.70)	-

Glucose homeostasis for up to 6hr after drug administration on Days 1 and 10 indicated decreasing trends in fasting glucose and increasing trends in fasting insulin concentrations following treatment for all groups. Mean AUC for fasting glucose were 27% and 15% lower for gatifloxacin and 13% and 11% lower for ciprofloxacin than placebo on Days 1 and 10, respectively. Mean AUC for fasting insulin was 43% and 6% higher for gatifloxacin and 28% and 53% higher than placebo on Days 1 and 10, respectively.

For fasting glucose, across the study time, there were variable changes for all treatment groups. For serum insulin, there was a 7-32% drop for gatifloxacin, a 1-30% drop for ciprofloxacin, and a 7-16% drop for placebo. For serum C-peptide, mean changes were small.

Study AI420-036: Glucose homeostasis in Type II Diabetics on Glyburide, n=18, single and multiple dose (10days) gatifloxacin (400mg); n=16, placebo; mean glyburide dose 4.05mg/day (range 1.25-10mg/day). The pharmacokinetic parameters for gatifloxacin was somewhat different in this study compared to normal, healthy volunteers with a 14% increase in Cmax, 30% increase in AUC(TAU), 35% increase in T-HALF, 25% decrease in CLT/F, and 21% decrease in %UR. The subjects in this study had lower creatinine clearance compared to those with healthy volunteers or subjects with diabetes controlled with diet/exercise.

The results following oral glucose tolerance testing are summarized below.

Variable	DRUG	Arithmetic Means		Pt. Est. and 90% CI for Ratios		
		Day -1	Day 11	Adj'd Geom. Means Ratio* (Day 11:-1)		Between Treatments GATI: Placebo
Glucose CMAX mg/dL	Placebo	327	312	0.96	(0.91, 1.02)	
	GATI	282	309	1.07	(1.01, 1.14)	1.12 (1.02, 1.22)
Glucose AUC (mg•h/dL)	Placebo	1070	1004	0.94	(0.87, 1.02)	
	GATI	983	1128	1.11	(1.02, 1.20)	1.18(1.05, 1.32)
Insulin CMAX (μU/mL)	Placebo	80	98	1.12	(0.98, 1.29)	
	GATI	118	83	0.67	(0.58, 0.77)	0.60(0.49, 0.73)
Insulin AUC (μU•h /mL)	Placebo	193	231	1.01	(0.90, 1.14)	
	GATI	312	213	0.74	(0.66, 0.84)	0.73(0.61, 0.87)
C-peptide CMAX (ng/ml)	Placebo	5.88	7.04	1.15	(1.02, 1.30)	
	GATI	6.97	5.80	0.86	(0.76, 0.97)	0.75 (0.63, 0.89)
C-peptide AUC (ng•h/mL)	Placebo	20.32	21.80	1.05	(0.97, 1.14)	
	GATI	23.23	19.55	0.85	(0.79, 0.93)	0.81(0.72, 0.91)

Following oral glucose tolerance test, glucose mean Cmax and AUC were 12% and 18% higher in those receiving gatifloxacin compared with placebo. Insulin mean Cmax and AUC were 40% and 27% lower in those receiving gatifloxacin compared with placebo. C-peptide mean Cmax and AUC were 25% and 19% lower in those receiving gatifloxacin compared with placebo.

Fasting pre-dose glucose, insulin and C-peptide remained constant during the study indicating no effect of gatifloxacin on these parameters.

