

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-158

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-158	Submission Date(s):	October 4, 2002
Brand Name	Factive™	
Generic Name	Gemifloxacin	
Reviewer	Seong H. Jang, Ph.D.	
PM Reviewer	Jenny J. Zheng, Ph.D.	
Team Leader	Phil M. Colangelo, Pharm.D., Ph.D.	
Clinical Review Division	DSPID (HFD-590)	
Sponsor	LG Life Sciences, Ltd.	
Submission Type; Code	Resubmitted NDA; AZ	
Formulation; Strength(s)	320 mg Gemifloxacin (400 mg Gemifloxacin Mesylate) Tablet	
Proposed Indications	Acute bacterial exacerbations of chronic bronchitis; Community-acquired pneumonia (of mild to moderate severity)	

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I. Executive Summary

On December 15, 1999, the applicant submitted an NDA for its product, Factive (gemifloxacin mesylate) tablet. The application was not approvable. The action letter was sent on December, 15, 2000. The major reason for "not approvable" was the high incidence of rash associated with gemifloxacin. The current NDA resubmission addressed each of the deficiencies identified in the FDA Action letter. In the resubmitted NDA, the sponsor performed additional studies, including Study 344 to characterize the rash associated with gemifloxacin. The sponsor is currently requesting the indications of community-acquired pneumonia (CAP) and acute bacterial exacerbation of chronic bronchitis (ABECB).

In the not approvable letter from the Division of Special Pathogen and Immunologic Drug Products (HFD-59), the sponsor was requested to evaluate (a) the relationship between gemifloxacin plasma exposure and rash incidence in Study 344 and (b) the pharmacokinetics and safety of gemifloxacin in individuals with severe hepatic impairment (Child-Pugh Class C). In addition to the information from Study 344, the resubmitted NDA also includes 8 other clinical pharmacology and biopharmaceutics studies. **The study designs and results are acceptable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewer.** The key results of the resubmitted NDA studies are summarized below.

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The Clinical Pharmacology and Biopharmaceutics Review of the original NDA submission for gemifloxacin tablets was performed by Dr. Phil Colangelo (Date: 12/11/2000).

Study 344: After repeat oral dose administration of gemifloxacin (320 mg qd for 7 days), population pharmacokinetic analysis was performed with data from 840 healthy female subjects participating in a double-blind, parallel group study characterizing gemifloxacin-associated rash. Systemic exposure (i.e., C_{max} and AUC) to gemifloxacin and N-acetyl gemifloxacin, its main metabolite, in subjects who experienced rash did not differ from those without rash. The incidence and severity of rash does not seem to be related with the systemic exposure of gemifloxacin or N-acetyl gemifloxacin.

Study 059: The mean systemic exposure, i.e., AUC and C_{max} , was ~40 to 45% higher in subjects with severe hepatic impairment (Child-Pugh C) receiving a single 320 mg oral dose of gemifloxacin as compared with healthy subjects. This difference is not considered to be significant based on overall similarity in the range of the individual AUC and C_{max} values between the severe hepatic impairment subjects and healthy subjects from Phase I pharmacokinetic studies in the original NDA. In addition, there was no apparent relationship between gemifloxacin systemic exposure and incidence of certain adverse events, e.g., LFT elevation from the original submission and skin rash from this resubmission. Thus, dosage adjustment would not be necessary in patients with severe hepatic impairment.

Study 056: In subjects with renal impairment ($CL_{cr} = 40-59$ mL/min), AUC was approximately 70% higher compared with healthy subjects, whereas C_{max} was not significantly affected (approximately 10% higher). As commented above, there was no apparent relationship between gemifloxacin systemic exposure and incidence of certain adverse events, e.g., LFT elevation and skin rash. In addition, individual AUC values in subjects with CL_{cr} of 40-59 mL/min were also within the range observed in healthy subjects from Phase I pharmacokinetic studies in the original NDA. In the original NDA submission, the sponsor proposed to reduce the dosage of gemifloxacin from 320 mg Q24 hr to 160 mg Q24 hr in patients with CL_{cr} of <40 mL/min. While this is generally acceptable, we will propose that the dosage be reduced at CL_{cr} of ≤ 40 mL/min.

Studies 024 and 077: Gemifloxacin can be co-administered with calcium products and cimetidine without dosage adjustment of gemifloxacin. Co-administration with either calcium carbonate 1,000 mg or cimetidine 400 mg qid resulted in < 20% decrease and <10% increase in the systemic exposure of gemifloxacin, respectively.

Studies 114 and 033: The absolute bioavailability of a pediatric suspension of gemifloxacin and oral tablet was 49% and 61%, respectively, in healthy subjects. Administration of a single 250 mg intravenous dose of gemifloxacin resulted in higher systemic exposure (C_{max} and AUC), which was not equivalent when compared with the 320 mg oral tablet. Another study demonstrated bioequivalence between two separate batches of the commercial tablet formulation of gemifloxacin with differing dissolution profiles (i.e., ———— dissolution at — min), indicating no correlation between dissolution rate and in vivo bioavailability of gemifloxacin.

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II. General Comments (Not for the sponsor)

Two comments from the review of the original NDA were modified based on the data from the current resubmitted NDA.

- A. The previous OCPB reviewer, Dr. Phil Colangelo, proposed dissolution specification of $Q = \dots$ (NLT 85% dissolution), based on the dissolution data that was provided by the sponsor. In the resubmitted NDA, the sponsor demonstrated the bioequivalence of two batches of the commercial tablet formulation of gemifloxacin with differing dissolution profiles, i.e., $Q = \dots$ dissolution at 30 min. Thus, the dissolution specification of $Q = \dots$ (NLT 75% dissolution), originally proposed by the sponsor, is considered to be acceptable.
- B. In the previous OCPB comments on the original submission, re-analysis of the data from Phase III studies showed that reduction of the gemifloxacin dose to 160 mg Q24 hr for the patients with CLcr <50 mL/min resulted in a more even distribution of the predicted AUC₀₋₂₄ estimates across the entire patient population that was studied, as compared to when dose reduction was at CLcr <40 mL/min. Thus, the previous OCPB reviewer (Dr. Colangelo) proposed that gemifloxacin dose should be reduced to 160 mg QD at CLcr < 50 mL/min, rather than <40 mL/min. The results of Study 056 in the resubmitted NDA showed that the difference of increases in AUC₀₋₂₄ between subjects with CLcr 50-59 and 40-49 mL/min is not significant. Therefore, we recommend CLcr of ≤ 40 mL/min as a cutoff to reduce gemifloxacin dose by half, i.e., 160 mg, in patients with renal impairment.

III. Labeling Comments

Labeling comments from the OCPB reviewers are incorporated into the final label (version 03/12/03) in Appendix 1.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Concurrence

Phil Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

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Summary of Clinical Pharmacology and Biopharmaceutics

Detailed reviews of individual studies are incorporated in Appendix 2.

A. Clinical Pharmacology Issues

1. **Is there any relationship between the incidence & severity of rash and gemifloxacin and N-acetyl gemifloxacin (NAG) plasma concentration? (Study 344)**

After repeat oral dose administration of gemifloxacin (320 mg qd for 7 days), population pharmacokinetic analysis was performed with data from 840 healthy female subjects participating in a double-blind, parallel group study characterizing gemifloxacin-associated rash.

Population pharmacokinetic analysis was reviewed by Pharmacometrics reviewer, Jenny J. Zheng, Ph.D. and considered to be acceptable. The PPK analysis indicated that the body weight was the only covariate that affected the CL of gemifloxacin. The estimated total clearance of gemifloxacin for a subject with body weight of 64.3 kg was 38.9 L/h, which was similar to the findings from the other studies (see Dr. Dan Wang's review as an appendix in Dr. Philip Colangelo's review). The Bayesian predicted mean AUC(0-24) of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 8.98 $\mu\text{g}\cdot\text{h}/\text{mL}$ with the standard deviation of 2.12, and ranged from 4.23 to 19.12 $\mu\text{g}\cdot\text{h}/\text{mL}$. The mean C_{max} of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 1.261 $\mu\text{g}/\text{mL}$ with the standard deviation of 0.235 and ranged from 0.668 to 2.747 $\mu\text{g}/\text{mL}$.

The estimate of N-acetyl gemifloxacin was based on the assumption that the oral bioavailability (F) of the input dose encompasses metabolic conversion and remains constant during the dosing period and the scaling of central compartment concentrations (S2) includes a stoichiometric correction factor of 1.107 to account for the N-acetylation of gemifloxacin. Due to the above assumptions the primary pharmacokinetic parameters, clearance (CL/F) and volume of distribution (V/F) are apparent and should not be used in a different population or in different models. The examinations on the individual fit of N-acetyl gemifloxacin showed that the model reasonably described the concentration vs time profile of day 1 but not day 6. Therefore, it is reasonable to compare N-acetyl gemifloxacin exposure of day 1 between individuals.

The pharmacokinetic parameters of Gemifloxacin and its main metabolite, N-acetyl gemifloxacin, in subjects with and without rash are summarized in Table 1. Gemifloxacin and N-acetyl gemifloxacin exposure (C_{max} or AUC) parameters in subjects who experienced rash did not differ from those without rash. **Thus, there were no trends for (a) higher exposure to the parent drug or N-acetyl gemifloxacin and (b) differences in extent of N-acetylation of gemifloxacin in subjects with rash, compared to those subjects without rash.** Furthermore, there was no relationship between occurrence of

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

Table 1. Individual predicted PK parameters in female subjects with (n=254) and without (n=584) rash

	AUC ₀₋₂₄ (µg·h/mL)		C _{max} (Day 1) (µg/mL)		C _{max} (Day 6) (µg/mL)	
	Rash	No rash	Rash	No rash	Rash	No rash
Gemifloxacin						
Mean ±SD	9.14±2	8.91±2.17	1.21±0.25	1.2±0.23	1.33±0.68	1.26±0.24
Median	8.92	8.64	1.2	1.18	1.25	1.24
95% CI	5.92-13.5	5.41-13.9	0.806-1.75	0.808-1.71	0.854-1.8	0.849-1.8
N-Acetyl Gemifloxacin						
Mean ±SD	1.59±3.6	1.42±3.48	0.177±0.15 7	0.158±0.14 9	0.197±0.2 3	0.178±0.22 4
Median	0.727	0.582	0.086	0.075	0.092	0.08
95% CI	0.146-6	0.123-5.14	0.024-0.641	0.022-0.551	0.024-0.72	0.022-0.623

2. Are there any alterations in pharmacokinetics of gemifloxacin in patients with severe hepatic impairment (Child-Pugh C)? (Study 059)

A previous study from the original NDA showed that subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment administered 320 mg gemifloxacin had, on average, ~30% and ~20% increases in gemifloxacin AUC_{0-inf} and C_{max}, respectively, compared to normal healthy subjects. The present study was designed to investigate the safety and pharmacokinetics of gemifloxacin in healthy subjects and subjects with severe hepatic impairment (Child-Pugh C) following a single oral dose of 320 mg, in order to determine dosing recommendations for this group of subjects. The linear, i.e., time-independent, pharmacokinetics of gemifloxacin was expected to permit extrapolation of single dose data to repeat doses.

This study was an open-label and parallel-group study. All subjects were classified at screening, within 7 days of dosing, into two groups; either healthy subjects or subjects with severe hepatic impairment according to Child's criteria with Pugh's modification (Category C). All subjects received a single oral dose of 320 mg gemifloxacin in the fasted state.

The results are summarized in Table 2.

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Table 2. Pharmacokinetic parameters of gemifloxacin after administration of 320 mg oral tablet in normal healthy subjects (Normal) and subjects with severe hepatic dysfunction (Severe).

Parameters	Normal (n=10)	Severe (n=10)	P.E. (Severe:Normal)	95% C.I.
AUC _{0-inf} (µg·h/mL)	7.62±2.19 (4.97-12.0) ^a	11.3±4.63 (6.86-22.1) ^a	1.45 ^c	(1.08, 1.94)
C _{max} (µg/mL)	1.08±0.42 (0.468-2.00) ^a	1.47±0.41 (0.857-2.08) ^a	1.41 ^c	(1.02, 1.95)
T _{1/2} (hours)	8.06±1.37 (5.84-10.2) ^a	9.68±1.24 (7.59-11.4) ^a	1.61 ^d	(0.39, 2.84)
T _{max} (hours)	1.00 (1-3) ^b	1.00 (0.5-2) ^b	-0.5 ^e	(-1.00, 0.00)

^a: Mean±SD (range), ^b: Median (range), ^c: Ratio of geometric means, ^d: difference of arithmetic means, ^e: median difference

The mean AUC_{0-inf} and C_{max} in subjects with severe hepatic dysfunction (Child-Pugh C) were increased by 45 and 41%, respectively, compared with normal subjects. These increases would not be considered significant based on overall similarity in the range of the individual AUC and C_{max} values between the severe hepatic impairment subjects and healthy subjects from Phase I pharmacokinetic studies in the original NDA. In addition, there was no apparent relationship between gemifloxacin systemic exposure and incidence of certain adverse events, e.g., LFT elevation from the original submission and skin rash from this resubmission. Thus, dosage adjustment would not be necessary in patients with severe hepatic impairment. However, it should be noted that the increases in several individual subjects were much greater than the average changes. For example, AUC_{0-inf} in subjects 204 (16.94 µg·h/mL) and 210 (22.1 µg·h/mL), who had severe hepatic dysfunction, were ~2- and ~3- fold higher than the average AUC in normal subjects, respectively. This inter-individual difference among subjects with severe hepatic dysfunction may be due to other factors such as renal function. Note that the creatinine clearance in subject 210 was significantly lower than the average value, i.e., 74.6 vs 110.5 mL/min.

