CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-085

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-085
Submission Date:	12/9/98
Drug:	Moxifloxacin hydrochloride (Avelox®) 400 mg Oral Tablets
Sponsor:	Bayer Corporation Bayer Pharmaceutical Division West Haven, CT
Type of Submission:	NME
Category:	1S
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

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I. BACKGROUND

Moxifloxacin (BAY 12-8039) is a new, synthetic C-8-methoxy-fluoroquinolone antibiotic. The molecule possesses two stereogenic centers and represents the pure S,S-enantiomer. Because the correct stereochemical configuration is introduced with the starting material, S,S-Pyrrolopiperidine, no stereoselective synthesis or racemate stereochemical synthesis or racemate separation is required in the synthesis of moxifloxacin. The C-8-methoxy structural modification confers increased bactericidal activity against Gram-positive and anaerobic organisms compared to ciprofloxacin. In addition, it possesses broad-spectrum activity against Gram-negative organisms, although it lacks activity against *Pseudomonas aeruginosa*.

The bactericidal action of moxifloxacin results from the inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV, required for DNA replication, repair, and recombination.

Moxifloxacin has been approved in 8 European countries. Germany approved the drug most recently in July of 1999.

A copy of the proposed labeling is provided as Appendix 1.

II. INDICATIONS AND DOSAGES

The applicant is seeking approval of moxifloxacin for four indications: acute sinusitis; acute bacterial exacerbations of chronic bronchitis; community-acquired pneumonia; [redacted]

A dosage of 400 mg once daily is proposed for all indications. The drug will be marketed as a 400-mg film-coated tablet. The indications and duration of therapy are listed below.

Infection *	Daily Dose	Usual Duration
Acute Sinusitis	400 mg	10 days
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	5 Days
Community Acquired Pneumonia	400 mg	10 days
[redacted]		

* due to designated pathogens

III. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS SYNOPSIS

Item 6 of this submission (Human Pharmacokinetics and Bioavailability) is comprised of 82 volumes containing data from 37 Phase I studies of moxifloxacin tablets. The basic pharmacokinetic parameters, including bioavailability, for moxifloxacin are characterized in single and multiple dose pharmacokinetic studies in healthy subjects and special patient populations (renal and hepatic impairment). The bioequivalence of the

moxifloxacin tablet formulation used up until Phase III and the late Phase III tablet, which is also to be the commercial form, is documented. Food effects, the effects of age and gender, and various drug-drug interactions (digoxin, warfarin, theophylline, glyburide, probenecid, ranitidine, Maalox, and iron) were studied. Special safety studies of the phototoxic potential and effect of IV and oral administration of moxifloxacin on the QT interval were also studied. In addition, tissue distribution studies evaluating the penetration of moxifloxacin into lung, sinus, and subcutaneous tissues, as well as saliva, and blister fluid are included. The validation and performance of the analytical method is adequately documented. These studies are summarized in Section VIII (Pharmacokinetic Summary) of this review. More detailed information can be found in Appendix 2.

What are the basic pharmacokinetics of moxifloxacin?

Absorption:
Moxifloxacin is extensively absorbed after oral administration. Absolute bioavailability is 86%.

Distribution:
Moxifloxacin is approximately 50% bound to [redacted] Moxifloxacin penetrates well into extravasular tissues. Tissue distribution studies demonstrate that moxifloxacin concentrations exceed the corresponding plasma concentrations in alveolar macrophages, bronchial mucosa, epithelial lining fluid, maxillary sinus mucosa, anterior ethmoid mucosa, and nasal polyps. Concentrations in blister fluid are identical to plasma. The penetration of moxifloxacin in subcutaneous tissue and skeletal muscle has also been investigated, but concentrations are less than in plasma. The volume of distribution is approximately [redacted]

Metabolism:
Moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate of moxifloxacin (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces. Approximately 14% of an oral dose of moxifloxacin is converted to a glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 1/2 those of the parent drug, while plasma concentrations of M1 are generally less than 1/10 those of moxifloxacin. Neither conjugated metabolite of moxifloxacin (M1 and M2) is pharmacologically active.

Elimination:
Approximately 45% of an oral dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). The mean (±SD) apparent total body clearance and renal clearance are 12 ± 1.2 L/hr and 2.5 ± 1.1 L/hr, respectively.

Are there any biopharmaceutics issues with moxifloxacin?

Food Effect
There is no change in the exposure to moxifloxacin, as determined by C_{max} and AUC when moxifloxacin is administered with a high-fat breakfast. Consumption of 1 cup of

yogurt with moxifloxacin does not significantly affect the AUC or C_{max} as seen in the following table.

Percent (%) Change in C_{max} of Moxifloxacin Alone Compared to Moxifloxacin + Yogurt

	Alone	With Yogurt	% Change
SUBJECT#	C_{max} [µg/L]	C_{max} [µg/L]	
3	2150	1560	-27.4
4	2650	2120	-20.0
5	3610	4170	15.5
6	2600	2280	-12.3
10	3850	3110	-19.2
12	1920	1680	-12.5
1	2240	2090	-6.7
2	2640	2930	11.0
7	2920	2000	-31.5
8	4780	2810	-41.2
9	2810	3780	34.5
11	3450	2040	-40.9
MEAN	**2968**	**2547.5**	**-12.6**
STD DEV	**819**	**822**	**23.2**
MIN	**1920**	**1560**	**-41.2**
MAX	**4780**	**4170**	**34.5**

Pivotal Bioequivalence (BE) Study

The bioequivalence of the proposed commercial 400 mg tablet (Formulation 231) and the formulation used in most clinical studies (Formulation 215) was established in the pivotal bioequivalence trial.

Point Estimates and 90% Confidence Intervals for the Ratios 'Test Formulation (231) / Reference Formulation (215)'

	Point Estimate (Range)	90 % Confidence Interval
AUC	105 %	[102 %; 108 %]
C_{max}	95 %	[89 %; 102 %]

The 90% confidence intervals for both AUC and C_{max} are within the accepted interval [80 %; 125 %] for establishing bioequivalence.