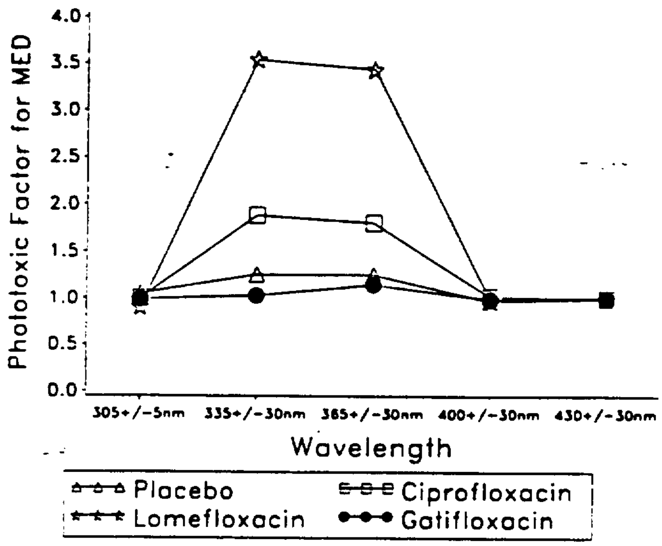
Study AI420-015: Phototoxicity study, n=48 (n=12/group) with four treatment groups: gatifloxacin, ciprofloxacin, lomefloxacin or placebo; multiple dose x 7d. Phototoxicity results are summarized below.

Wavelength (nm)		placebo (n=12)	ciprofloxacin (n=12)	lomefloxacin (n=12)	gatifloxacin (n=12)
305 ± 5	Mean ± SD	1.05 ± 0.14	1.0 ± 0.21	0.91 ± 0.23	0.99 ± 0.19
	Range				
	p-value		0.54	0.08	0.45
335 ± 30	Mean ± SD	1.26 ± 0.31	1.88 ± 0.75	3.54 ± 1.8	1.03 ± 0.24
	Range				
	p-value		0.13	<0.001	0.58
365 ± 30	Mean ± SD	1.25 ± 0.38	1.8 ± 0.81*	3.44 ± 1.30	1.15 ± 0.34
	Range				
	p-value		0.11	<0.001	0.75
400 ± 30	Mean ± SD	0.97 ± 0.07	1.02 ± 0.06	0.98 ± 0.05	0.99 ± 0.10
	Range				
	p-value		0.118	0.657	0.535
430 ± 30	Mean ± SD	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
	Range				
	p-value		1.000	1.000	1.000

*Data were only available for 11 subjects in the ciprofloxacin group at 365 ± 30nm wavelength.

Mean phototoxic factor (PF) for delayed MED from baseline on Day 6 is graphically represented below:

Mean Phototoxic Factor for Delayed MED from Baseline to During Treatment



Gatifloxacin and placebo did not cause significant phototoxicity as demonstrated by a change in MED values over a range of UVA, UVB and visible wavelengths. The comparators (and positive controls), ciprofloxacin and lomefloxacin, caused phototoxicity of a mild and moderate severity respectively, at wavelengths of 335 ± 30 nm and 365 ± 30 nm.

E. DRUG- DRUG INTERACTIONS

No significant interaction, or an interaction with only minor effect, of gatifloxacin on the pharmacokinetics of the following co-administered drugs was demonstrated:

Theophylline 200mg BID with gatifloxacin 400mg both at steady state (Study AI420-042).
Midazolam 0.0145mg/kg single dose with gatifloxacin 400mg at steady state (Study AI420-056).
Warfarin 25mg single dose with gatifloxacin 400mg at steady state (Study AI420-034).