A total of two subjects experienced two AEs, i.e., mild and moderate diarrhea in severely hepatically impaired subjects, which were considered to have a suspected relationship to study medication. According to safety results, single oral dose of gemifloxacin 320 mg seems safe to the subjects with severe hepatic dysfunction. **However, the safety of repeat dose in subjects with severe hepatic dysfunction may need to be addressed separately.** Study 005 in the original submission showed that the higher doses, i.e., 480 and 640 mg, resulted in higher tendency for the increase in LFT compared with 320 mg. Therefore, presumably, higher systemic exposure of gemifloxacin in patients with severe hepatic dysfunction may have greater potential for hepatic toxicity. Unlike pharmacokinetics, safety after repeat dose cannot be extrapolated from data after single dose.

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**3. Is dosage adjustment necessary for patients with CLCr of 40 to 59 mL/min?
(Study 056)**

Because 20 to 40% of gemifloxacin is excreted via kidney, it is important that the dosing regimen for patients with renal impairment is adequately defined. Prior to the present study, the repeat dose pharmacokinetics of 320 mg gemifloxacin in subjects with renal impairment has not been investigated directly. Population pharmacokinetic analysis of data from Phase III studies showed a 40% increase in AUC in patients with CLCr of >40mL/min. Thus, it is proposed that no dose adjustment is required in subjects with CLCr of >40mL/min. In the FDA comments for the original submission of this NDA, the sponsor was requested to investigate the pharmacokinetics of 320 mg gemifloxacin, given once daily in subjects with renal impairment (CLCr = 40-59 mL/min) compared to normal subjects, to confirm the previous findings. This study was designed to address this issue.

This study was conducted to an open label, repeat dose, and parallel group design involving subjects with renal impairment (CLCr = 40-59mL/min) and healthy volunteers. All subjects were administered a single dose of 320 mg gemifloxacin on Day 1 and repeated doses (qd) on Days 3-7.

Table 3 summarizes the pharmacokinetic results of the study. After repeat dose of 320 mg gemifloxacin, subjects with renal impairment (CLCr= 40-59 mL/min) had 70% increase in AUC_{0-inf} compared with normal healthy volunteers, whereas only 14% increase in C_{max}. Half-life was, on average, 2.44 hours longer in subjects with renal impairment relative to normal healthy volunteers. This difference in half-life resulted in ~20 % increase in the observed accumulation ratio (AUC_{0-24(repeat dose)}/AUC_{0-24(single dose)}) in subjects with renal impairment, i.e., 1.22 vs 1.01. Because C_{max} was not significantly changed between normal subjects and subject with renal impairment, the increase in AUC may be mainly due to the reduction in clearance, as evidenced by the increase in terminal T_{1/2} in subjects with renal impairment. T_{max} was not significantly different between subjects with renal impairment and normal healthy volunteers.

Table 3. Pharmacokinetic parameters of gemifloxacin after single and once daily repeat dose of 320 mg tablet to subjects with renal impairment (CLCr = 40-59 mL/min) and to healthy volunteers.

Parameters	Normal (n=16)		Renal impairment (n=17)		P.E. (95% C.I.)	
	Single	Repeat	Single	Repeat	Single	Repeat
AUC _{0-inf} (µg·h/mL) ^a	7.05 (2.71) 3.40-15.0	—	10.4 (2.19) 6.72-15.0		1.53 ^c (1.25, 1.88)	
AUC _{0-24h} (µg·h/mL) ^a	6.16 (1.86) 3.11-10.5	6.04 (1.09) 4.06-7.91	8.45 (1.72) 5.60-12.8	10.3 (2.32) 6.60-15.1		1.70 ^c (1.47, 1.97)
C _{max} (µg/mL) ^a	1.32 (0.64) 0.531-2.99	1.19 (0.3) 0.873-1.98	1.31 (0.32) 0.806-1.87	1.34 (0.27) 0.918-2.10	1.06 ^c (0.82, 1.38)	1.14 ^c (0.97, 1.33)
T _{1/2} (hours) ^a	7.66 (1.81) 5.70-13.1	8.92 (2.04) 2.95-11.4	10.4 (1.55) 8.17-13.8	11.4 (1.43) 9.05-14.3	2.77 ^d (1.58, 3.97)	2.44 ^d (1.19, 3.68)
T _{max} (hours) ^b	1.25 (0.75-2.00)	1.00 (0.50-2.00)	1.02 (0.75-2.00)	1.00 (0.75-2.00)		

^a: Mean (SD) and range, ^b: Median (range), ^c: Ratio of geometric means, ^d: difference of arithmetic means

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In the previous OCPB comments on the original submission, re-analysis of the data from Phase III studies showed that reduction of the gemifloxacin dose to 160 mg Q24 hr for the patients with CLcr <50 mL/min resulted in a more even distribution of the predicted AUC₀₋₂₄ estimates across the entire patient population that was studied, as compared to when dose reduction was at CLcr <40 mL/min. Table 4 shows the comparison of AUC and C_{max} of gemifloxacin in sub-groups split according to the creatinine clearance (40-49 or 50-59 mL/min) with normal healthy subjects. The values of AUC_{0-24h} (repeat dosing) were 66 and 74% higher in 50-59 mL/min and 40-49 mL/min group, respectively, compared with healthy subjects. However, C_{max} was not significantly altered between these two subgroups, as compared to healthy subjects. The increases in AUC estimates between the two subgroups are considered to be similar. In addition, based on the results of the present study, reducing dose by one-half is likely to result in ~50% decrease in C_{max} as well as ~20% decrease in AUC in patients with renal impairment (CLcr = 40-59 mL/min). As commented in the review of Study 059, there was no apparent relationship between gemifloxacin systemic exposure and incidence of certain adverse events, e.g., LFT elevation and skin rash. In addition, individual AUC values in subjects with CLcr of 40-59 mL/min were within the range observed in healthy subjects from Phase I pharmacokinetic studies in the original NDA. Thus, the dosage adjustment does not seem to be necessary for patients with CLcr of >40mL/min. **We recommend CLcr of ≤40 mL/min as a cutoff to reduce gemifloxacin dose by half, i.e., 160 mg, in patients with renal impairment.**

Table 4. Comparisons of AUC between groups (CLcr = 40-49 or 50-59 mL/min)

	Regimen	Comparison	PE	95% CI
AUC _{0-inf}	Single dose	(40-49):Normal	1.58	(1.22,2.06)
		(50-59):Normal	1.49	(1.16,1.91)
AUC ₀₋₂₄	Repeat dose	(40-49):Normal	1.74	(1.45,2.09)
		(50-59):Normal	1.66	(1.39,1.99)
C _{max}	Single dose	(40-49):Normal	1.10	(0.79,1.53)
		(50-59):Normal	1.03	(0.75,1.41)
C _{max}	Repeat dose	(40-49):Normal	1.20	(0.99,1.46)
		(50-59):Normal	1.08	(0.90,1.30)

4. Are there any additional drug-drug interactions with gemifloxacin?

(A) Calcium 1000 mg (Study 024)

Chronic bronchitis patients receiving steroid medication, often require calcium supplements to prevent osteoporosis, as steroids are known to affect bone metabolism. Thus, calcium and gemifloxacin are likely to be co-administered. Calcium is thought to chelate quinolones, thus, its co-administration may reduce the absorption of gemifloxacin. This study was designed to assess the effect of calcium co-administration on the absorption of gemifloxacin, depending on therapeutic time windows in which both drugs can be co-administered without clinically significant effects on absorption of gemifloxacin.

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This study was conducted to an open, randomized, single dose, and four-way crossover design. Subjects received single doses of calcium and gemifloxacin, or gemifloxacin alone on 4 occasions, at least 6 days apart. The dosing regimens were:

- A: Gemifloxacin (320 mg) administered alone
- B: Calcium (1000 mg) administered **2 hours before** gemifloxacin (320 mg)
- C: Calcium (1000 mg) administered **simultaneously** with gemifloxacin (320 mg)
- D: Calcium (1000 mg) administered **2 hours after** gemifloxacin (320 mg)

Subjects were randomized to one of the following treatment sequences, i.e., ABDC, BCAD, CDBA or DACB.

The results are summarized in Table 5. **The co-administration of calcium 2 hours before or after gemifloxacin does not affect AUC and C_{max} of gemifloxacin, whereas the simultaneous administration of calcium with gemifloxacin decreased AUC and C_{max} of gemifloxacin by 21 and 17%, respectively.** Considering the range of individual AUC and C_{max} in Group A (gemifloxacin alone) and Group C (Simultaneous calcium with gemifloxacin), i.e., 3.04-10.2 vs 2.95-8.01 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 0.28-1.99 vs 0.568-1.64 $\mu\text{g}/\text{mL}$ for AUC and C_{max} , respectively, the average reduction of ~20% does not seem clinically significant. Therefore, regardless of time of calcium dosing, co-administration of calcium 1,000 mg does not seem to affect the absorption of gemifloxacin. **Based on these results, the reviewer agrees with the sponsor's proposal; gemifloxacin can be co-administered with products containing up to 1,000 mg calcium.** $T_{1/2}$, T_{max} , and CL_r of gemifloxacin were not significantly changed by the co-administration with calcium 1,000 mg.

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Table 5. Pharmacokinetic parameters after a single oral dose of 320mg gemifloxacin alone or given at various times relative to administration of calcium carbonate to healthy subjects.

	Regimen A Gemifloxacin Alone	Regimen B Calcium given 2 hours before gemifloxacin	Regimen C Calcium given simultaneously with gemifloxacin	Regimen B Calcium given 2 hours after gemifloxacin
AUC _{0-inf} ^a (µg·h/mL)	6.79±2.13 (3.04-10.2)	6.12±1.39 (3.52-7.58)	5.22±1.40 (2.95-8.01)	6.34±1.65 (3.18-9.18)
Comparison of AUC to Regimen A ^c		0.93 (0.78, 1.1)	0.79 (0.66, 0.93)	0.95 (0.8, 1.13)
C _{max} ^a (µg/mL)	1.13±0.41 (0.28-1.99)	1.01±0.26 (0.477-1.479)	0.902±0.287 (0.568-1.64)	1.13±0.39 (0.633-1.90)
Comparison of C _{max} to Regimen A ^c		0.93 (0.71, 1.22)	0.83 (0.63, 1.08)	1.03 (0.79, 1.35)
T _{1/2} ^a (hours)	7.33±2.51 (4.4-15.5)	6.68±1.19 (4.69-8.63)	6.81±1.3 (5.28-9.65)	6.42±1.26 (3.99-8.21)
T _{max} ^b (hours)	1.00 (0.5-2.02)	1.01 (0.52-2.08)	1.00 (1.00-2.00)	1.00 (0.50-2.02)
Ae ₀₋₄₈ ^a (% dose)	17.8±3.7 (12.3-23.2)	16.4±4.9 (7.64-25.3)	15.6±4.5 (8.37-26.9)	19.2±5.1 (10.1-29.8)
CL _r ^a (L/h)	9.00±2.58 (6.07-16.0)	8.59±1.78 (6.08-12.3)	9.86±2.47 (5.22-13.0)	9.99±2.87 (6.45-19.2)

^a: Mean±SD (range); ^b:Median (range); ^c: P.E. (95% CI)

Ten subjects reported a total of 13 adverse experiences during or after the treatment phase of the study, all of which had resolved at the end of the study. Of the 13 treatment emergent adverse experiences, 10 were mild and 3 were of moderate severity. Of these, 11 were suspected to be related to study medication. When the two medications were given simultaneously, there was a higher number of diarrhea (4/16 vs 1/16) which was the most frequently reported AE, compared to gemifloxacin administration alone, 2 hours before or after co-administration with calcium. Because of limited data, it is not clear if a higher incidence of diarrhea when calcium and gemifloxacin were administered simultaneously is clinically significant.

(B) Cimetidine 400 mg qid (Study 077)

Cimetidine is known to inhibit base transport in the proximal tubule and has been shown to inhibit renal secretion and affect reabsorption of some quinolones. The renal clearance of gemifloxacin exceeds the accepted typical value for glomerular filtration (GFR) of 120 ml/min, indicating that active renal secretion is involved in the elimination of gemifloxacin. Hence, inhibition of tubular secretion may increase systemic exposure of gemifloxacin. This study was designed to investigate the effects of cimetidine on the pharmacokinetic profile of a single oral 320 mg dose of gemifloxacin.

This study was conducted as a double blind, randomized, and placebo-controlled two period crossover design in healthy volunteers. Subjects were randomized to one of two treatment sequences, AB or BA, where:

- A: Days 1-7: Cimetidine (400 mg qid);
 Day 5: Gemifloxacin (320 mg single dose).
 B: Days 1-7: Placebo with respect to cimetidine (qid);
 Day 5: Gemifloxacin (320 mg single dose).

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There was a washout period of at least 7 days between each dosing session.

Table 6 summarizes the results. **Administration of cimetidine with gemifloxacin decreased CL_r by 28%, resulting in the increase in AUC_{0-inf} and C_{max} by 10 and 6%, respectively.** Mean terminal T_{1/2} was not significantly affected by cimetidine. Because 20% to 40% of the dose is excreted in urine, the effect on systemic exposure was less than that on CL_r, i.e., 10% increase in AUC vs 28% decrease in CL_r. An approximate 10% increase in systemic exposure of gemifloxacin due to co-administration with cimetidine does not seem clinically significant. Based on these results, **the reviewer agrees with the sponsor's proposal; cimetidine and gemifloxacin can be co-administered without a dosing adjustment of gemifloxacin.**

Table 6. Pharmacokinetic parameters after single oral administration of gemifloxacin 320 mg with cimetidine (400 mg qid for 5 days) or placebo to healthy volunteers (n=20).