What do we know about the pharmacokinetics of moxifloxacin in special populations?

Renal Impairment

In a single-dose study of age-matched (± 10 years) subjects, aged between 18 and 75 years, and either with or without renal function impairment were investigated. Renal function was determined by creatinine clearance, which was obtained from a 24-hour urine collection within 1 week before dosing. The following four groups of subjects were defined as follows:

Group 1: CL_{CR} > 90 mL/min (n=8)
Group 2: CL_{CR} > 60 and ≤ 90 mL/min (n=31)
Group 3: CL_{CR} > 30 and ≤ 60 mL/min (n=7)
Group 4: CL_{CR} ≤ 30 mL/min (n=4) [not on dialysis from recruitment up to the end-of-study evaluation]

The mean C_{max} of moxifloxacin was reduced by 22% and 20% in the patients with moderate (CL_{CR} > 30 and ≤ 60 mL/min) and severe (CL_{CR} ≤ 30mL/min) renal impairment, respectively. The mean AUC was also increased by 14% in the moderately impaired patients and unchanged in the severely impaired. The mean AUC in the moderately and severely impaired patients increased 1.7-fold (range up to 2.8-fold) for the sulfate conjugate (M1). The mean AUC and C_{max} for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-fold) and 1.4-fold (ranging up to 2.5-fold), respectively in severely impaired patients. See tables below. The sulfate and glucuronide conjugates are not microbiologically active. The clinical implication of increased exposure to the M1 and M2 metabolites in patients with renal impairment is unknown.

Point Estimate (%) and 90% CI of the True Mean Ratios for the Various Groups of the Plasma C_{max} and AUC of Moxifloxacin

Parameter	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
	PE	90% CI	PE	90% CI	PE	90% CI
AUC	103.1	82.6 to 1.29	113.6	88.0 to 146.6	101.3	81.5 to 149.2
C_{max}	105.0	80.9 to 136.3	77.6	57.5 to 104.8	80.5	56.4 to 114.9

Point Estimate (%) and 90% CI of the True Mean Ratios for the Various Groups of the Plasma C_{max} and AUC of Metabolite M1

Parameter	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
	PE	90% CI	PE	90% CI	PE	90% CI
AUC	75.4	49.4 to 115.1	173.4	106.5 to 282.4	112.7	63.3 to 200.7
C_{max}	74.2	53.6 to 102.8	111.2	76.4 to 161.8	79.4	50.9 to 123.7

Point Estimate (%) and 90% CI of the True Mean Ratios for the Various Groups of the Plasma C_{max} and AUC of Metabolite M2

Parameter	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
	PE	90% CI	PE	90% CI	PE	90% CI
AUC	135.5	91.0 to 201.8	182.5	117.1 to 284.4	282.3	167.0 to 477.3
C_{max}	109.1	69.9 to 170.1	95.4	57.6 to 157.8	140.3	77.3 to 254.6

Reviewer's Comment: The applicant was requested to provide the efficacy profile (i.e. microbiologic and/or clinical success rates) for each indication for patients with a creatinine clearance of (1) < 30 mL/min, (2) >30 but < 60 mL/min, and (3) ≥ 60 mL/min enrolled in the Phase III trials. The resulting analysis showed similar clinical cure rates regardless of renal function.

Therefore, no dosage adjustment of moxifloxacin is required in renally impaired patients. There is no experience in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Hepatic Impairment

In a single 400 mg dose study of 6 patients with mild, (Child-Pugh Class A) and two patients with moderate cirrhosis (Child Pugh class B), moxifloxacin systemic exposure (AUC and peak concentration (C_{max}) were reduced by approximately 23% and 16%, respectively. The mean AUC of the sulfate conjugate (M1) increased by 4.4-fold and ranged up to 7-fold, while the mean C_{max} increased by 3.4-fold and ranged up to 5.5-fold. The mean C_{max} of the glucuronide conjugate (M2) increased by 1.6-fold and ranged up to 3.4-fold. See tables below. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. The pharmacokinetics of moxifloxacin in patients with moderate and severe hepatic insufficiency (Child Pugh Classes B and C), however, have not been adequately studied.

Point Estimates and 90% CI of the True Mean Ratios of the Plasma C_{max} and AUC of Moxifloxacin in Patients with Impaired Hepatic Function Relative to Healthy Subjects

Parameter	Point Estimate (%)	90% CI
C_{max}	84.49	65.89 to 108.35
AUC	76.48	61.73 to 94.74

Point Estimates and 90% CI of the Plasma C_{max} and AUC of Metabolite M1 in Patients with Impaired Hepatic Function Relative to Healthy Subjects

Parameter	Point Estimate (%)	90% CI
C_{max}	335.69	204.47 to 551.14
AUC	436.80	269.44 to 708.11

Point Esfimates and 90% CI of the True Mean Ratios of the Plasma C_{max} and AUC of Metabolite M2 in Patients with Impaired Hepatic Function Relative to Healthy Subjects

Parameter	Point Estimate (%)	90% CI
C_{max}	156.09 †	72.47 to 336.20
AUC	108.43 *	56.42 to 208.38

† based on data from 7/10 subjects

* based on data from 6/10 subjects

Reviewer's Comment: The sponsor was requested to provide the safety profile for patients with a Child Pugh Class of B or C compared to normals enrolled in the Phase III trials, but they were unable to provide the information.

Therefore, no dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh Class A). However, moxifloxacin should not be used in patients with moderate to severe insufficiency (Child Pugh Classes B and C).

Gender

Following a single 200-mg dose of moxifloxacin to 16 healthy elderly subjects, the mean AUC and C_{max} were 29% and 24% higher, respectively, in healthy elderly females compared to healthy elderly males. There are no significant differences in moxifloxacin pharmacokinetics between elderly male and female subjects when differences in body weight are taken into consideration.