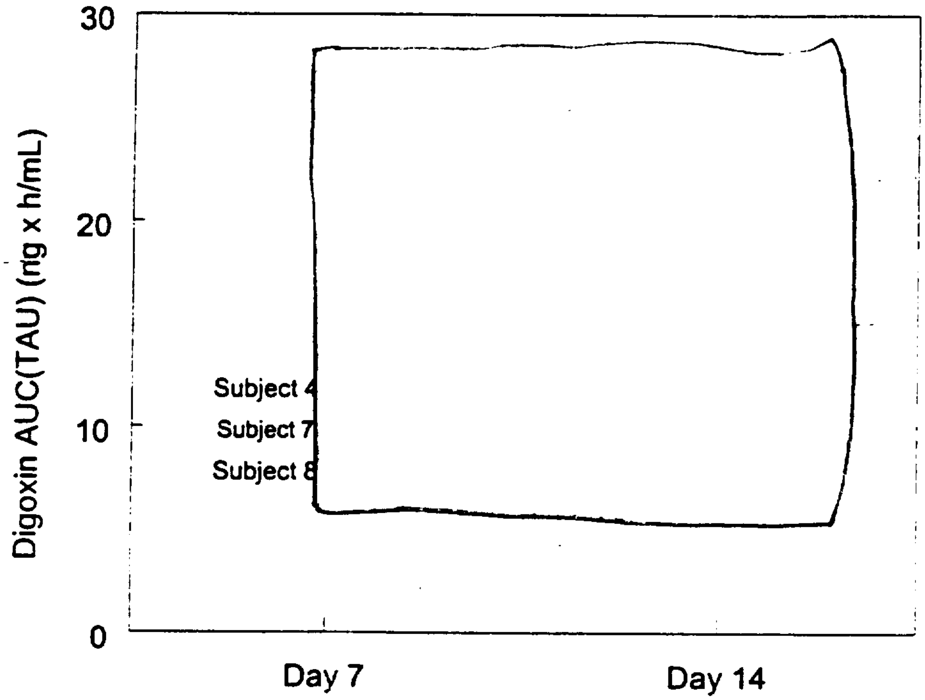
No significant interaction, or an interaction with only minor effect, of the following co-administered drugs on the pharmacokinetics of gatifloxacin was demonstrated:

Glyburide 1.25-10mg/d with gatifloxacin 400mg at steady state (Study AI420-036).
Cimetidine 200mg single dose with gatifloxacin 200mg single dose (Study AM1155-T104).
Calcium Carbonate 1000mg with gatifloxacin 200mg single dose (Study AI420-057).
Digoxin 0.25mg/d at steady state with gatifloxacin 400mg at steady state (Study AI420-035).
Theophylline 200mg BID with gatifloxacin 400mg both at steady state (Study AI420-042).
Midazolam 0.0145mg/kg single dose with gatifloxacin 400mg at steady state (Study AI420-056).
Warfarin 25mg single dose with gatifloxacin 400mg at steady state (Study AI420-034).

The most significant pharmacokinetic interactions, and potentially, the interactions to have the greatest clinical relevance were demonstrated with the following drugs:

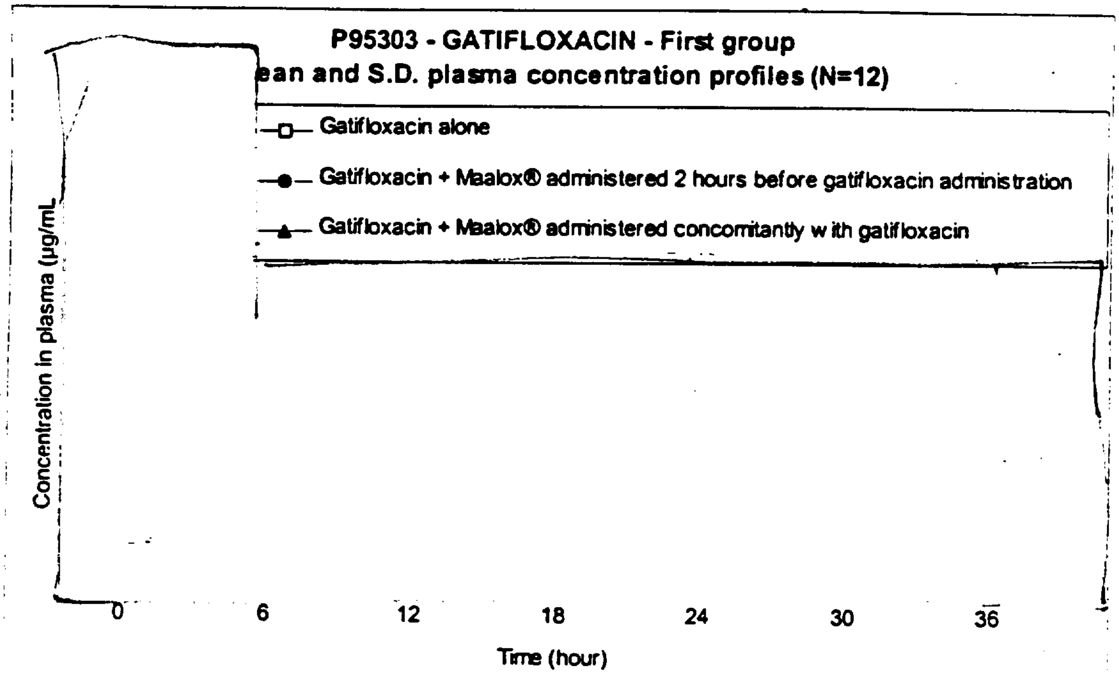
Study AI420-035: Digoxin 0.25mg/d at steady state with gatifloxacin 400mg at steady state. The oral pharmacokinetics of digoxin in this study demonstrate a 17% decrease in CLT/F with a corresponding 9% and 11% increase in arithmetic mean Cmax and AUC(TAU), and a 12 and 19% increase in geometric mean Cmax and AUC(TAU), respectively. The 90% CI for Cmax was [1.00, 1.26] and for AUC(TAU) was [1.001.41]. The corresponding point estimates for Cmax and AUC(TAU) were 1.12 and 1.19. There were no changes in digoxin trough levels (Cmin) when gatifloxacin was administered concomitantly.