	Cimetidine+ Gemifloxacin (A)	Placebo+ Gemifloxacin (B)	P.E. (A:B or A-B)	95% C.I.
AUC _{0-inf} (µg·h/mL) ^a	5.68±1.87 (3.09-9.95)	5.18±1.67 (2.57-8.10)	1.10 ^c	(0.96, 1.25)
C _{max} (µg/mL) ^a	0.849±0.299 (0.435-1.53)	0.796±0.259 (0.332-1.28)	1.06 ^c	(0.94-1.20)
T _{1/2} (hours) ^a	7.81±1.26 (5.53-10.7)	7.06±1.32 (5.12-9.92)	0.75 h ^d	(-0.14h, 1.64h)
T _{max} (hours) ^b	1.50 (0.98-2.05)	1.50 (0.50-3.00)	-0.01 h ^d	(-0.51h, 0.30h)
Ae ₇₂ (% dose) ^{a,c}	22.8±5.45 (12.6-31.4)	28.4±4.76 (17.3-36.2)	-5.58% ^d	(-8.4%, -2.76%)
CL _r (L/h) ^{a,c}	13.7±3.31 (9.29-22.0)	19.0±5.29 (11.3-30.3)	0.72 ^c	(0.65, 0.81)

^a: Mean±SD, range; ^b:Median, range; ^c: A:B; ^d:A-B; ^e:n=19

A. Biopharmaceutical Issues

1. Does the difference in dissolution rate affect the bioavailability of gemifloxacin in vivo? (Study 033)

In the original submission of this NDA, the sponsor proposed a dissolution specification of Q=——(NLT 75% of label claim released). The previous OCPB reviewer, Dr. Phil

Colangelo, recommended to change this dissolution specification to Q=—% (of label claim released), based on the dissolution data that was provided by the sponsor. This study was conducted to investigate if the differences in dissolution rate affect the *in vivo* bioavailability of gemifloxacin.

This study was conducted to an open label, randomized, two-treatment, four-period, replicated crossover design in healthy male and female volunteers. Each volunteer participated in four sessions and was administered, in a randomized order, one single oral dose of 320 mg gemifloxacin of either batch with differing dissolution profiles, i.e., **Batch A (—% release at 30 minutes)** and **Batch B (—% release at 30 minutes)**. Each subject received each batch twice on separate dosing sessions.

The results are summarized in Table 7. The 90% confidence intervals for the ratio of adjusted geometric means for the primary endpoints AUC_{0-inf} and C_{max} for gemifloxacin were completely contained within the equivalence range of 0.80 to 1.25, indicating that the two formulations are bioequivalent. On average, gemifloxacin T_{max} was similar for both formulations. The results suggest that the difference in dissolution rate does not affect *in vivo* bioavailability of gemifloxacin. **Since the results of this study demonstrated the *in vivo* bioequivalence of two batches of the commercial formulation tablet of gemifloxacin with differing dissolution profiles, i.e. —% vs —% dissolution at 30 min, the dissolution specification of Q=—% (NLT —% dissolution), originally proposed by the sponsor, is considered to be acceptable.**

Table 7. Pharmacokinetic parameters after administration of two batches of the commercial formulation of gemifloxacin (320 mg) with different dissolution profiles, given on separate dosing days. Batch A: — at 30 min, Batch B: — at 30 min.

	C_{max} ($\mu\text{g/mL}$) ^a	T_{max} (h) ^b	AUC ($\mu\text{g}\cdot\text{h/mL}$) ^a	$T_{1/2}$ (h) ^a
Batch A (Dose 1) (n=22)	0.898±0.291 0.444-1.684	1.00 0.75-2.05	5.62±1.51 2.66-8.68	6.66±1.06 5.17-8.92
Batch A (Dose 2) (n=19)	0.847±0.220 0.473-1.219	1.50 0.73-2.98	5.64±1.48 3.36-8.67	6.46±1.06 4.88-8.51
Combined ^c	0.853±0.226 0.559-1.326	1.26 0.75-2.00	5.49±1.43 2.99-8.07	6.55±0.99 4.88-8.92
Batch B (Dose 1) (n=22)	0.905±0.245 0.459-1.363	1.03 0.75-3.10	5.70±1.47 3.15-8.28	6.51±0.95 5.29-8.64
Batch B (Dose 2) (n=19)	0.882±0.343 0.319-1.649	1.02 0.75-3.02	5.74±1.96 2.33-9.75	6.45±1.13 5.03-8.72
Combined	0.883±0.263 0.415-1.46	1.26 0.75-3.00	5.57±1.45 2.71-8.98	6.45±0.97 5.07-8.61
P.E.	1.02 ^d	-0.06 ^e	1.01 ^d	
90% C.I.	(0.91, 1.15)	(-0.24, 0.19)	(0.91, 1.09)	

^a: Mean±SD, range; ^b: Median, range; ^c: Average of geometric means of two doses; ^d: ratio of adjusted geometric means; ^e: median difference between formulations

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2. Absolute bioavailability of pediatric suspension of gemifloxacin (Study 114)

A new suspension formulation was developed for adults having difficulty in swallowing the tablet and for pediatric patients. This is the first study to administer this suspension formulation to humans. On the other hand, data from different clinical studies showed similar systemic exposures after 250 mg intravenous (iv) and 320 mg oral administration. The objectives of this study were two-fold; (a) to investigate the absolute bioavailability of pediatric suspension of gemifloxacin compared with that of oral tablet and (b) to assess pharmacokinetic equivalence between the 250 mg iv dose and 320 mg oral tablet in the same subjects. The sponsor expected to use the 320 mg oral safety database in support of the iv formulation.

This study was an open-labeled, randomized, single dose, three-session crossover study in healthy male and female volunteers. Each volunteer participated in three sessions and was administered a single gemifloxacin dose of either tablet, intravenous or suspension formulations in each session. An interval of at least 5 days separated each of the three sessions. The following treatments were administered:

- 320mg gemifloxacin pediatric suspension administered orally in 10mL solution
- 320mg gemifloxacin tablet taken orally
- 250mg gemifloxacin intravenously infused over 1 hour

The results are summarized in Table 8. The absolute bioavailability was 49 and 61% for pediatric suspension and oral tablet, respectively. For both formulations, the individual maximum plasma gemifloxacin concentration was observed between 0.5 and 2 hours after administration. The 90% confidence interval for AUC_{0-inf} and C_{max} did not completely fall within the range 0.80-1.25 and, hence, the equivalence criteria have not been met between iv formulation and oral tablet. The terminal half-lives of gemifloxacin were independent of formulation and dose route.

Unlike the sponsor's intention to use safety database of 320 mg oral tablet in support of the intravenous formulation, the pharmacokinetics of the 250 mg intravenous dose was not equivalent with that of the 320 mg oral tablet. Based on the bioavailability of the oral tablet in the present study, i.e., 60%, an intravenous dose of 200 mg (0.6×320 mg = 192mg) is recommended to be tested if the sponsor plans to develop the intravenous formulation of gemifloxacin using the safety database of oral tablet.

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Table 8. Pharmacokinetic parameters of gemifloxacin after single administration of pediatric suspension 320 mg, tablet formulation 320 mg and intravenous formulation 250 mg (n=23).

	Suspension (320 mg)	Tablet (320 mg)	i.v. (250 mg)
AUC _{0-inf} (µg·h/mL) ^a	5.38±1.68 2.76-9.25	6.78±2.06 3.77-13.13	8.60±1.90 5.94-13.81
C _{max} (µg/mL) ^a	0.755±0.204 0.453-1.11	1.03±0.24 0.483-1.587	1.57±0.34 0.893-2.123
T _{max} (h) ^b	1.00 0.52-1.50	1.00 0.52-2.02	1.00 0.75-1.08
T _{1/2} (h) ^a	7.58±1.66 5.44-13.1	8.21±2.26 5.32-13.3	8.33±2.16 5.13-12.0
CL (L/h) ^a			30.3±6.0 18.1-42.1
V _{ss} (L/kg) ^a			3.52±0.56 2.49-4.41
F (%) ^a	48.5±10.1 31.6-65.1	61.3±10.1 40.9-80.8	

^a: Mean±SD, range; ^b: median, range

The intravenous administration of gemifloxacin (250mg) was associated with mild or moderate pain in the infusion arm during and post infusion in the majority of subjects (16 of 24). Gemifloxacin 320mg suspension formulation was variable in the acceptability of its taste, and left a bitter aftertaste in some subjects (4 of 24).

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Appendix 1

Proposed Labeling with OCPB Reviewer Revision

NDA-21-158: Factive™

(Gemifloxacin mesylate; SB-265805)

Version: March 26, 2003

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42 Pages have been redacted in full
from this document

Reason:

_____ b(2) 'low'

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Attorney Client and Attorney Work
Product Privilege

_____ b(6) Personal Privacy

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Appendix 2
Individual study Review
NDA-21-158 Factive™
(Gemifloxacin mesylate; SB-265805)

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1. Study 344: A two part study to characterize the histology and clinical features of rash associated with gemifloxacin and to assess the potential for cross-sensitization to another quinolone in healthy female volunteers.

This study was reviewed by OPPB pharmacometric reviewer, Dr. Jenny J. Zheng.

Study 344 was designed to assess the association of rash with gemifloxacin exposure and the potential for cross sensitization to another quinolone in healthy female volunteers. To estimate exposure of gemifloxacin and its metabolite, N-acetyl gemifloxacin, in the individual subject, sparse plasma samples were collected in the trial and a population pharmacokinetic analysis (PPK) was conducted. Using estimated exposure obtained from PPK analysis, the association between individual exposure to gemifloxacin or N-acetyl gemifloxacin and the occurrence of rash was examined.

A total of 7943 gemifloxacin plasma concentrations from 838 subjects and 7934 N-acetyl gemifloxacin plasma concentrations from 837 subjects were used in the final population pharmacokinetic analysis. Plasma concentration-time data were analyzed separately for gemifloxacin and N-acetyl gemifloxacin, respectively, using NONMEM. A 2-compartment model with first order absorption was used to describe the pharmacokinetic for both gemifloxacin and N-acetyl gemifloxacin.

The PPK analysis indicated that the body weight was the only covariate that affected the CL of gemifloxacin. The estimated total clearance of gemifloxacin for a subject with body weight of 64.3 kg was 38.9 L/h, which was similar to the findings from the other studies (see Dr. Dan Wang's review as an appendix in Dr. Philip Colangelo's review). The Bayesian predicted mean AUC_{0-24} of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 8.98 $\mu\text{g}\cdot\text{h}/\text{mL}$ with the standard deviation of 2.12, and ranged from 4.23 to 19.12 $\mu\text{g}\cdot\text{h}/\text{mL}$. The mean C_{max} of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 1.261 $\mu\text{g}/\text{mL}$ with the standard deviation of 0.235 and ranged from 0.668 to 2.747 $\mu\text{g}/\text{mL}$. The estimate of N-acetyl gemifloxacin was based on the assumption that the oral bioavailability (F) of the input dose encompasses metabolic conversion and remains constant during the dosing period and the scaling of central compartment concentrations (S2) includes a stoichiometric correction factor of 1.107 to account for the N-acetylation of gemifloxacin. Due to the above assumptions the primary pharmacokinetic parameters, clearance (CL/F) and volume of distribution (V/F) are apparent and should not be used in a different population or in different models. The examinations on the individual fit of N-acetyl gemifloxacin showed that the model reasonably described the concentration vs time profile of day 1 but not day 6. Therefore, it is reasonable to compare N-acetyl gemifloxacin exposure of day 1 between individuals.

The relationship between gemifloxacin or N-acetyl gemifloxacin exposure and the occurrence of rash was assessed graphically. The exposures included AUC_{0-24} and C_{max} of gemifloxacin and N-acetyl gemifloxacin at day 1, the ratio of AUC_{0-24} for gemifloxacin and AUC_{0-24} for N-acetyl gemifloxacin. The results showed that it appeared that the

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exposure to gemifloxacin or N-acetyl gemifloxacin in the subjects who experienced rash were similar to the subjects who did not experience rash. A logistic regression analysis was conducted by the reviewer and the results showed that there is no statistically significant association between exposure to gemifloxacin or N-acetyl gemifloxacin and the occurrence of rash.

In conclusion, the PPK analysis was acceptable. However, no association between gemifloxacin or N-acetyl gemifloxacin exposure and the occurrence of rash was found in this study. However, cautions need to be taken to interpret the results from this study. Firstly, only one dose level was studied in the study, which limited the power of detecting any exposure response relationship. On the other hand, the occurrence of rash might be immunological reaction that may require the presence of drug but not necessarily is dose related.

RECOMMENDATION:

The population pharmacokinetic analysis is acceptable. However, a definitive conclusion that the occurrence of rash is not dose-related can not be made from this study because only one dose level was used in the study, which limit the power of detecting any dose response relationship.

Objective:

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

Study design:

This study was performed in two parts. Both Part A and Part B were conducted to a double-blind, double-dummy, repeat dose design with Part B only being placebo-controlled. There was a washout period of 4-6 weeks from the last doses administered in Part A. A final follow-up was performed 7-14 days after dosing.