A 400 mg single dose study was conducted in 18 young males and females. The comparison of moxifloxacin pharmacokinetics in this study (9 young females and 9 young males) showed no differences in AUC or C_{max} due to gender.

Dosage adjustments based on gender are not necessary.

Geriatrics
In 16 healthy elderly male and female volunteers (66-81 years of age with normal renal function for their age) given a single 200 mg dose of moxifloxacin, the mean AUC and C_{max} were not statistically different between young and elderly males and elimination half-life appeared unchanged. No dosage adjustment is required based on age alone.

Whether pharmacokinetic differences exist between young and elderly females is unknown.

There is no information on accumulation of moxifloxacin with repeated administration in elderly patients.

Are there any covariates that influence the exposure or elimination of moxifloxacin?

Steady state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those determined in Caucasian subjects, with a mean C_{max} of 4.1 µg/mL, an AUC_{24} of 47 µg*h/mL, and an elimination half-life of 14 hours. Dosage adjustment is not necessary for Japanese males.

Does moxifloxacin have any potential for drug-drug interactions?

Pharmacokinetic Interactions
In vitro: There is evidence to support no metabolism of moxifloxacin by CYP450 enzymes. Results suggest that moxifloxacin and its major metabolite (M1) do not inhibit CYP isozymes 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4.

In vivo: There was no clinically significant effect of moxifloxacin on theophylline, warfarin, digoxin, or glyburide. Theophylline, digoxin, probenecid, and ranitidine did not affect the pharmacokinetics of moxifloxacin.

However, as with all other quinolones, iron and antacids significantly reduced the bioavailability of moxifloxacin.

Antacids: When moxifloxacin (single 400 mg dose) was administered two hours before, concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 12 healthy volunteers there was a 26%, 60% and 23% reduction in the mean AUC of moxifloxacin, respectively. See table below.

Point Estimates and 90% CIs for the Ratios of Moxifloxacin + Maalox 70®/Moxifloxacin Alone for Various Moxifloxacin Pharmacokinetic Parameters (N=12)

Parameter	Ratio*	Geometric mean ratio (%)	90 % confidence interval
AUC	D / A	73.76	[65.22 ; 83.41]
	B / A	40.73	[36.02 ; 46.06]
	C / A	77.36	[68.41 ; 87.48]
C_{max}	D / A	92.49	[77.42 ; 110.50]
	B / A	38.74	[32.43 ; 46.28]
	C / A	98.97	[82.85 ; 118.24]

A = moxifloxacin alone
B = moxifloxacin simultaneously Maalox® 70
C = moxifloxacin given 4 hours after the administration Maalox® 70
D = moxifloxacin given 2 hours before the administration of Maalox® 70

Iron: When moxifloxacin was administered concomitantly with iron (ferrous sulfate 100 mg once daily for two days), the mean AUC and C_{max} of moxifloxacin was reduced by 39% and 59%, respectively.

Point Estimates and 90% Confidence Intervals for the Ratio of Moxifloxacin + Iron/Moxifloxacin Alone for Moxifloxacin Pharmacokinetic Parameters (N=12)

	Point Estimate (range, %)	90% Confidence Interval (%)
AUC	61	54 – 69
C_{max}	41	34 – 49

Therefore, oral doses of moxifloxacin should only be administered more than four hours before antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution

No clinical studies have been conducted to evaluate the effect of moxifloxacin on the metabolism of CYP3A4 substrates.

Pharmacodynamic Interactions – Cardiac Toxicity

In vivo: The potential for a pharmacodynamic interaction between moxifloxacin and other drugs that prolong the QT interval has not been studied in humans. However, an enhanced QT prolonging effect between sotalol, a Class III antiarrhythmic, and IV moxifloxacin at high doses was demonstrated in dogs. Therefore, moxifloxacin should not be used with Class IA and Class III antiarrhythmics, or other drugs known to prolong the QT interval such as bepridil, erythromycin, cisapride, pentamidine, tricyclic antidepressants, and some antipsychotics including phenothiazines.

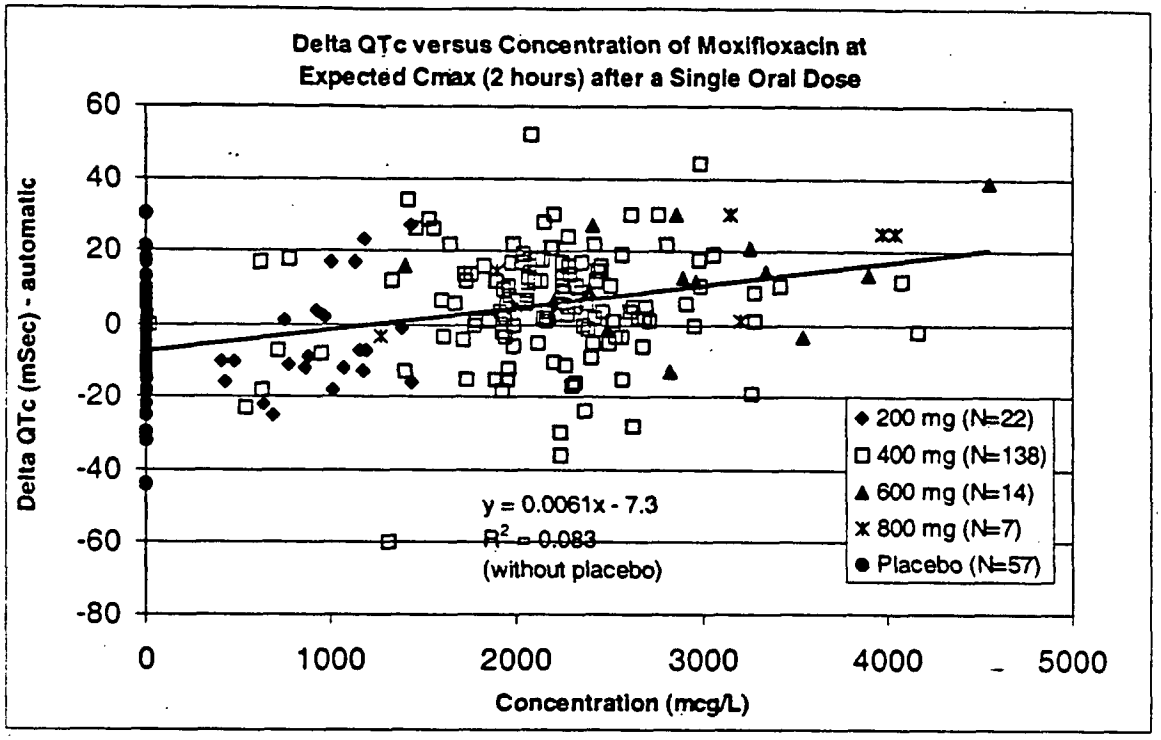
Is there any relationship between moxifloxacin concentration and QT_c prolongation?