Individual subject data indicated that the observed increases in geometric Cmax and AUC(TAU) values for digoxin were due to increases in the values of 3 individual subjects (25% of total subjects). The mean Cmin with digoxin alone vs. digoxin + gatifloxacin increased by approximately 40% in these three subjects, but the digoxin concentration remained within the therapeutic range (and less than 0.65ng/mL). The data from these three subjects contribute to much of the variability in the data, with Cmax values increased by 18, 58, and 29% and AUC values increased by 66, 79, and 104% (graph below), respectively, when digoxin was administered with gatifloxacin. CLT/F was decreased by 40, 45, and 51% in these subjects when digoxin was administered with gatifloxacin.



Despite a statistically non-significant interaction with digoxin and gatifloxacin, there are serious potential interactions when individual data is evaluated. A narrow therapeutic index drug, such as digoxin, may not warrant dosing adjustment, but more intense therapeutic drug level monitoring when co-administered with gatifloxacin.

Study AI420-024: **Maalox®** single use 70 (10mL, 600mg magnesium hydroxide and 900mg aluminum oxide) with gatifloxacin 400mg single dose. Maalox was administered either 2hr before, concomitantly, 2hr after, or 4 hr after gatifloxacin. Mean CMAX and AUC(INF) of gatifloxacin were 47% and 40% lower when the antacid was administered 2 hours before gatifloxacin. Mean CMAX and AUC(INF) of gatifloxacin were 69% and 64% lower when the antacid was administered concomitantly with gatifloxacin. Mean CMAX and AUC(INF) of gatifloxacin were 15% and 17% lower when the antacid was administered 2 hours after gatifloxacin. Mean CMAX and AUC(INF) of gatifloxacin were almost comparable (7% and <1% lower) when the antacid was administered 4 hours after gatifloxacin.



AI420-024		
	Cmax	AUC(INF)
Gati alone (400mg)	3.643 (0.748)	29.010 (5.025)
Maalox 2 hr BEFORE	1.917 (1.158)	17.474 (6.871)
Point estimate		
90% CI	[0.33-0.62]	[0.45-0.71]
Concomitant	1.138 (0.437)	10.565 (3.101)
Point estimate		
90% CI	[0.22-0.41]	[0.28-0.45]
Gati alone	4.030 (1.160)	30.369 (3.047)
Maalox 2 hr AFTER	3.421 (1.450)	25.298 (5.426)
Point estimate		
90% CI	[0.69-0.95]	[0.75-0.89]
Maalox 4 hr AFTER	3.743 (1.041)	30.359 (2.944)
Point estimate		
90% CI	[0.80-1.10]	[0.95-1.08]