Part A: Each subject participated in one repeat dose session and was administered a single 320 mg dose (one tablet) of gemifloxacin once daily in the morning or a single dose of 500 mg ciprofloxacin (2 x 250 mg capsules) twice daily for a maximum of 10 days, or until a rash was reported. Subjects were randomized to receive gemifloxacin or ciprofloxacin in a 5:1 ratio. A double dummy technique was used to blind the study. Ciprofloxacin tablets were over-encapsulated to ensure blinding. Subjects in whom rash was reported underwent skin biopsies, standardized photographic assessment, dermatological and clinical examinations, blood sampling for immunoglobulin levels, drug levels, liver function tests, eosinophils, Epstein-Barr virus (EBV) serology and urine sampling for eosinophils. Individuals who reported rash stopped dosing with study

medication until enrolled in Part B of the study. All subjects with gemifloxacin-associated rash in Part A were expected to take part in Part B of this protocol, with the exception of those with Type I (bronchospasm, angioedema, early onset etc) or other severe reactions (extensive, associated with systemic symptoms, abnormal labs, mucosal involvement etc). An interim follow-up examination was conducted within 7 to 14 days of completion of dosing of Part A.

Part B: Subjects commenced Part B four to six weeks after their last dose in Part A. Depending on their Part A treatment allocation and occurrence of rash (see below) each subject entering Part B was randomized (in a double blind fashion) to receive 10 days dosing of either 320 mg gemifloxacin once daily in the morning or 500 mg ciprofloxacin bid or placebo. Dosing was discontinued if rash occurred and the same procedures as in Part A were conducted. A final follow-up examination was conducted 7-14 days after completion of the final dosing day in Part B.

Sampling: Blood samples for pharmacokinetic analysis (approximately 5 mL) were collected in Part A only on Days 1 and 6 at the following nominal times:
Odd numbered subjects: - pre-dose and at 1.5, 3, 6 and 12 h following dosing in Part A only.

Even numbered subjects: at 1, 2, 4, 8 and 24 h (i.e. pre-dose on Days 2 and 7) following dosing in Part A only.

Part A, Day 6 pharmacokinetic procedures may have been performed on Day 7, if subject availability deemed that they could not attend an entire pharmacokinetic assessment day. All efforts should have been made to perform the pharmacokinetic day on Day 6, however this was implemented at the Investigators discretion.

Additional blood samples for measurement of drug levels were taken as soon as possible after reporting in all subjects who experienced rash in either Part of the study.

Analysis Method:

Data preparation:

Non-quantifiable (NQ) data was set to the half the LLQ (i.e. $\frac{1}{2}$ $\mu\text{g/mL}$). NQ concentrations comprised approximately 0.2% and 14% of the final dataset for parent and metabolite, respectively.

The criteria for accepting a NONMEM model included: (i) convergence of the objective function, (ii) standard error of estimates not larger than half the estimates, (iii) number of significant digits at least equal to 3, (iv) termination of the covariance step without warning messages, (v) correlation between model parameters < 0.95 , (vi) all gradients at the last iteration no greater than 10.

Goodness of fit was assessed by graphical methods based on predicted parameters, residuals and weighted residuals.

Structure Model:

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A compartmental model is chosen which is based on prior knowledge of the pharmacokinetics of the drug.

Statistical model:

Pharmacokinetic parameters were assumed to be log normally distributed and characterized by a constant coefficient of variation error model.

$$\theta_i = \theta * \text{EXP}(\eta_{i\theta})$$

where $\eta_{i\theta}$. represents the proportional difference between the typical parameter value in the population θ and the parameter value for the subject i , θ_i . The η s are normally distributed random variables with a mean zero and variance ω^2 .

The residual error was modeled by the combination of both additive and an exponential component (homoscedastic/heteroscedastic model).

$$C_p = F * \text{EXP}(\epsilon_1) + \epsilon_2$$

where C_p is the observed drug concentration, F is the predicted concentration and ϵ represents the difference in the log domain between the two values. The distribution of ϵ s is assumed to be normal, with a mean of zero and variance of σ^2 . The additive component of the residual error model was used to account for observations near the lower limit of detection of the assay.

Both the first order estimation (FO) and the first order with conditional estimation (FOCE) methods were examined during the modeling approach. *A priori* estimation of interindividual variability, as determined with FOCE was not feasible with the current dataset. All evaluations were therefore performed with the first order estimation method (FO).

MODEL 1: Parent Drug

Gemifloxacin absorption followed a first order process and was characterized by a lag-time (ALAG1) and a first order absorption rate constant (k_a).

MODEL 2: Metabolite

The numerous attempts to simultaneously model metabolite concentrations in conjunction with gemifloxacin were not successful. A purely descriptive model was used to characterize the concentration-time course of N-acetyl gemifloxacin in the study population. The modeling approach was therefore based on the following assumptions:

- The oral bioavailability fraction (F) of the input dose encompasses metabolic conversion and remains constant during the dosing period.
- Scaling of central compartment concentrations (S_2) includes a stoichiometric correction factor of 1.107 to account for the N-acetylation of gemifloxacin.
- The primary pharmacokinetic parameters, clearance (CL/F) and volume of distribution (V/F) are apparent and should not be used in a different population or in different models.

- k_a reflects the rate of appearance of the metabolite in plasma. This rate constant is also apparent since metabolic conversion (extent and rate) is unknown.

Covariate test:

Essentially the effect of height, weight, age, ethnic origin, and contraceptive drug therapy were assessed on clearance and volume of distribution. The covariate was remained in the model if the changes of objective function value was >7.88 after incorporation of the covariate into the model.

Individual Pharmacokinetic Estimates

Individual pharmacokinetic parameter estimates were obtained by *post-hoc* Bayesian approach (POSTHOC). Subsequently, a pharmacokinetic simulation was performed with NONMEM, using the SIMULATION command to generate individual peak concentrations for each subject.

Pharmacokinetic parameters have been listed as arithmetic mean, standard deviation (SD), minimum (min), median and maximum (max). In addition, the geometric mean, between subject-variability and the corresponding 95% confidence intervals were calculated where:

$$\begin{aligned} \text{geometric mean} &= \exp(\text{mean on loge scale}) \\ \text{between-subject CV} &= \text{SQRT}[\exp(\text{SD on loge scale})^2 - 1] \times 100 \end{aligned}$$

Possible Pharmacokinetic/Adverse Event Exploratory Analysis:

Exploratory analyses were to be conducted to investigate whether any relationship existed between occurrence of rash and the N-acetyl metabolite of gemifloxacin and/or acetylator status based on DNA variation from specific NAT genotype assessments. A similar exploratory analysis was also to be conducted for parent gemifloxacin.

Results:

A summary of the demographic data for the 840 subjects included in the population pharmacokinetic analysis is presented in Table 1.

As the pharmacokinetics of parent drug and metabolite could not be fitted simultaneously, concentration data were analyzed separately. The final datasets for gemifloxacin and N-acetyl gemifloxacin included therefore data from 838 and 837 subjects, respectively.

A total of 7943 and 7934 plasma concentration-time data, respectively for gemifloxacin and N-acetyl gemifloxacin, were used in the final population pharmacokinetic analysis.

62 observations from 34 subjects were removed from the initial gemifloxacin data set because they were found to cause the iteration process to be aborted or precluded adequate minimization. These observations represented approximately 0.78% of the evaluable concentration data, but had marked effect on objective function values and on

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the magnitude of residuals (weight residuals >6 or < -6). Most of these samples were pre-dose samples (trough concentrations),

Due to the larger number of concentrations of N-acetyl gemifloxacin below the limit of quantification at pre-dose sampling time, only 3 corresponding observations were actually excluded from the initial data set for the analysis of the metabolite.

The population pharmacokinetic parameters for gemifloxacin for the final model are presented in Table 2. It showed that absorption is rapid with the rate constant of 0.371 h⁻¹. However, the intersubject variability was also high. Body weight was the only covariate that showed a relevant effect on the estimates of clearance. None of the demographic covariates showed relevant effect on the apparent volume of distribution. The population clearance (CL) was 38.9 L/h for the subject with bodyweight of 63.4 kg. The CV% of CL between subjects was approximately 23%. The central volume of distribution (V₂) was 230 L, with an inter-individual variability of 24%. The data also allowed inter-individual variability in peripheral volume (101 L) to be estimated (143%). Inter-compartmental clearance was 6.76 L/h. The individual pharmacokinetic parameter was obtained by *post-hoc* Bayesian approach and the summary of the parameters was presented in Table 3. The Bayesian predicted mean AUC(0-24) of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 8.98 $\mu\text{g}\cdot\text{h}/\text{mL}$ with the standard deviation of 2.12, and ranged from 4.23 to 19.12 $\mu\text{g}\cdot\text{h}/\text{mL}$. The mean C_{max} of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 1.261 $\mu\text{g}/\text{mL}$ with the standard deviation of 0.235 and ranged from 0.668 to 2.747 $\mu\text{g}/\text{mL}$.

The goodness of fit is presented in Figure 1. It shows that the population PK model does not predict well for some of the observed concentration. However, the individual *post-hoc* predictions were comparable to the observed concentrations.

The pharmacokinetic parameters for N-acetyl gemifloxacin are presented in Table 4. In this analysis, the N-acetyl gemifloxacin was modeled independently from the parent compound, gemifloxacin. The fraction of gemifloxacin that converted to N-acetyl gemifloxacin and the rate constant of the conversion were not known. The estimated K_a for this metabolite was a hybrid parameter for both absorption rate constant of gemifloxacin and the conversion rate constant of gemifloxacin to N-acetyl gemifloxacin. Similarly, the estimated F is a hybrid parameter that represented both the fraction of absorption of gemifloxacin and the fraction of gemifloxacin that converted to N-acetyl gemifloxacin. Therefore, the estimated parameters for the metabolite can not be interpreted. However, the examination of the individual *post hoc* fit of the metabolite indicated that the individual fit appears reasonable. The summaries of the individual pharmacokinetic parameters are presented in Table 5. The Bayesian predicted mean AUC(0-24) of N-acetyl gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 1.472 $\mu\text{g}\cdot\text{h}/\text{mL}$ with the standard deviation of 3.51, and ranged from 0.114 to 58.44 $\mu\text{g}\cdot\text{h}/\text{mL}$. The mean C_{max} of N-acetyl gemifloxacin at day 1 after oral administration of 320 mg gemifloxacin was 0.164 $\mu\text{g}/\text{mL}$ with the standard deviation of 0.151 and ranged from 0.027 to 0.886 $\mu\text{g}/\text{mL}$. The mean C_{max} of N-acetyl

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gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin was 0.183 $\mu\text{g/mL}$ with the standard deviation of 0.224 and ranged from 0.028 to 3.014 $\mu\text{g/mL}$. For majority of the subjects, the predicted C_{max} for the metabolite is similar between day 1 and day 5. The examination of individual fit for the metabolite found that in 5 subjects the samples were collected only after the single dose at day 1 but no samples were collected on day 6. The predicted C_{max} at day 6 in these six subjects were higher than 0.8 $\mu\text{g/mL}$. It is believed that the predicted C_{max} at day 1 is more reliable than the C_{max} at Day 6.

The goodness of fit for N-acetyl gemifloxacin model is presented in Figure 2. It shows that a significant bias existed in the population PK model. However, the observed concentrations were in reasonable agreement with the predicted individual post-hoc predictions.

The pharmacokinetic exposure parameters of gemifloxacin and N-acetyl gemifloxacin in subjects who experienced rash did not differ from those without rash. The summary statistics for these parameters are presented separately for subjects with and without rash in Table 6 and Table 7 and represented graphically as box and whisker plots in Figure 3.

N-acetyl transferase type 2 (NAT2) mediates the formation of N-acetyl gemifloxacin and NAT2 shows diverse human variation in enzyme function ranging from slow to fast. However, NAT2 status was only available in approximately 64% of the subjects included in the population pharmacokinetic analysis and has therefore, not been formally evaluated in the pharmacokinetic model. The ratio between the AUC of the metabolite and parent compound ($\text{AUC}_{\text{met}}/\text{AUC}_{\text{par}}$) was used to identify potential differences between poor and fast metabolisers in terms of sensitivity to gemifloxacin. The AUC ratio was similar in subjects with and without rash. These results are summarized in Table 8 and presented as a box and whisker plot in Figure 4. The results showed that there is no association between the ratio of AUC_{met} to AUC_{par} and the occurrence of rash.

Conclusion:

- In general the PPK analysis is acceptable. The estimated CL, 38.9L/h, for gemifloxacin is in reasonable agreement with the CL obtained from previous study. The Bayesian predicted mean $\text{AUC}(0-24)$ of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 8.98 $\mu\text{g}\cdot\text{h/mL}$ with the standard deviation of 2.12, and ranged from 4.23 to 19.12 $\mu\text{g}\cdot\text{h/mL}$. The mean C_{max} of gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 1.261 $\mu\text{g/mL}$ with the standard deviation of 0.235 and ranged from 0.668 to 2.747 $\mu\text{g/mL}$.
- The estimated pharmacokinetic parameters for N-acetyl gemifloxacin are not interpretable. However, the inspection on the individual goodness of fit for data collected on day 1 showed that the fit was reasonable. The estimated AUC value for each individual is acceptable. The Bayesian predicted mean $\text{AUC}(0-24)$ of N-acetyl gemifloxacin at day 6 after oral administration of 320 mg gemifloxacin once daily was 1.472 $\mu\text{g}\cdot\text{h/mL}$ with the standard deviation of 3.51, and ranged from 0.114 to 58.44 $\mu\text{g}\cdot\text{h/mL}$. The mean C_{max} of N-acetyl gemifloxacin at day 1 after oral

administration of 320 mg gemifloxacin was 0.164 $\mu\text{g/mL}$ with the standard deviation of 0.151 and ranged from 0.027 to 0.886 $\mu\text{g/mL}$.