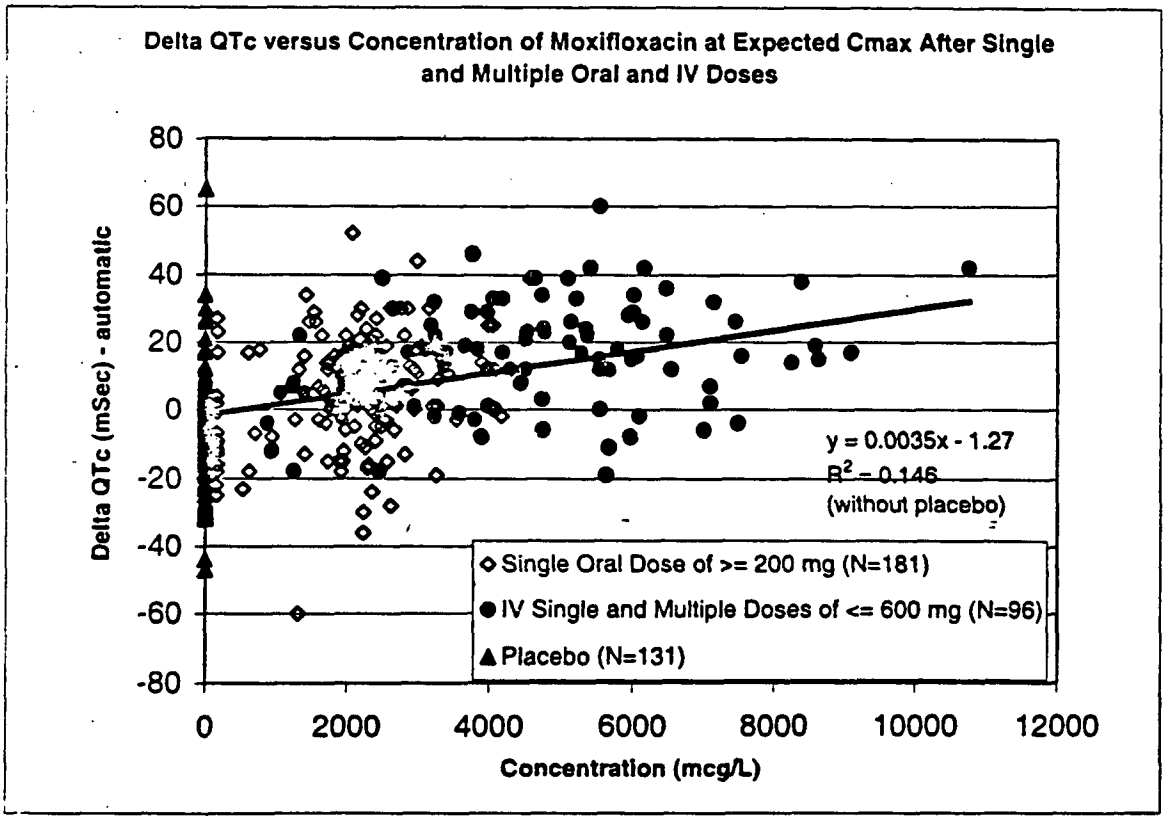
The potential for moxifloxacin to cause prolongation of the QT interval of the electrocardiogram (ECG) has been a major safety issue in the review of this drug. In an *in vitro* cardiac cell model, moxifloxacin has been shown to block the rapid delayed rectifier current (I_{Kr}), one of the four potassium currents that regulate the cardiac resting membrane potential and the cardiac action potential. Blockade of the I_{Kr} channel by drugs prolongs the action potential duration and increases the QT interval.

The applicant obtained ECGs during their Phase I studies at baseline and serially after drug administration. The ECGs were timed to coincide with blood sampling for moxifloxacin pharmacokinetic analysis. The change in QT_c (corrected for heart rate by [redacted] in these studies was measured at 2 hours after oral administration and at the end of an IV infusion, which corresponds to the expected C_{max} for the drug. It is believed that the maximum prolongation of QT_c occurs at or near the C_{max} for all drugs with this potential.

The relationship between concentration at the expected C_{max} and change in QT_c (ΔQT_c) can be shown for oral moxifloxacin using single oral doses of 200-800 mg. In addition, data from single and multiple oral and IV doses can also be plotted. The resulting graphs are shown below.

In summary, moxifloxacin exhibits a concentration-dependent prolongation of the QT_c interval.


Delta QTc versus Concentration of Moxifloxacin at Expected Cmax (2 hours) after a Single Oral Dose
Delta QTc (mSec) - automatic
60
40
20
0
-20
-40
-60
-80
0
1000
2000
3000
4000
5000
Concentration (mcg/L)
y = 0.0061x - 7.3
R2 = 0.083
(without placebo)
200 mg (N=22)
400 mg (N=138)
600 mg (N=14)
800 mg (N=7)
Placebo (N=57)


Delta QTc versus Concentration of Moxifloxacin at Expected Cmax After Single and Multiple Oral and IV Doses
Delta QTc (mSec) - automatic
80
60
40
20
0
-20
-40
-60
-80
0
2000
4000
6000
8000
10000
12000
Concentration (mcg/L)
y = 0.0035x - 1.27
R2 = 0.146
(without placebo)
Single Oral Dose of >= 200 mg (N=181)
IV Single and Multiple Doses of <= 600 mg (N=96)
Placebo (N=131)

V. GENERAL COMMENTS TO BE FORWARDED TO THE SPONSOR

1. *The sulfate (M1) and glucuronide (M2) metabolites of moxifloxacin accumulate in patients with renal and hepatic impairment after a single 400 mg dose. The toxicologic implication in patients dosed up to 10 days is unknown. Therefore, the applicant is requested to perform a study to evaluate the toxicologic profile of these metabolites as a Phase IV commitment.*

2.