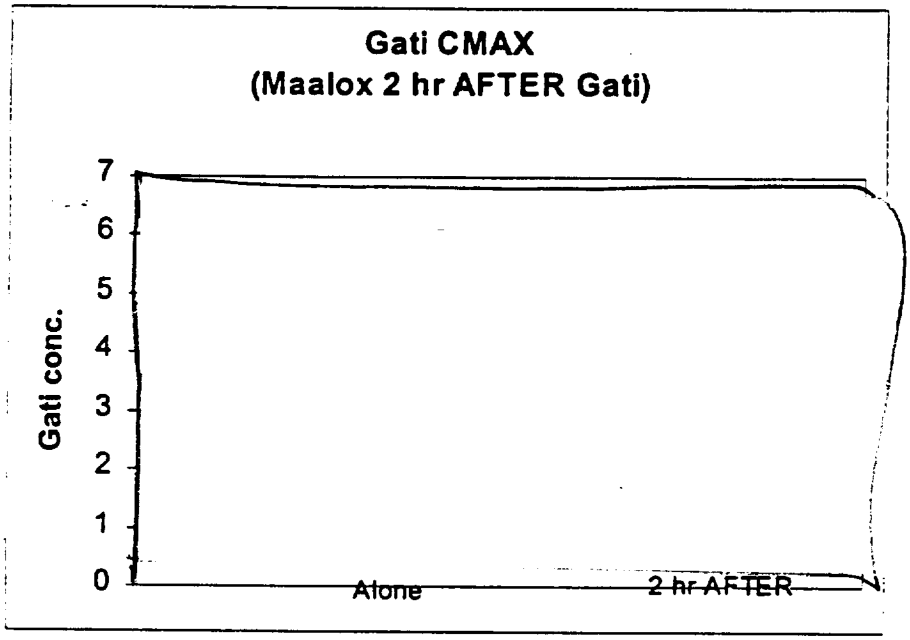
Maalox, 2 X 10mL single use flasks: each 10mL contains 600mg Mg hydroxide and 900mg aluminum oxide)

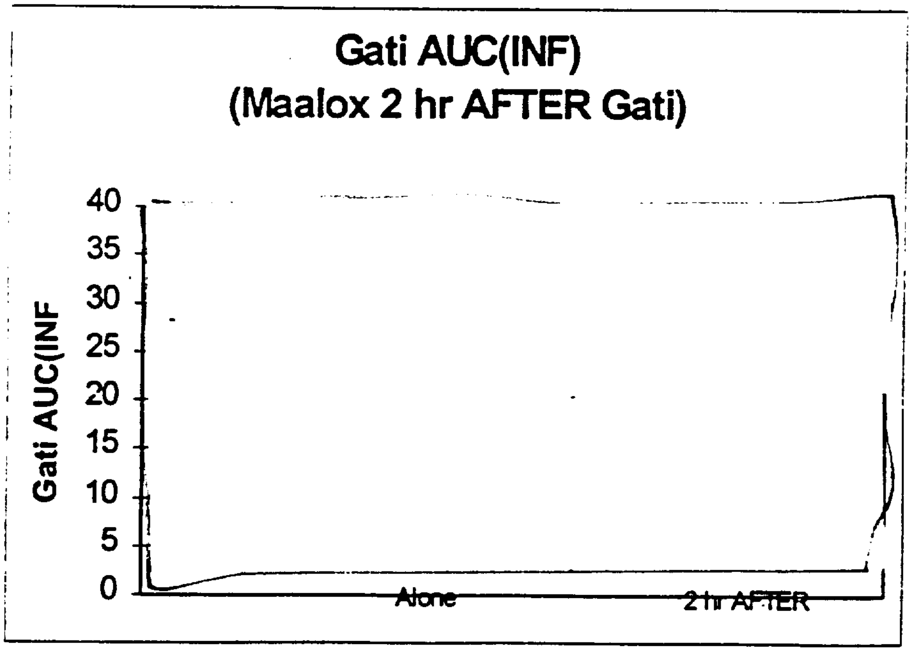
The range for Cmax and AUC are as follows (arithmetic means are presented in the above table):

	Cmax (µg/mL)			AUC(µg•h/mL)		
	Gati Alone	2 hrs after	4 hrs after	Gati Alone	2 hrs after	4 hrs after
Minimum	2.185	1.301	2.622	24.886	15.29	26.491
Maximum	5.749	5.997	5.895	36.055	32.736	36.123

Based on these results, Maalox® (or other aluminum/magnesium containing antacids) can be given 4 hours after gatifloxacin without any change in the pharmacokinetics of gatifloxacin. Additionally, Maalox® (or other aluminum/magnesium containing antacids) should not be taken concomitantly, up to 4hrs before or 4 hrs after gatifloxacin administration.