- There is no association between gemifloxacin exposure and the occurrence of rash.
- There is no association between N-acetyl gemifloxacin exposure and the occurrence of rash.
- There is no association between the ratio of N-acetyl gemifloxacin to gemifloxacin and the occurrence of rash.

Comments:

1. The pharmacokinetic of N-acetyl gemifloxacin is pure descriptive. The estimated pharmacokinetic parameters are not interpretable. Since the goodness of fit for individual data was reasonable, the AUC estimate of N-acetyl gemifloxacin was acceptable for exposure comparison between subjects.
2. Only one dose level was studied in the study, which limited the power of detecting any exposure response relationship.
3. The occurrence of rash might be immunological reaction that may require the presence of drug but not necessarily is dose related.

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2. **Study 059: A study to compare the pharmacokinetics of gemifloxacin following a single oral dose of 320 mg to healthy subjects and subjects with severe hepatic impairment**

NDA Vol. 6.012 – 6.014, pp 1-489

A previous study from the original NDA showed that subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment administered 320 mg gemifloxacin had, on average, ~30% and ~20% increases in gemifloxacin AUC_{0-inf} and C_{max} , respectively, compared to normal healthy subjects. The present study was designed to investigate the safety and pharmacokinetics of gemifloxacin in healthy subjects and subjects with severe hepatic impairment (Child-Pugh C) following a single oral dose of 320 mg, in order to determine dosing recommendations for this group of subjects. The linear, i.e., time-independent, pharmacokinetics of gemifloxacin was expected to permit extrapolation of single dose data to repeat doses. The results showed ~45% increase in AUC_{0-inf} in subjects with severe hepatic dysfunction (Child-Pugh C) compared with normal subjects. This difference is not considered to be significant based on overall similarity in the range of the individual AUC and C_{max} values between the severe hepatic impairment subjects and healthy subjects from Phase I pharmacokinetic studies in the original NDA. In addition, there was no apparent relationship between gemifloxacin systemic exposure and incidence of certain adverse events, e.g., LFT elevation from the original submission and skin rash from this resubmission. Thus, dosage adjustment would not be necessary in patients with severe hepatic impairment.

Study date:

The first subject was screened on 28 March 2000. The first dose of study medication was administered on 3 April 2000 and the final dose was administered on 12 May 2000. The last study visit was on the 22 May 2000.

Objectives:

- (a) To investigate the effect of severe hepatic impairment on the pharmacokinetics of a single oral dose of 320 mg gemifloxacin.
- (b) To assess the safety and tolerability of a single oral dose of 320 mg gemifloxacin in subjects with severe hepatic impairment.

Study Design:

This study was an open-label and parallel-group study. All subjects were classified at screening, within 7 days of dosing, into two groups; either healthy subjects or subjects with severe hepatic impairment according to Child's criteria with Pugh's modification (Category C). All subjects received a single oral dose of 320 mg gemifloxacin (Batch number: N99116) in the fasted state. Subjects with severe hepatic impairment were permitted to take their routine medication until the night prior to the study day (before midnight). A light breakfast was provided to all subjects at 2 hours after dosing.

Study Population and Demographic Data:

Ten healthy subjects and 10 subjects with severe hepatic impairment (Child-Pugh C patients) were to be recruited to this study. An effort was made to include approximately 50% alcoholic cirrhotic patients in the hepatically impaired subject population. Some degree of renal impairment may be concomitant with severe hepatic disease. In addition, the previous study showed that mild renal impairment has been shown not to have clinically important effects on gemifloxacin pharmacokinetics. Therefore, subjects whose CrCL is >50 ml/min were included in the study. Based on a 12 lead ECG at the pre-study, subjects with prolonged QTc were to be excluded (>450 msec for men or >470 msec for women). Key demographic data for all 20 subjects are shown in Table 1.

Table 1. Demographic data

Group	Parameter	Age (years)	Weight (kg)	Height (cm)	Sex/Race
Severe Hepatic	n	10	10	10	70% male
	Mean	53	83.4	175	30% female
	SD	3.90	16.52	8.40	100% white
	Range	45-58	61.5-109.0	161-183	
Healthy	n	10	10	10	70% male
	Mean	48	78.5	173	30% female
	SD	3.50	15.60	13.50	100% white
	Range	42-54	58.0-97.5	155-196	
All Subjects	n	20	20	20	70% male
	Mean	51	80.9	174	30% female
	SD	4.30	15.84	10.90	100% white
	Range	42-58	58.0-109.0	155-196	

Reviewer's comment: The healthy subject group and severely hepatically impaired subject group were well matched in terms of age (ideally ± 10 years), weight, sex and race.

Safety Parameters:

Adverse event (AE) information was taken by standard 'non-leading' questioning pre-dose and at 12, 24 and 48 hours post-dose, and follow-up. **Vital signs and Electrocardiogram (ECG)** were measured pre-study, pre-dose (3 baseline ECG recordings) and then at 1, 2 and 24 hours post-dose, and at follow-up. Blood and urine samples for **hematology, clinical chemistry and urinalysis** were collected pre-study, pre-dose and at follow-up. A routine drug screen for **undeclared drugs** was conducted on 50 mL urine samples collected at screening and pre-dose. A routine **alcohol breath test** was performed at screening and pre-dose to test for the presence of alcohol. Urine samples (first void of the day) were collected from female subjects at screening, pre-dose and at follow-up for **pregnancy testing**.

Pharmacokinetic Parameters:

Blood samples (approximately 3 mL) were taken pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hour after dosing. Plasma samples were assayed for gemifloxacin using a method based on _____ by the _____

The samples

were analyzed by _____ employing _____ with a lower limit of quantification of _____ using a 50 μ L aliquot. The assay was linear with the range of _____. The within and between-run precisions were acceptable _____.

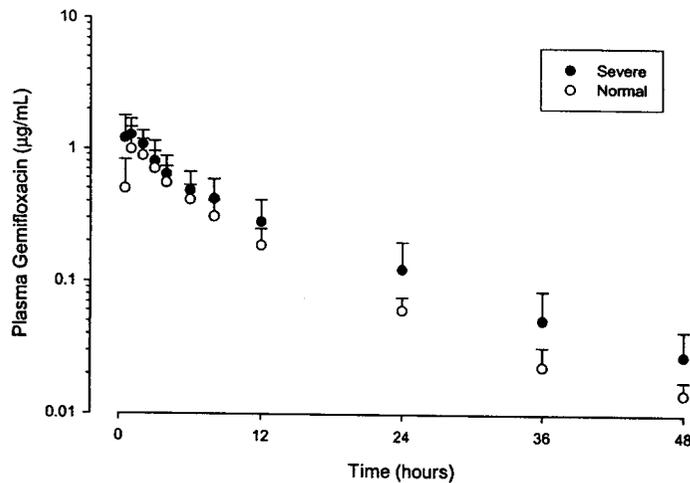
Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}), and the apparent terminal half-life ($T_{1/2}$).

Statistical Methods:

Log-transformed AUC and C_{max} of gemifloxacin were analyzed by ANOVA. Point estimates and 90% confidence intervals for the ratio of subjects with severe hepatic dysfunction to healthy normal volunteers were derived.

Pharmacokinetic Results:

Mean plasma concentration of gemifloxacin and its relevant pharmacokinetic parameters after administration of 320 mg oral tablet to healthy subjects and subjects with severe hepatic dysfunction are shown in Figure 1 and Table 2, respectively. Subjects with severe hepatic dysfunction had, on average, 45% and 41% increases in AUC_{0-inf} and C_{max} , respectively, relative to normal healthy volunteers. Half-life was, on average, 1.61 hours longer in subjects with severe hepatic impairment relative to normal healthy volunteers.



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Figure 1. Plasma concentration of gemifloxacin after oral administration of 320 mg tablet to healthy subjects (n=10) and subjects with severe hepatic dysfunction (Child Pugh C) (n=10). Bars represent standard deviation.

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Table 2. Pharmacokinetic parameters of gemifloxacin after administration of 320 mg oral tablet in normal healthy subjects (Normal) and subjects with severe hepatic dysfunction (Severe).

Parameters	Normal	Severe	P.E. (Severe:Normal)	95% C.I.
AUC _{0-inf} (µg·h/mL)	7.62±2.19 (4.97-12.0) ^a	11.3±4.63 (6.86-22.1) ^a	1.45 ^c	(1.08, 1.94)
C _{max} (µg/mL)	1.08±0.42 (0.468-2.00) ^a	1.47±0.41 (0.857-2.08) ^a	1.41 ^c	(1.02, 1.95)
T _{1/2} (hours)	8.06±1.37 (5.84-10.2) ^a	9.68±1.24 (7.59-11.4) ^a	1.61 ^d	(0.39, 2.84)
T _{max} (hours)	1.00 (1-3) ^b	1.00 (0.5-2) ^b	-0.5 ^e	(-1.00, 0.00)

^a: Mean±SD (range), ^b: Median (range), ^c: Ratio of geometric means, ^d: difference of arithmetic means, ^e: median difference

Reviewer's comment: The 40 to 45% increases in the mean systemic exposure is not considered to be significant based on overall similarity in the range of the individual AUC and C_{max} values between the severe hepatic impairment subjects and healthy subjects from Phase I pharmacokinetic studies in the original NDA. In addition, there was no apparent relationship between gemifloxacin systemic exposure and incidence of certain adverse events, e.g., LFT elevation from the original NDA and skin rash from this resubmission. Thus, dosage adjustment would not be necessary in patients with severe hepatic impairment. However, it should be noted that the increases in several individual subjects were much greater than the average changes. For example, AUC_{0-inf} in subjects 204 (16.94 µg·h/mL) and 210 (22.1 µg·h/mL), who had severe hepatic dysfunction, were ~2- and ~3- fold higher than the average AUC in normal subjects, respectively. This inter-individual difference among subjects with severe hepatic dysfunction may be due to other factors such as renal function. Note that the creatinine clearance in subject 210 was significantly lower than the average value, i.e., 74.6 vs 110.5 mL/min.

Safety Results:

A total of two subjects experienced two AEs, i.e., mild and moderate diarrhea in severely hepatically impaired subjects, which were considered to have a suspected relationship to study medication. There were no changes in vital signs and the electronic and manual ECG data.

Reviewer's comment: According to safety results, single oral dose of gemifloxacin 320 mg seems safe to the subjects with severe hepatic dysfunction. However, the safety of repeat dose in subjects with severe hepatic dysfunction should be addressed separately. Study 005 in the original submission showed that the higher doses, i.e., 480 and 640 mg, resulted in higher tendency for the increase in LFT compared with 320 mg. Therefore, presumably, higher systemic exposure of gemifloxacin in patients with severe hepatic dysfunction may have greater potential for hepatic toxicity. Unlike pharmacokinetics, safety after repeat dose cannot be extrapolated from data after single dose.

Conclusions:

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1. AUC_{0-inf} and C_{max} for gemifloxacin were 40 - 45% higher, on average in subjects with severe hepatic impairment, when compared to healthy subjects. Dosage adjustment may not be necessary in patients with severe hepatic impairment, as the sponsor suggested.
2. The single oral dose of gemifloxacin 320 mg seems safe to the subjects with severe hepatic dysfunction. However, the safety of gemifloxacin after repeat dose remains unanswered.

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3. **Study 056:** A study to compare the pharmacokinetics of gemifloxacin following repeat doses of 320mg gemifloxacin in subjects with renal impairment (creatinine clearance 40-59mL/min) and healthy volunteers

NDA Vol. 6.007 – 6.011, pp 1-1195

Because 20 to 40% of gemifloxacin is excreted via kidney, it is important that dosing regimen for patients with renal impairment is adequately defined. Prior to the present study, the repeat dose pharmacokinetics of 320 mg gemifloxacin in subjects with renal impairment has not been investigated directly. Population pharmacokinetic analysis of data from Phase III studies showed a 40% increase in AUC in patients with CLcr of >40mL/min. Thus, it is proposed that no dose adjustment is required in subjects with CLcr of >40mL/min. In the FDA comments for the original submission, the sponsor was requested to investigate the pharmacokinetics of 320 mg gemifloxacin, given once daily in subjects with renal impairment (CLcr= 40-59 mL/min) compared to normal subjects, to confirm the previous findings. This study was designed to address this issue. The results showed 66% and 74% increases in AUC₀₋₂₄ for subjects with CLcr of 50-59 and 40-49 mL/min, respectively, compared with normal subjects. As commented in the review of Study 059, there was no apparent relationship between gemifloxacin systemic exposure and incidence of certain adverse events, e.g., LFT elevation and skin rash. In addition, individual AUC values in subjects with CLcr of 40-59 mL/min were within the range observed in healthy subjects from Phase I pharmacokinetic studies in the original NDA. Based on the results of this study, in conjunction with safety and efficacy considerations, the dosage adjustment does not seem to be necessary for patient with CLcr of >40mL/min. Thus, we recommend CLcr of ≤40 mL/min as a cutoff to reduce gemifloxacin dose by half, i.e., 160 mg, in patients with renal impairment.

Study Dates:

The first subject was screened on 22 May 2000. The first dose of study medication was administered on 7 June 2000 and the final dose was administered on 9 October 2000. The last study visit was on the 24 October 2000.

Objectives:

- (a) To compare the repeat-dose pharmacokinetics of gemifloxacin in subjects with renal impairment (CLcr = 40-59mL/min) and in subjects with normal renal function (healthy volunteers).
- (b) To assess the safety and tolerability of repeat oral doses of 320 mg gemifloxacin in subjects

Study Design:

This study was conducted to an open, repeat dose, and parallel group design involving subjects with renal impairment (CLcr = 40-59mL/min) and healthy volunteers. All subjects were administered a single dose of 320 mg gemifloxacin (Batch number: N99116) on Day 1 and repeated doses (qd) on Days 3-7. Blood samples were collected up to 48 hours post-dose on Day 1 and Day 7 for assay of gemifloxacin.