VI. LABELING COMMENTS TO BE FORWARDED TO THE SPONSOR

1. **Randomized, Open-label Investigation with Fourfold Crossover Design on Safety, Tolerability of BAY 12-8039 and the Influence of a 10 mL Suspension of Maalox® 70 on the Pharmacokinetics after Single Dose Administration of 400 mg BAY 12-8039 Given to Healthy Male Volunteers (Study Report 019; PH 26911/0123)**

   Moxifloxacin absorption is decreased when given 2 hours before or 4 hours after antacids. Reduced AUCs are observed in 50% of patients in these treatment groups below the lowest AUC value obtained when moxifloxacin is given alone. The dose of antacids used in this study is lower than the dose expected to be used in the clinical setting. The wording in the proposed label would allow administration of moxifloxacin 2 hours before or 4 hours after antacids. Since the applicant has not proven that the clinical relevance of this reduction in exposure is not signficant, this proposed wording is not acceptable. As a result, the wording in the label will be changed to state that moxifloxacin should be given at least 4 hours before or 8 hours after antacids. In addition, the applicant will be asked to make a Phase IV commitment to study moxifloxacin when given alone and at timepoints before and after a clinically relevant dose of antacids.

2. **Pharmacokinetics, safety and tolerability of a single oral dose of 200 mg of BAY 12-8039 in healthy young and elderly volunteers (Study Report 026; D95-029/0105)**

The absence of data from young females and the dose studied (200 mg versus the 400 mg proposed dosage) makes the conclusions reached from this study questionable. The applicant is requested to perform a study to adequately characterize the pharmacokinetic profile of moxifloxacin and its metabolites in males and females over a broad range of ages after single and multiple doses.

VII. RECOMMENDATION

The information contained in Item 6: Human Pharmacokinetics and Bioavailability of NDA 21-085 for moxifloxacin oral tablets has been reviewed and was found to be acceptable and adequate to support approval. The dissolution method and specifications are acceptable. The applicant will be asked to conduct Phase IV studies to enhance our understanding of the pharmacokinetics of moxifloxacin.

/S/ 12/1/99

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) /S/ 12/1/99

OCPB Briefing November 23, 1999 (attendees): Shiew-Mei Huang, John Lazor, Arzu Selen, Kathleen Uhl, Chandra Sahajwalla, Funmi Ajayi, Frank Pelsor, Dennis Bashaw, Kellie Reynolds, Sandra Suarez, Kofi Kumi, and Phil Colangelo.

cc: HFD-590: /NDA 21-085
/PM/JensenV
/MOTL/HopkinsR
/MO/MeyerhoffA
/MO/SacksL
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ
/Biopharm/ColangeloP
HFD-205: FOI

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

IX. ANALYTICAL METHODS SUMMARY

X. PHARMACOKINETIC STUDIES SUMMARY

The following is a summary of the results of the relevant pharmacokinetics and biopharmaceutics studies of moxifloxacin (BAY 12-8039).

A. *IN VITRO* STUIDES

Binding to Human Plasma Proteins and Erythrocyte Plasma Partitioning - Study Report 37; PH 25644

Moxifloxacin binds primarily to [redacted] in humans, as determined by ultrafiltration and equilibrium dialysis, but at a low percentage (~ 50%) that is independent of sex and concentration (0.1-10 mg/L). This suggests that moxifloxacin is unlikely to significantly alter the pharmacokinetics of highly protein bound drugs via a protein binding interaction. The affinity of moxifloxacin for erythrocytes is moderate, suggesting that moxifloxacin is not likely to be preferentially partitioned into human red blood cells.

Biotransformation in Man - Study Report 38; PH 27326

The metabolism and excretion of moxifloxacin was investigated in three healthy male volunteers after a single oral dose of 600 mg. Moxifloxacin undergoes two conjugation reactions in humans, sulfate conjugation and glucuronidation, accounting for [redacted] (M1 or BAY 31-8061) and [redacted] (M2) of the administered dose. Unchanged moxifloxacin represents [redacted] of the dose. In total [redacted] of the administered dose could be assigned to known structures. It does not appear that oxidative metabolism plays a significant role in the elimination of moxifloxacin in humans.

Determination of the Inhibitory Potency of BAY 12-8039 and its Major Metabolite M1 (BAY 31-8061) Towards Human Cytochrome P-450 Isozymes - Study Report 39; PH 27337

The inhibitory potency of moxifloxacin and its major metabolite, M1 (BAY 31-8061), towards eight human cytochrome P-450 isoenzymes was determined. Recombinant CYP isozymes (1A2, 2A6, 2C8, 2C19, 2D6, 2E1, and 3A4) were incubated in the absence and presence of moxifloxacin or M1 in order to compare the degree of inhibition of metabolite formation from standard probes.

The probe concentrations used were in 4-10 fold excess compared to the substrate concentration (one exception: 50-fold excess in the CYP 2A6 assay). The addition of moxifloxacin (BAY 12-8039) or M1 (BAY 31-8061) revealed turnover rates of standard probes compared to control of 89-100%. See tables below.