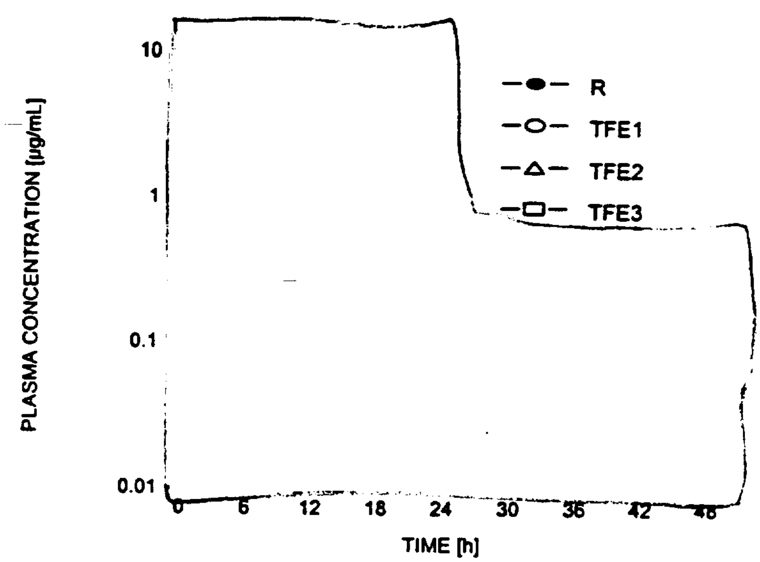
The sponsor claims in their proposed label that an aluminum-containing antacid may be give 2-3 hours after gatifloxacin. The sponsor had proposed apriori the 90% confidence intervals of [80-125] for AUC and [70-143] for Cmax, as per Draft Guidance on In Vivo Drug-Drug Interactions. Stick Plots for Gatifloxacin Cmax and AUC alone and with Maalox given 2 hr after gatifloxacin are presented below.





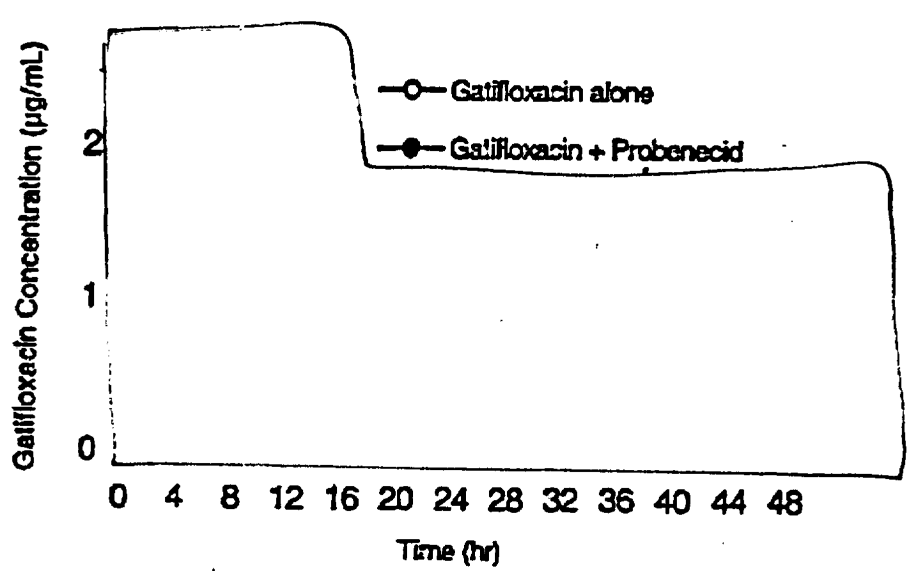
The results of this study are published in Antimicrobials Agents and Chemotherapy, May 1999, 43(5), 1067-1071. The authors of this study conclude that " the optimal time between gatifloxacin administration and the intake of an aluminum-containing antacid should be 4 hr to avoid substantial interaction".