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Study Population and Demographic Data:

A total of 17 subjects with renal impairment and 16 healthy subjects were screened, entered and completed this study. Key demographic data of all subjects are shown in Table 1. Healthy subjects and those with renal impairment were allocated into groups according to the mean of two serum creatinine clearances (CLcr) as calculated using the Cockcroft and Gault equation. Subjects were to have CLcr of either, 40-49mL/min, 50-59mL/min or ≥ 80 mL/min. Based on a 12 lead ECG at the pre-study, subjects with prolonged QTc were to be excluded (>450 msec for men or >470 msec for women).

Table1. Demographic data

Group	Parameter	Age (years)	Height (cm)	Weight (kg)	Sex/Race
40-49 mL/min	n	8	8	8	7 Male (88%)
	Mean	50	173	76.9	1 Female (13%)
	SD	15.2	8.8	9.69	White (100%)
	Range	22-69	155-182	64.0-88.0	
50-59 mL/min	n	9	9	9	5 Male (56%)
	Mean	52	174	81.8	4 Female (44%)
	SD	11.6	9.4	10.33	White (100%)
	Range	25-67	162-191	60.0-96.0	
>80 mL/min	n	16	16	16	11 Male (69%)
	Mean	48	174	82.4	5 Female (31%)
	SD	10.9	6.1	9.38	White (100%)
	Range	23-61	158-183	65.0-105.0	
All Subjects	n	33	33	33	23 Male (70%)
	Mean	49	174	80.9	10 Female (30%)
	SD	11.9	7.5	9.68	33 White (100%)
	Range	22-69	155-191	60.0-105.0	

Reviewer's comment: The healthy subject group and renal impaired subject group were well matched in terms of age (ideally ± 10 years), weight, sex and race.

Safety Parameters:

Adverse event (AE) information was taken by standard 'non-leading' questioning pre-dose and at 12, 24 and 48 hours post-dose, and follow-up. **Vital signs** were measured at screening, pre-dose 2 and 24 hours post-dose on Days 1 and 7-dose, and follow-up.

Electrocardiogram (ECG) were measured at screening; pre-dose (3 baseline ECG recordings), 1, 2, 3 and 24 hours post-dose on Day 1; pre-dose (3 baseline ECG recordings) on Day 3; pre-dose (3 baseline ECG recordings), 1, 2, 3 and 24 hours post-dose on Day 7; and follow-up. Blood and urine samples for **hematology, clinical chemistry and urinalysis** were collected at screening, pre-dose and 24 hours post-dose on Days 1 and 7, and follow-up. A routine drug screen for **undeclared drugs** was conducted on 50 mL urine samples collected at screening, pre-dose on Days 1, 3, and 7. Urine samples (first void of the day) were collected from female subjects at screening, pre-dose Days 1, 3 and 7, and follow-up for **pregnancy testing**.

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Pharmacokinetic Parameters:

Blood samples (approximately 3 mL) were taken pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hour after dosing on Days 1 and 7. Pre-dose samples were also collected on Days 4, 5 and 6. Plasma samples were assayed for gemifloxacin using a method based on _____ by the Drug Analysis Department, DMPK, SmithKline Beecham (Welwyn, UK). The samples were analyzed by _____ employing _____ with a lower limit of quantification of _____ using a 50 μ L aliquot. The assay was linear with the range of _____ The within and between-run precisions were acceptable _____

Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}), oral clearance (CL/F) and the apparent terminal half-life ($T_{1/2}$).

Statistical Methods:

Log-transformed AUC, C_{max} , CL/F and untransformed $T_{1/2}$ were analyzed by analysis of variance (ANOVA) to estimate differences between groups. The point estimates and 95% confidence intervals for the difference between the subjects with renal impairment and the normal group were constructed using the residual variance from the ANOVA.

Pharmacokinetic Results:

Mean plasma concentration of gemifloxacin and its relevant pharmacokinetic parameters after administration of 320 mg oral tablet to healthy subjects and subjects with renal impairment were shown in Figure 1 and Table 2, respectively. After repeat dose of 320 mg gemifloxacin, subjects with renal impairment (CrCL= 40-59 mL/min) had, on average, 70% increase in AUC_{0-inf} compared with normal healthy volunteers, whereas only 14% increase in C_{max} . Half-life was, on average, 2.44 hours longer in subjects with renal impairment relative to normal healthy volunteers. This difference in half-life resulted in ~20 % increase in the observed accumulation ratio ($AUC_{0-24(repeat\ dose)}/AUC_{0-24(single\ dose)}$) in subjects with renal impairment, i.e., 1.22 vs 1.01. T_{max} was not significantly different between subjects with renal impairment and normal healthy volunteers.

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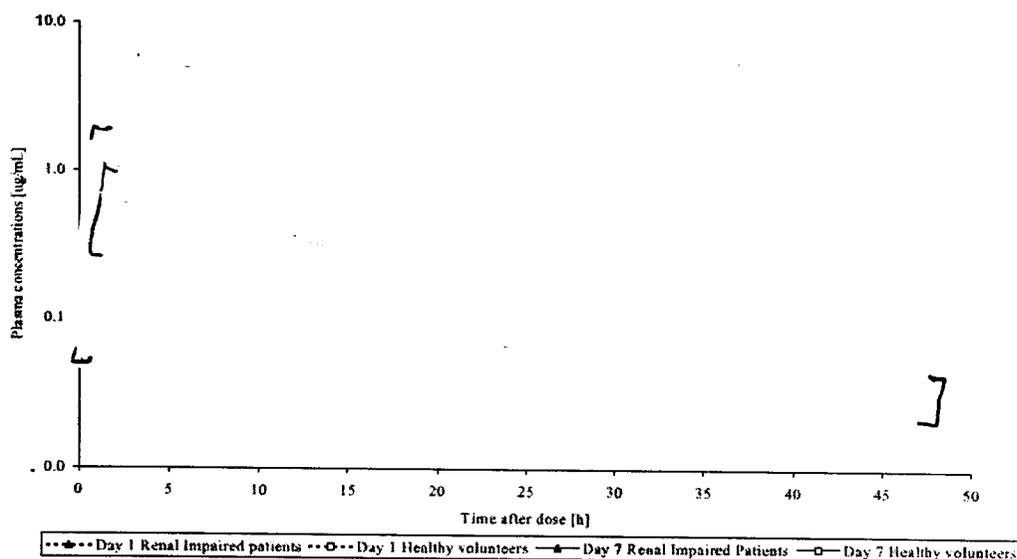


Figure 1. Plasma concentration of gemifloxacin after single and once daily repeat dose of 320 mg tablet to subjects (n=17) with renal impairment (CL_{cr} = 40-59 mL/min) and to healthy volunteer (n=16). Bars represent standard deviation.

Table 2. Pharmacokinetic parameters of gemifloxacin after single and once daily repeat dose of 320 mg tablet to subjects with renal impairment (CL_{cr} = 40-59 mL/min) and to healthy volunteers.

Parameters	Normal (n=16)		Renal impairment		P.E. (95% C.I.)	
	Single	Repeat	Single	Repeat	Single	Repeat
AUC _{0-inf} (µg·h/mL) ^a	7.05 (2.71) 3.40-15.0		10.4 (2.19) 6.72-15.0		1.53 ^c (1.25, 1.88)	
AUC _{0-24h} (µg·h/mL) ^a	6.16 (1.86) 3.11-10.5	6.04 (1.09) 4.06-7.91	8.45 (1.72) 5.60-12.8	10.3 (2.32) 6.60-15.1		1.70 ^c (1.47, 1.97)
C _{max} (µg/mL) ^a	1.32 (0.64) 0.531-2.99	1.19 (0.3) 0.873-1.98	1.31 (0.32) 0.806-1.87	1.34 (0.27) 0.918-2.10	1.06 ^c (0.82, 1.38)	1.14 ^c (0.97, 1.33)
T _{1/2} (hours) ^a	7.66 (1.81) 5.70-13.1	8.92 (2.04) 2.95-11.4	10.4 (1.55) 8.17-13.8	11.4 (1.43) 9.05-14.3	2.77 ^d (1.58, 3.97)	2.44 ^d (1.19, 3.68)
T _{max} (hours) ^b	1.25 (0.75-2.00)	1.00 (0.50-2.00)	1.02 (0.75-2.00)	1.00 (0.75-2.00)		

^a: Mean (SD) and range, ^b: Median (range), ^c: Ratio of geometric means, ^d: difference of arithmetic means

Reviewer's comment: Because C_{max} was not significantly changed between normal subjects and subject with renal impairment, the increase in AUC may be mainly due to the reduction in clearance, as evidenced by the increase in terminal T_{1/2} in subjects with renal impairment.

Table 3 shows the comparison of gemifloxacin pharmacokinetic parameters in sub-groups split according to the creatinine clearance (40-49 or 50-59 mL/min) with normal healthy subjects. AUCs were slightly different between 40-49 and 50-59 mL/min groups; AUC_{0-inf} (single dosing) and AUC_{0-24h} (repeat dosing) were, on average, 58 and 74%

higher in 40-49 mL/min group, respectively, compared with healthy subjects, whereas 49 and 66% higher in 50-59 mL/min group. Changes in C_{max} was not significantly different between 40-49 and 50-59 mL/min groups.

Table 3. Comparisons between groups (CLcr = 40-49 or 50-59 mL/min) for gemifloxacin pharmacokinetic parameters.

Parameter	Regimen	Comparison	PE	95% C.I.
AUC (0-inf)	Single Dose	(40-49):Normal	1.58	(1.22, 2.06)
AUC (0-inf)	Single Dose	(50-59):Normal	1.49	(1.16, 1.91)
AUC (0-24)	Repeat Dose	(40-49):Normal	1.74	(1.45, 2.09)
AUC (0-24)	Repeat Dose	(50-59):Normal	1.66	(1.39, 1.99)
C_{max}	Single Dose	(40-49):Normal	1.10	(0.79, 1.53)
C_{max}	Single Dose	(50-59):Normal	1.03	(0.75, 1.41)
C_{max}	Repeat Dose	(40-49):Normal	1.20	(0.99, 1.46)
C_{max}	Repeat Dose	(50-59):Normal	1.08	(0.90, 1.30)

Reviewer's comment: Because the difference of increases in AUC_{0-24} between subjects with CLcr 50-59 and 40-49 mL/min is not significant, we recommend CLcr of ≤ 40 mL/min as a cutoff to reduce gemifloxacin dose by half, i.e., 160 mg, in patients with renal impairment. In the previous OCPB comments on the original submission, re-analysis of the data from Phase III studies showed that reduction of the gemifloxacin dose to 160 mg Q24 hr for the patients with CLcr < 50 mL/min resulted in a more even distribution of the predicted $AUC(0-24)$ estimates across the entire patient population that was studied, as compared to when dose reduction was at CLcr < 40 mL/min. However, based on the results of the present study, reducing dose by one-half is likely to result in $\sim 50\%$ decrease in C_{max} as well as $\sim 20\%$ decrease in AUC in patients with renal impairment having CLcr = 49-40 mL/min. It is also noteworthy to mention that the AUC and C_{max} values reported in this study (Study 056) for the healthy subjects are lower than those values reported in the PK studies from the original NDA in healthy subjects receiving 320 mg Q24hr; mean (range) AUC ~ 8 to 10 (5-20) $\mu\text{g}\cdot\text{h}/\text{mL}$ and mean (range) C_{max} 1.6 (0.7-2.6) $\mu\text{g}/\text{mL}$. Thus, the dosage adjustment does not seem to be necessary for patient with CLcr of > 40 mL/min.

Safety Results:

A total of 16 subjects experienced 23 adverse experiences (AEs) of which 21 were treatment-emergent AEs (TEAEs) during this study. Of the 21 TEAEs, 5 AEs were suspected to be related to gemifloxacin; maculo-papular rash (healthy), headache (healthy), eczema (one healthy and one subject with renal impairment) and elevated prothrombin time (renal impaired subject).

On average, subjects with renal impairment (40-59 mL/min) had longer pre-dose QTc intervals than the healthy volunteers (419.4 ± 17.7 vs 402.5 ± 20.8 msec). This difference in baseline values was reflected post-dose in the average maximal QTc values, but the

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maximum change from baseline in QTc over 3 hours post-dose was, on average, similar for both the healthy subjects and the subjects with renal impairment (Table 4).

Table 4. Summary statistics for QTc changes from baseline in subjects with renal impairment (CrCL=40-59 mL/min) and healthy subjects.