Inhibitory Effects of Moxifloxacin on Formation of Metabolites of Standard Probes Mediated by Cytochrome P-450 Isozymes

CYP Isozyme	Substrate	$C_{substrate}$ [µM]	$C_{moxifloxacin}$ [µM]	Formation of Probe Metabolites (% of control)	
				Measured	Calculated*
1A2	7-Ethoxycoumarin	10.0	100.0	92.8	77.6
2A6	Coumarin	2.0	100.0	96.2	75.8
2C8	Taxol	10.0	50.0	93.9	74.3
2C9-Arg	Tolbutamide	50.2	250.0	97.8	36.6
2C19	S-Mephentyoin	42.8	200.0	102.3	52.2
2D6-Val	Dextromethorphan	50.0	250.0	103.2	83.7
2E1	Chlorzoxazone	51.3	249.9	89.3	38.5
3A4	Testosterone	49.6	200.0	107.7	44.8

* inhibition, given as % of control. Calculations are performed according to I.H. Segel (Enzyme kinetics, John Wiley, 1993) assuming K_i-values of 100 µM and competitive inhibition.

Inhibitory Effects of BAY 31-8061 (M1) on Formation of Metabolites of Standard Probes Mediated by Cytochrome P-450 Isozymes

CYP Isozyme	Substrate	$C_{substrate}$ [µM]	$C_{moxifloxacin}$ [µM]	Formation of Probe Metabolites (% of control)	
				Measured	Calculated*
1A2	7-Ethoxycoumarin	10.0	100.0	94.6	77.6
2A6	Coumarin	2.0	100.0	89.3	75.8
2C8	Taxol	50.0	250.0	91.3	56.3
2C9-Arg	Tolbutamide	59.1	250.0	107.8	37.9
2C19	S-Mephentyoin	47.0	250.0	95.0	47.9
2D6-Val	Dextromethorphan	10.1	100.0	96.2	77.1
2E1	Chlorzoxazone	58.3	250.0	109.0	39.7
3A4	Testosterone	48.9	250.0	89.5	39.2

* inhibition, given as % of control. Calculations are performed according to I.H. Segel (Enzyme kinetics, John Wiley, 1993) assuming K_i-values of 100 µM and competitive inhibition.

Reviewer's comment: C_{max} values for BAY 12-8039 are approximately 10 µM after a single oral dose of 600 mg. Therefore, the concentrations used in these experiments are approximately 10-25 fold higher than clinically achievable concentrations.

In vitro results suggest that moxifloxacin and its major metabolite (M1) do not inhibit CYP isozymes 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4.

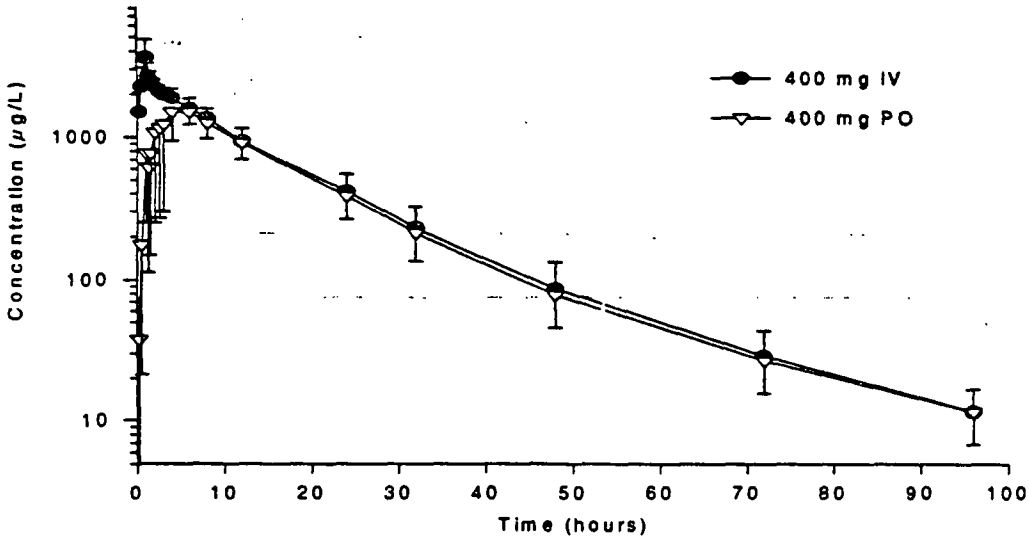
B. BASIC PHARMACOKINETICS

1. Mass Balance - Study Report 005; PH 27517/0139

This is a randomized, open-label, crossover study with administration of 400 mg moxifloxacin as a single oral or IV infusion over 60 minutes in 12 healthy male volunteers.

The mean plasma concentration versus time profile for moxifloxacin after a single oral or IV dose is shown below.

Geometric Mean Plasma Concentration Time Curves of Moxifloxacin Following a Single Dose of 400 mg Moxifloxacin Given Orally or as Intravenous Infusion (n=12)



The point estimates and 90% confidence intervals of the moxifloxacin AUC and C_{max} oral/IV ratios are given below. The absolute bioavailability of moxifloxacin is almost complete at 86%.

Point Estimates and 90 % Confidence Intervals for Oral/IV Ratios

Parameter	Point estimate (range)	90 % confidence interval
AUC	86 %	[81 ; 91 %]
C_{max}	69 %	[62 ; 77 %]

The plasma concentration of M1 (sulfate conjugate) and M2 (glucuronide conjugate) were determined in a subgroup of 8 subjects. The mean plasma concentration versus time profiles for M1 and M2 following oral and IV dosing are shown below.