Study AI420-057: Ferrous sulfate 325mg with gatifloxacin 400mg single dose. Ferrous sulfate was administered either 2hr before (TFE2), concomitantly (TFE1), or 2hr after gatifloxacin (TFE3) or gatifloxacin was administered alone (R). Co-administration of gatifloxacin with $FeSO_4$ decreased mean AUC(INF) by 35% and mean CMAX by 54%. TMAX was delayed when gatifloxacin was administered concomitantly with $FeSO_4$. T-half was unchanged.



Data from this study demonstrate that iron supplements should not be co-administered with gatifloxacin, but may be taken either 2 hr before or 2 hr after gatifloxacin.

Study AM1155-T101: Probenecid 2 x 250mg with single dose gatifloxacin 2 x 100mg. Probenecid administration resulted in a 42% increase in mean AUC(INF), 44% increase in mean T-HALF, 30% decrease in mean CLT/F and 38% decrease in mean CLR for gatifloxacin.



F. POPULATION PK/PD

The population PK and PK/PD reports were reviewed in conjunction with [redacted]

A population PK analysis of the phase I renal impairment study was performed as a basis for the rationale for dose adjustment in renal insufficiency. The phase I data were used to build the structure model. Based on estimated Pop PK parameters, various dosing regimens in renal impairment were simulated. The proposed dosing frequency for 400mg on Days 1 and 2, followed by 400mg every other day in patients with creatinine clearance less than 30mL/min allows for exposures with AUC less than 100µg•h/mL and Cmax in the range of 4-5µg/mL.

A population PK/PD analysis using Phase II and III data (acute exacerbation of chronic bronchitis, AI420-003, and community acquired pneumonia, AI420-037/-038) was performed by the sponsor. Phase I data were used to build the structure model. The model building process was appropriate but a stability problem was noted. There were not enough data to perform logistic regression analysis. Conclusions about covariates were limited by the small number of subjects and the narrow distribution range within each group. With respect to the number of patients, 21% of patients in the Phase II studies and approximately 25% of patients in the Phase III studies had both PK and bacteriologic data. The major covariate for total gatifloxacin clearance was creatinine clearance, which eliminated age and weight as covariates. This analysis suggests that the levels of exposure (either AUC or Cmax) did not correlate well with efficacy outcome. Adverse event check shows that there was the same frequency of adverse events across all ranges of exposures for both AUC and Cmax (broken into 8-9 strata). The sponsor did not provide any data in these reports about the severity of the AEs, however.

In study AI420-003, chronic bronchitis, a total of 40 patients (19%) experienced AEs related to gatifloxacin, 23 mild and 14 moderate in severity. Three patients had 4 severe AEs and two had Population PK/PD samples drawn. Patient 005-001 experienced severe vaginitis treated with nystatin and fluconazole, and had a trough level of 0.560µg/mL and AUC of 27.60µg•h/mL. These concentrations are in the lowest strata when comparing with AEs. Patient 012-004 had diaphragmatic cramping and diaphoresis on Day 2, resolved without treatment on Day 5, and had a peak level of 4.489µg/mL, a trough level of 1.117µg/mL and AUC of 44.26µg•h/mL. These concentrations are in the fourth strata when comparing with AEs. The remaining patients who had PK sampling had either mild or moderate severity AEs, and had AUCs up to 100µg•h/mL and Cmax up to 9.0µg/mL. There were too few severe adverse events to draw a comfortable conclusion about the relationship between exposure and the frequency of severe AEs.

The population PK/PD assessment is suggestive, but not confirmative of a relationship between efficacy and Cmax/MIC or AUC/MIC ratios. This analysis was limited by the small number of patients in the Phase II/III clinical studies that had PK and bacteriologic assessment.

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