Parameter	Group	Day	Time	N	Mean	SD	Median	Min	Max
Max change from baseline	Normal	1	-	16	10.7	9.2	9.8	-6	36
		7	-	16	9.5	13.7	9.5	-13	38
	Renal	1	-	17	11.5	9.7	9.0	-4	25
		7	-	17	13.3	12.2	11.0	-6	32
Change from baseline	Normal	1	1	16	-5.6	3.7	-6.0	-12	0
			2	16	-4.5	9.2	-3.0	-20	16
			3	16	9.0	11.7	9.8	-16	36
		7	1	16	-4.0	10.7	-3.0	-23	12
			2	16	-8.3	13.7	-8.3	-33	18
			3	16	6.6	15.2	7.8	-15	38
	Renal	1	1	17	-0.8	11.3	-1.0	-28	21
			2	17	-0.4	14.5	-4.0	-33	25
			3	17	10.7	10.3	10.3	-12	25
		7	1	17	-2.6	16.7	0.2	-44	20
			2	17	-1.4	13.7	0.0	-40	17
			3	17	11.9	13.5	10.3	-8	32

Conclusions:

1. AUC was higher in subjects with renal impairment by, on average, 53 and 70%, respectively, following single and once daily repeat administration. C_{max} was slightly higher (6-14%) in subjects with renal impairment compared to healthy subjects.
2. Accumulation was modest in both groups and consistent with that predicted from single dose data. The steady-state ratio was close to unity (up to 1.22) and consistent with linear pharmacokinetics following repeated dosing.
3. AUC_{0-24h} after repeat dosing were 66 and 74% higher in CLcr 50-59 and 40-49 mL/min groups, respectively, compared with healthy subjects. **We recommend that the gemifloxacin dose be reduced to 160 mg Q24 hr at CLcr \leq 40 mL/min.**
4. Gemifloxacin 320 mg administered as single and repeat doses were well tolerated in subjects with renal impairment (CLcr = 40-59mL/min).

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4. **Study 024:** An open, randomized, four-way crossover study to investigate the effects of calcium on the bioavailability of a 320 mg single oral dose of gemifloxacin in healthy volunteers

NDA Vol. 6.002, pp 1-400

Chronic bronchitis patients receiving steroid medication, often require calcium supplements to prevent osteoporosis, as steroids are known to affect bone metabolism. Thus, calcium and gemifloxacin are likely to be co-administered. Calcium is thought to chelate quinolones, thus, its co-administration may reduce the absorption of gemifloxacin. This study was designed to assess the effect of calcium co-administration on the absorption of gemifloxacin, depending on therapeutic time windows in which both drugs can be co-administered without clinically significant effects on absorption of gemifloxacin. The results showed that the co-administration of calcium 2 hours before or after gemifloxacin does not affect AUC and C_{max} of gemifloxacin, whereas the simultaneous administration of calcium with gemifloxacin decreased AUC and C_{max} of gemifloxacin by 21 and 17%, respectively, which is considered to be of limited clinical relevance. Based on these results, the reviewer agrees with the sponsor's proposal; gemifloxacin can be prescribed with products containing up to 1,000 mg calcium.

Study Dates:

The first subject was screened on 24 September 1999, and the first dose of study medication was administered on 20 October 1999. The last dose of study medication given on 10 November 1999, and the last visit date of the last subject was the 12 November 1999.

Objectives:

1. To estimate the effect of the co-administration of calcium on the bioavailability of gemifloxacin.
2. To estimate the effect of the time of administration of calcium relative to time of dosing of gemifloxacin on the bioavailability of gemifloxacin.

Study Design:

This study was conducted to an **open, randomized, single dose, and four-way crossover** design. Subjects received single doses of calcium and gemifloxacin, or gemifloxacin alone on 4 occasions, at least **6 days apart**. The dosing regimens were:

Treatment:

- A: Gemifloxacin (320 mg) administered alone
- B: Calcium (1000 mg) administered **2 hours before** gemifloxacin (320 mg)
- C: Calcium (1000 mg) administered **simultaneously** with gemifloxacin (320 mg)
- D: Calcium (1000 mg) administered **2 hours after** gemifloxacin (320 mg)

Subjects were randomized to one of the following treatment sequences, i.e., ABDC, BCAD, CDCA or DACB. Calcium was administered as a single oral dose of a 200 mL

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solution (one effervescent calcium carbonate tablet containing 1000 mg calcium) and gemifloxacin (Batch number: N98146) swallowed with 240 mL water. Calcium carbonate was provided in the commercial pack as Calcium Sandoz Fortissimum® effervescent tablets (one tablet contains 1000 mg calcium). All doses were administered in the fasted state.

Study Population and Demographic Data:

Ten healthy male and 6 female subjects, with a body weight within -15% to +10% of ideal weight for height, were screened and enrolled into the study. Females had a negative pregnancy test at the pre-study examination (within 21 days of study start) and at pre-dose testing. Subjects refrained from receiving antacids, iron, calcium or zinc containing medications, and multivitamins in 14 days prior to the first dosing day, until the completion of the last procedure of Day 4 on each study session. Demographic data were presented in Table 1.

Table 1. Demographic data.

Group	Parameter	Age (years)	Weight (kg)	Height (cm)
Male	n	10	10	10
	Mean	28	78.1	181
	SD	3.9	8.32	9.2
	Range	22-35	70-98	173-203
Female	n	6	6	6
	Mean	32	61.5	165
	SD	4.1	8.96	5.1
	Range	27-38	50-73	159-172
Total	n	16	16	16
	Mean	29	71.9	175
	SD	4.3	11.71	11.0
	Range	22-38	50-98	159-203

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Safety Parameters:

Hematology, clinical chemistry and urinalysis were measured at pre-study, pre-dose, 24 hours post-dose on each dosing occasion, and again at follow-up (48h after last dose of study medication, session 4). **BP and pulse** were recorded at pre-study, pre-dose and at 12 and 24h post-dose on each dosing occasion, and again at follow-up. **ECG** was recorded at pre-study and follow-up. **Adverse experiences** were collected pre-dose with respect to the first dose (baseline) and at 12, 24 and 48 hours after the gemifloxacin dose on each study day.

Pharmacokinetic Parameters:

Blood samples (approximately 5 mL) were collected, pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36 and 48 hours following dosing with gemifloxacin. Urine samples were collected into pre-weighed polyethylene containers at each dosing session, pre-dose and over the intervals 0-6, 6-12, 12-24 and 24-48 h post-dose. All the plasma and urine samples were analyzed by _____ analysis employing _____

_____ (Drug Analysis Department, DMPK, SmithKline Beecham, Welwyn, UK).

The lower limits of quantification for each of the assays for gemifloxacin in human plasma and urine were each _____ using a 50 μ L aliquot. The assay was linear with the range of _____. The within and between-run precisions were acceptable _____.

Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}). Urinary excretion (A_e), was calculated for each collection period by multiplying the urine concentration by the total volume of urine collected in that period. Renal clearance, CL_r , was calculated as the ratio of A_{e0-4h}/AUC_{0-inf} .

Statistical Methods:

Log-transformed AUC_{0-inf} and C_{max} were subjected to analysis of variance, fitting terms for sequence, subject (sequence), period and dosing regimen. Point estimates and adjusted 95% confidence intervals were computed for the ratios between the regimens, i.e., B:A, C:A, and D:A.

Pharmacokinetic Results:

Figure 1 and Table 2 show the plasma concentration profiles of gemifloxacin and its relevant pharmacokinetic parameters, respectively, after oral administration of (A) gemifloxacin (320 mg) alone, (B) Calcium (1,000 mg) administered 2 hours before gemifloxacin (320 mg), (C) Calcium (1,000 mg) administered simultaneously with gemifloxacin (320 mg) and (D) Calcium (1,000 mg) administered 2 hours after gemifloxacin (320 mg). Table 3 also shows the point estimates and adjusted 95% confidence intervals (C.I.) between regimens. After the administration of calcium 2 hours before or after gemifloxacin, AUC_{0-inf} and C_{max} were changed by <7% compared with gemifloxacin alone. In contrast, following the administration of calcium simultaneously with gemifloxacin, AUC_{0-inf} and C_{max} were decreased by 21% and 17%, respectively, compared with gemifloxacin alone.

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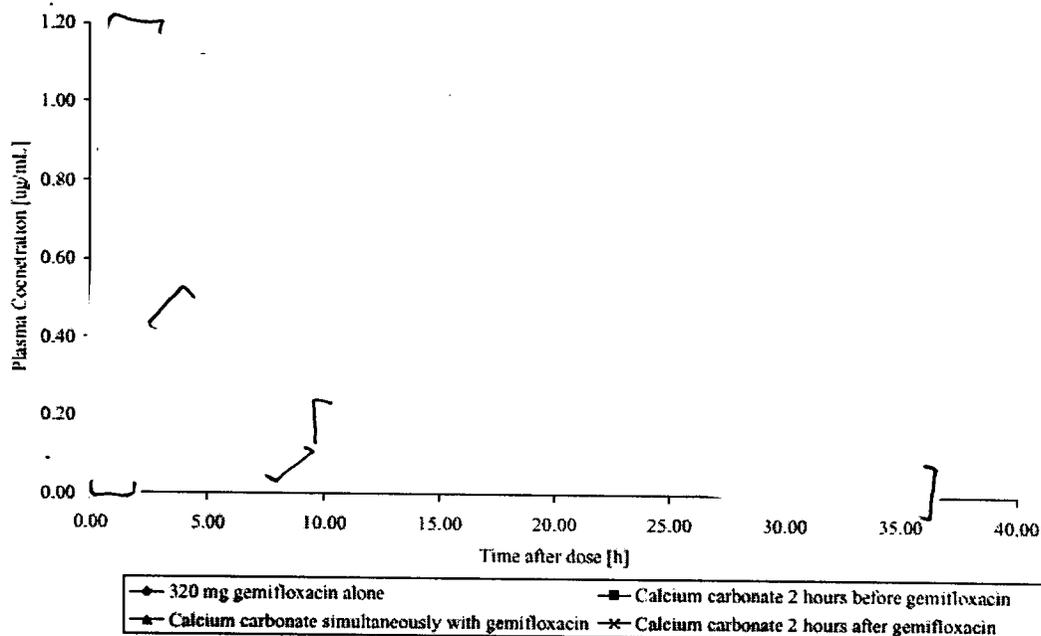


Figure 1. Plasma concentration-time profiles of gemifloxacin following a single oral dose of gemifloxacin (320 mg) given alone or at various times relative to calcium carbonate administration (n=16).

Table 2. Pharmacokinetic parameters after a single oral dose of 320mg gemifloxacin alone or given at various times relative to administration of calcium carbonate to healthy subjects.

	Regimen A Gemifloxacin Alone	Regimen B Calcium given 2 hours before gemifloxacin	Regimen C Calcium given simultaneously with gemifloxacin	Regimen B Calcium given 2 hours after gemifloxacin
AUC _{0-inf} ^a (µg·h/mL)	6.79±2.13 (3.04-10.2)	6.12±1.39 (3.52-7.58)	5.22±1.40 (2.95-8.01)	6.34±1.65 (3.18-9.18)
C _{max} ^a (µg/mL)	1.13±0.41 (0.28-1.99)	1.01±0.26 (0.477-1.479)	0.902±0.287 (0.568-1.64)	1.13±0.39 (0.633-1.90)
T _{1/2} ^a (hours)	7.33±2.51 (4.4-15.5)	6.68±1.19 (4.69-8.63)	6.81±1.3 (5.28-9.65)	6.42±1.26 (3.99-8.21)
T _{max} ^b (hours)	1.00 (0.5-2.02)	1.01 (0.52-2.08)	1.00 (1.00-2.00)	1.00 (0.50-2.02)
Ae ₀₋₄₈ ^a (% dose)	17.8±3.7 (12.3-23.2)	16.4±4.9 (7.64-25.3)	15.6±4.5 (8.37-26.9)	19.2±5.1 (10.1-29.8)
CL _r ^a (L/h)	9.00±2.58 (6.07-16.0)	8.59±1.78 (6.08-12.3)	9.86±2.47 (5.22-13.0)	9.99±2.87 (6.45-19.2)

^a: Mean±SD (range); ^b:Median (range)

Table 3. Comparison of pharmacokinetic parameters between regimens.

Parameter	Comparison	Point Estimate	95% C.I. *
AUC(0-inf)	B:A	0.93	(0.78 , 1.10)
	C:A	0.79	(0.66 , 0.93)
	D:A	0.95	(0.80 , 1.13)
Cmax	B:A	0.93	(0.71 , 1.22)
	C:A	0.83	(0.63 , 1.08)
	D:A	1.03	(0.79 , 1.35)

A, Gemifloxacin alone; B, Calcium administered 2 hours before gemifloxacin; C, Calcium administered simultaneously with gemifloxacin; D, Calcium administered 2 hours after gemifloxacin.

Reviewer's Comment: Considering the range of individual AUC and C_{max} in Group A (Gemifloxacin alone) and Group C (Simultaneous calcium with gemifloxacin), i.e., 3.04-10.2 vs 2.95-8.01 µg·h/mL and 0.28-1.99 vs 0.568-1.64 µg/mL for AUC and C_{max}, respectively, the average reduction of ~20% does not seem clinically significant. Therefore, regardless of time of calcium dosing, co-administration of 1000 mg of calcium does not seem to affect the absorption of gemifloxacin. Based on these results, the reviewer agrees with the sponsor's proposal; gemifloxacin can be prescribed with products containing up to 1,000 mg calcium.

Safety Results:

Ten subjects reported a total of 13 adverse experiences during or after the treatment phase of the study, all of which had resolved at the end of the study. Of the 13 treatment emergent adverse experiences, 10 were mild and 3 were of moderate severity. Of these, 11 were suspected to be related to study medication. When the two medications were given simultaneously, there was a higher number of diarrhea which was the most frequently reported AE, compared to gemifloxacin administration alone, 2 hours before or after co-administration with calcium (Table 4).

Table 4. Treatment-emergent adverse experiences

Adverse Experience	Number of Subjects with Treatment Emergent Adverse Experiences (incidences in > 1 subject)			
	Gemifloxacin alone	Calcium 2 hours before gemifloxacin	Calcium simultaneous gemifloxacin	Calcium 2 hours after gemifloxacin
Diarrhoea	0	1	4	1
Headache	1	0	1	1
Fatigue	0	1	2	0
Flatulence	0	0	0	1
Number of AEs reported	1	2	7	3
Number of Subjects with AEs	1	2	7	3
Number of Subjects Exposed	16	16	16	16

Reviewer's comment: Because of limited data, it is not clear if a higher number of diarrhea when calcium and gemifloxacin were administered simultaneously is clinically significant. However, because 3 of 4 cases were determined as mild severity, it does not seem clinically significant.