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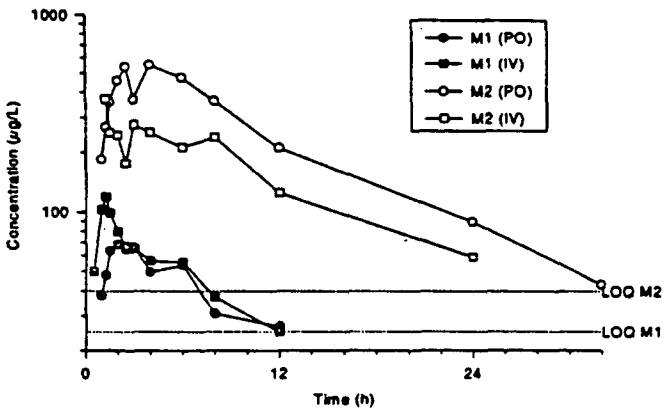
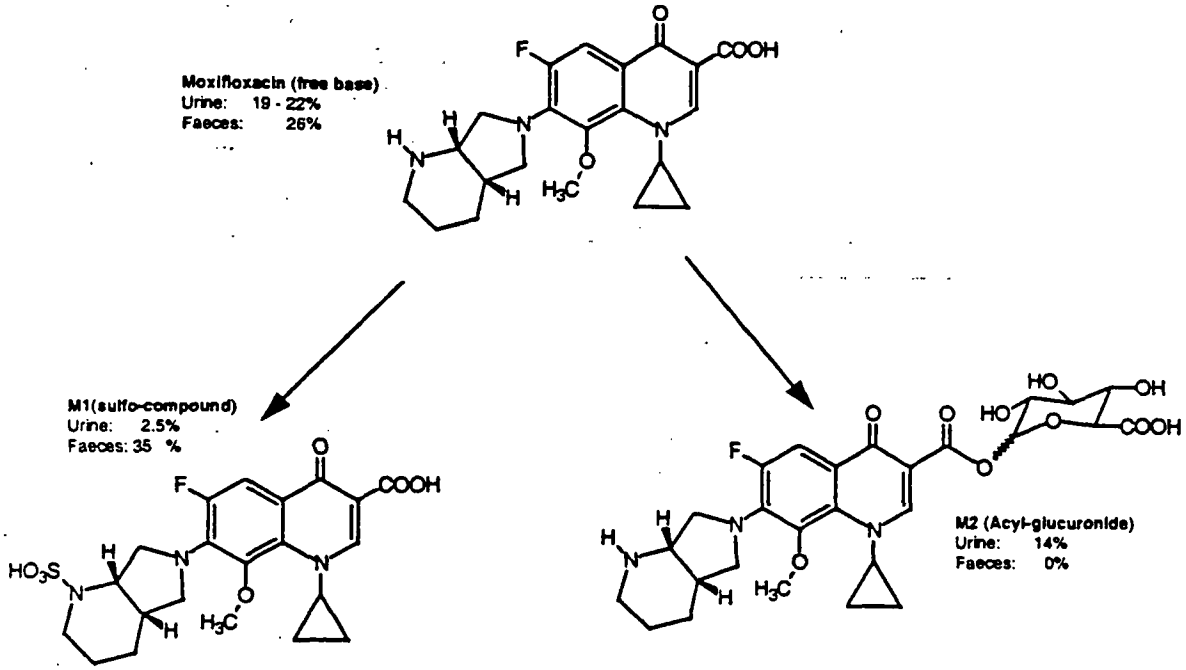
Geometric Mean Plasma Concentration Time Curves of M1 and M2 Following a Single Dose of 400 mg Moxifloxacin Given Orally or as Intravenous Infusion (N=8)



The M1 conjugated metabolite is detected in plasma in very low concentrations only, whereas M2 seems to be the main metabolite present in the plasma for both routes of administration. The C_{max} of M2 is approximately 1/2 that obtained with the parent drug after oral administration with concentrations approximately twice higher for the oral formulation compared to the infusion. The reason for this is unclear.

Elimination pathways of the drug were also quantitatively elucidated in the subset of 8 volunteers in the study. Elimination is independent from the mode of drug administration. Of the administered dose, 20% is excreted renally and 26% is excreted in the feces as unchanged drug. The M1 metabolite is mainly excreted in feces, 35% versus 2.5% of unchanged drug excreted in the urine. The M2 metabolite is found only in the urine (14% of unchanged drug). See figure below.

Metabolism of Moxifloxacin in Man Following a Single Dose of 400 mg Moxifloxacin Administered Orally or as Intravenous Infusion



As seen below, recovery of the drug amounted to 96.3% (oral) and 98.4% (IV) of the dose. Thus, the elimination pathways of the drug after single dose application in healthy male volunteers could be elucidated quantitatively.

Summary of Mass Balance Data (Arithmetic Mean ± SD)

	Percent (%) Recovered			
	Moxifloxacin (BAY 12-8039)	BAY 31-8061 (M1)	M2	Σ
Urine PO	19.4 ± 1.2	2.5 ± 0.6	13.6 ± 2.8	35.4 ± 1.8
Feces PO	25.4 ± 3.1	35.5 ± 3.2	-	60.9 ± 5.1
Σ PO (n=6)	**44.8 ± 3.3**	**37.9 ± 3.6**	**13.6 ± 2.8**	**96.3 ± 4.3**
Urine IV	21.9 ± 3.6	2.5 ± 0.9	13.8 ± 2.0	38.1 ± 2.1
Feces IV	25.9 ± 4.3	34.4 ± 5.6	-	60.2 ± 9.2
Σ IV (n=5)	**47.8 ± 7.2**	**36.8 ± 5.9**	**13.8 ± 2.0**	**98.4 ± 10.5**