Conclusions:

1. Calcium carbonate, 1,000 mg, given either 2 hours before or 2 hours after gemifloxacin dosing did not affect gemifloxacin systemic exposure significantly.
2. Calcium carbonate, 1,000 mg, administered simultaneously with gemifloxacin resulted in an approximately 20% reduction in exposure to gemifloxacin, which is considered to be of limited clinical relevance.
3. Gemifloxacin was well tolerated in the healthy male and female volunteers following dosing with 320 mg in co-administration with calcium carbonate.
4. Based on the results from this study, gemifloxacin can be prescribed with products containing up to 1000 mg calcium.

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5. **Study 077:** A double-blind, randomized, placebo-controlled, two period crossover study to investigate the effects of cimetidine (400 mg qid) on the pharmacokinetics of a single oral 320 mg dose of gemifloxacin in healthy volunteers

NDA Vol. 6.0015-6.017, pp 1-736

Cimetidine is known to inhibit base transport in the proximal tubule and has been shown to inhibit renal secretion and affect reabsorption of some quinolones. The renal clearance of gemifloxacin exceeds the accepted typical value for glomerular filtration (GFR) of 120 ml/min, indicating that active renal secretion is involved in the elimination of gemifloxacin. Hence, inhibition of tubular secretion may increase systemic exposure of gemifloxacin. This study was designed to investigate the effects of cimetidine on the pharmacokinetic profile of a single oral 320 mg dose of gemifloxacin. The results showed that cimetidine (400 mg qid for 5 days) had only a minimal impact (>10% increase in AUC and C_{max}) on the systemic exposure of gemifloxacin. Based on these results, the reviewer agrees with the sponsor's proposal; cimetidine and gemifloxacin can be co-administered without a dosing adjustment of gemifloxacin.

Study Dates:

The first subject was screened on the 10 January 2000 and the first dose was administered on the 24 January 2000. The last dose was administered on the 16 February 2000 and the last follow-up visit was on the 20 March 2000.

Objectives:

To estimate the effect of co-administration of cimetidine (400mg qid, 7 days) on the pharmacokinetic profile of a single oral dose of gemifloxacin (320mg).

Study Design:

This study was conducted as a double blind, randomized, and placebo-controlled two period crossover design in healthy volunteers. Subjects were randomized to one of two treatments sequences, AB or BA, where:

- A: Days 1-7: Cimetidine (400 mg qid);
Day 5: Gemifloxacin (320 mg single dose).
B: Days 1-7: Placebo with respect to cimetidine (qid);
Day 5: Gemifloxacin (320 mg single dose).

There was a washout period of at least 7 days between each dosing session. Gemifloxacin 320 mg tablet (Batch number: N99116) and Cimetidine 400 mg (Batch number: N99337). During each dosing session, study medication was administered in the Unit on Day 1 (first dose cimetidine/placebo only) and Day 5 (all doses except the fourth cimetidine/placebo dose). All other doses of cimetidine/placebo were self-administered at home. All subjects were required to return to the Unit on Day 3 with medication packs and diary cards for a compliance check.

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Continuation of cimetidine for 2 days after the single dose of gemifloxacin ensured that any inhibitory effect of cimetidine was present during the entire elimination period of gemifloxacin. The dose of cimetidine (400 mg qid) was based on the maximum clinical daily dose recommended in the UK.

Study Population and Demographic Data:

Twelve healthy females and 10 healthy males entered this study and were randomized to treatment. There were no withdrawals from this study. Demographic data were presented in Table 1.

Table 1. Demographic data.

Parameter	Age (years)	Weight (kg)	Height (m)	Race
n	22	22	22	21 white
Mean	34	74.85	1.71	1 Anglo Indian
SD	7.1	12.89	0.10	
Range	22 - 56	54.10 - 100.20	1.55 - 1.92	

Safety Parameters:

Pulse, blood pressure and 12 Lead ECG were measured at pre-study; Day 1: pre-dose; Day 5: pre-dose, 12 h post-dose; and at follow-up. **Hematology, clinical chemistry and urinalysis** were measured at pre-study; Day 1: pre-dose; Day 5: pre-dose and 24 h post-dose; and at follow-up. **Adverse experiences** were collected at the Day 1: pre-dose; Day 5: pre-dose, 12, 24, 48 and 72 hours post-dose; and at follow-up. AEs for Days 1 (post-dose) to 4 were reported on diary cards.

Pharmacokinetic Parameters:

Blood samples (approximately 5 mL) were collected, pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 32 and 48 hours following dosing with gemifloxacin. Urine samples were collected into pre-weighed polyethylene containers at each dosing session, pre-dose and over the intervals 0-2, 2-6, 6-12, 12-24, 24-48 and 48-72h post-dose. All the plasma and urine samples were analyzed by _____ analysis employing _____

_____ The lower limits of quantification for each of the assays for gemifloxacin in human plasma and urine were each _____ using a 50 µL aliquot. The assay was linear with the range of _____ The within and between-run precisions were acceptable _____

Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}). Urinary excretion (A_e), was calculated for each collection period by multiplying the urine concentration by the total volume of urine collected in that period. Renal clearance, CL_r , was calculated as the ratio of A_{e0-72}/AUC_{0-inf} .

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Statistical Methods:

Log-transformed AUC_{0-inf} , C_{max} , and CL_r were subjected to analysis of variance, fitting terms for sequence, subject (sequence), period and dosing regimen. Point estimates and adjusted 95% confidence intervals were computed for the ratios between the regimens, i.e., A:B.

Pharmacokinetic Results:

Figure 1 and Table 2 show the plasma concentration profiles of gemifloxacin and its relevant pharmacokinetic parameters, respectively, after oral administration of 320 mg gemifloxacin with cimetidine (400 mg qid for 5 days) or placebo to healthy volunteer. There are two deviations from randomization schedule; one subject took cimetidine (400mg qid) up to and including the third dose on Day 5, after which this subject took placebo from the fourth dose on Day 5 to Day 7, and vice versa for the other subject. Therefore, two subjects were excluded from the formal statistical analysis and summary statistics for pharmacokinetics. In addition, due to the missing urine volume, $Ae\%$ and CL_r could not be obtained in one subject of each regimen. Therefore, only 19 subjects were included in the formal statistical analysis of CL_r and $Ae\%$. Administration of cimetidine with gemifloxacin decreased CL_r by 28%, resulting in the increase in AUC_{0-inf} and C_{max} by 10 and 6%, respectively. Mean terminal $T_{1/2}$ was not significantly affected by cimetidine.

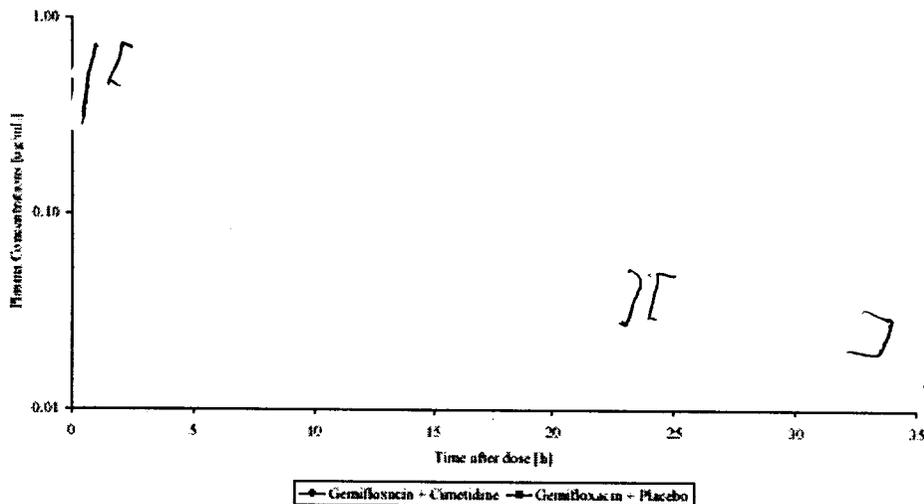


Figure 1. Plasma concentration-time profiles of gemifloxacin following a single oral dose of 320mg gemifloxacin administered with cimetidine (400 mg qid for 5 days) or placebo to healthy volunteers (n=20).

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Table-2. Pharmacokinetic parameters after single oral administration of gemifloxacin 320 mg with cimetidine (400 mg qid for 5 days) or placebo to healthy volunteers (n=20).

	Cimetidine+ Gemifloxacin (A)	Placebo+ Gemifloxacin (B)	P.E. (A:B or A-B)	95% C.I.
AUC _{0-inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$) ^a	5.68±1.87 (3.09-9.95)	5.18±1.67 (2.57-8.10)	1.10 ^c	(0.96, 1.25)
C _{max} ($\mu\text{g}/\text{mL}$) ^a	0.849±0.299 (0.435-1.53)	0.796±0.259 (0.332-1.28)	1.06 ^c	(0.94-1.20)
T _{1/2} (hours) ^a	7.81±1.26 (5.53-10.7)	7.06±1.32 (5.12-9.92)	0.75 h ^d	(-0.14h, 1.64h)
T _{max} (hours) ^b	1.50 (0.98-2.05)	1.50 (0.50-3.00)	-0.01 h ^d	(-0.51h, 0.30h)
Ae ₇₂ (% dose) ^{a,c}	22.8±5.45 (12.6-31.4)	28.4±4.76 (17.3-36.2)	-5.58% ^d	(-8.4%, -2.76%)
CLr (L/h) ^{a,c}	13.7±3.31 (9.29-22.0)	19.0±5.29 (11.3-30.3)	0.72 ^c	(0.65, 0.81)

^a: Mean±SD, range; ^b:Median, range; ^c: A:B; ^d:A-B; ^e:n=19

Reviewer's comment: Because only 20% of dose were excreted in urine, the effect on systemic exposure was less than that on CLr, i.e., 10% increase in AUC vs 28% decrease in CLr. An approximate 10% increase in systemic exposure of gemifloxacin due to co-administration with cimetidine does not seem clinically significant. Based on these results, the reviewer agrees with the sponsor's proposal; cimetidine and gemifloxacin can be co-administered without a dosing adjustment of gemifloxacin.

Safety Results:

A total of 34 treatment emergent adverse events were reported by 18 subjects. All had resolved at the end of the study. Twenty two and 11 adverse events were reported with regimen A (gemifloxacin + cimetidine) and regimen B (gemifloxacin + placebo), respectively. One AE were reported with subjects who received deviated cimetidine dosing (See **Pharmacokinetic Results**). Twenty-three AEs were mild and 11 were of moderate severity. Twenty-eight of the 34 AEs were considered not related or unlikely to be related to study medication. Two AEs were suspected to be related to study medication and four were considered probably related to study medication. The most frequently reported adverse events were headache, upper respiratory tract infection, diarrhea and flatulence. There are no changes in vital signs, ECG, or clinical laboratory parameters during the study considered to be of clinical significance or treatment related by the Principal Investigator.

Conclusions:

1. Cimetidine (400 mg qid for 5 days) had only a minimal impact on the systemic exposure of Gemifloxacin, i.e., less than 10% increase, on average, in AUC_{0-inf} and C_{max}.

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2. Single dose of gemifloxacin 320 mg was well tolerated by healthy volunteers when co-administered with cimetidine.
3. Cimetidine and gemifloxacin can be co-administered without a dosing adjustment of gemifloxacin.

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6. **Study 036: An open, single dose study to investigate the tissue penetration of gemifloxacin (SB-265805) and trovafloxacin into an inflammatory site, in healthy male volunteers**

NDA Vol. 6.006, pp 1-257

Study Dates:

The first subject was included in the study on 17 June 1999 (first screening). The first dose of study medication was received on 29 June 1999 and the last dose was received on 8 February 2000. The date of the last subject visit was 9 February 2000.

Objectives:

To investigate the penetration of gemifloxacin into a site of inflammation, following a single oral dose of 320mg.

Study Design:

This study was conducted to an **open single dose** study design. Each subject participated in one session and was administered a single dose of gemifloxacin 320 mg (Batch number: N98144), in the fasted state. Subjects had two **cantharide plasters** placed on a forearm the evening before the dosing day to **induce blisters**. Samples of inflammatory fluid were taken from the blisters and plasma samples were drawn from an IV cannula at intervals up to 24h post-dose. In the original protocol, trovafloxacin was included as a benchmark/control. Following the withdrawal of trovafloxacin from the market for safety reasons the protocol was modified to remove this arm of the study.

Study Population and Demographic Data:

Ten healthy male subjects aged 20-39 years were included into the study. There were no withdrawals from this study. Demographic data were presented in Table 1.

Table 1. Demographic data.

Parameter	Age (years)	Weight (kg)	Height (cm)
n	10	10	10
Mean	27	77.8	177
SD	7.4	6.35	3.9
Range	20-39	68.0-87.1	173-184

* 8 White, 1 White/Asian and 1 Afro-Caribbean

Safety Parameters:

Blood pressure and pulse were measured at pre-study, pre-dose and 24-26 hours post-dose; **12-lead ECG** at pre-study; and **adverse experiences** questioning at pre-study, pre-dose and at 1, 2, 12 and 24 hours post-dose. Adverse experience questioning was also performed over the telephone 7-14 days after the dose. **Hematology, clinical chemistry and urinalysis** at pre-study, pre-dose and 24-26 hours post-dose. **Drugs screen** at pre-study and pre-dose.