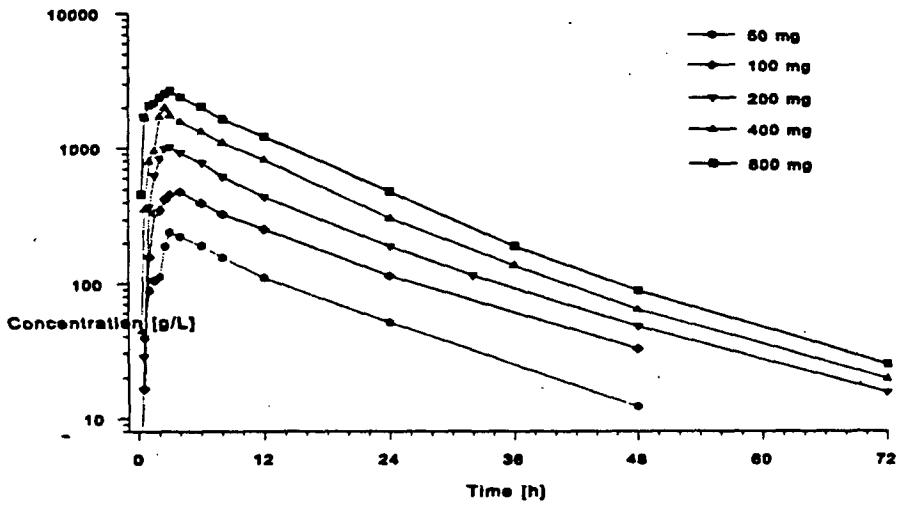
2. **Single Dose Pharmacokinetics** - Study Report 001; PH 26024/0101

This is a double blind, randomized, placebo-controlled study with five different moxifloxacin dose steps (50, 100, 200, 400, and 600 mg) in healthy male subjects. Dose steps of 50, 100, and 200 mg were investigated in a parallel-group design (6 of the 8 volunteers received the active treatment and the remaining 2 volunteers placebo). Dose steps of 400 mg and 600 mg were studied in a double crossover

design of 7 subjects each. Thirty-eight healthy male subjects participated in and completed the study. All are valid for analysis of pharmacokinetics.

An overview of the geometric mean plasma concentration versus time profiles and pharmacokinetic parameters for moxifloxacin following administration of the five single oral doses are shown in the figure and table below. *Please note the units on the y-axis of the figure should read "µg/L".*

Geometric Mean Plasma Concentration Time Curves of Moxifloxacin Following Administration of Ascending Oral Doses of Moxifloxacin (50 - 300 mg N=6, 400 and 600 mg N=7)



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3. **Multiple Dose Pharmacokinetics** - Study Report 008; D96-009/0110•MMRR 1387

This is a randomized, double blind, placebo-controlled trial in which healthy subjects received 400 mg of moxifloxacin (n=10) or placebo (n=5) orally once daily for 10 days in a fasted state.

Active drug (7 males, 3 females); placebo (3 males, 2 females).

The geometric means for all pharmacokinetic variables evaluated in this study on Day 1 and Day 10 are shown in the table below.

Summary Statistics of Pharmacokinetic Variables Moxifloxacin 400 mg Once Daily
Geometric Mean (Approximate Coefficient of Variation)

Variable	Units	Day 1	Day 10
$AUC_{0-\infty}$	(mg*h/L)	36.68 (13.2%)	--
$AUC_{0-\infty norm}$	(kg*h/L)	6.81 (12.4%)	--
AUC_{0-24}	(mg*h/L)	30.24 (14.2%)	47.97 (5.8%)
$AUC_{0-24norm}$	(kg*h/L)	5.66 (10.5%)	8.98 (16.9%)
C_{max}	(mg/L)	3.36 (21.5%)	4.52 (12.2%)
$C_{max,norm}$	(g/L)	0.63 (28.4%)	0.85 (18.8%)
T_{max}	(h)	1.49 (62.2%)	1.24 (48.0%)
$T_{1/2}$ (24)	(h)	9.30 (12.1%)	11.95 (10.8%)
$T_{1/2}$ (48)	(h)	--	12.71 (15.3%)
Accumulation Ratio		--	1.59 (13.1%)
Linearity Index		--	1.31 (12.8%)

After 10 days of repeated dosing, the mean AUC_{0-24} increases from 30.24 mg*h/L to 47.97 mg*h/L and the calculated accumulation ratio is 1.6. This result suggests that accumulation of moxifloxacin in plasma is [redacted] at steady state. The mean half-life estimate is prolonged after repeated dosing [redacted] The linearity index indicates there is a modest (30%) deviation from true linear pharmacokinetics. The mean T_{max} estimates remained stable between Days 1 and 10, although there was more interpatient variability on Day 1.

The plasma concentration of moxifloxacin is estimated to reach the steady state after at least 3 days of once daily administration based on the trough levels obtained in Study 0137 (400 mg po qd x 7 days).

C. TISSUE DISTRIBUTION

Study Report 33; PH-27947/0138
Study Report 031; PH-27932/0145
Study Report 030; PH-/0156
Study Report 32; PH-27994/0162

The sponsor conducted four tissue distribution studies to demonstrate moxifloxacin concentrations in alveolar macrophages, bronchial mucosa, epithelial lining fluid, maxillary sinus mucosa, anterior ethmoid mucosa, nasal polyps, blister fluid, subcutaneous tissue, and skeletal muscle relative to plasma. The drug concentrations in plasma and tissue at 3 hours following a single 400 mg oral dose are shown in the table below.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Dosing with 400 mg[$]

Tissue or Fluid	N	Plasma Concentration (µg/mL)	Tissue or Fluid Concentration (µg/mL or µg/g)}	Tissue: Plasma Ratio
Respiratory				
Alveolar macrophages	5		61.8 ± 27.3	
Bronchial Mucosa	8		5.5 ± 1.3	
Epithelial Lining Fluid	5		24.4 ± 14.7	
Sinus				
Maxillary Sinus Mucosa	4		7.6 ± 1.7	
Anterior ethmoid mucosa	3		8.8 ± 4.3	
Nasal polyps	4		9.8 ± 4.5	
Skin, Musculoskeletal				
Blister Fluid	5		2.6 ± 0.6	
Subcutaneous Tissue	6		0.9 ± 0.3*	
Skeletal muscle	6		0.9 ± 0.2*	

[$] all moxifloxacin concentrations were measured after a single 400 mg dose, except the sinus concentrations which were measured after 5 days of dosing

[†] N=5

[‡] N=7

[#] N=12

* reflects only non-protein bound concentrations of drug.

Moxifloxacin distributes into alveolar macrophages, bronchial mucosa and ELF and reaches concentrations higher than in serum. The highest concentrations are seen in the alveolar macrophages. The concentrations in alveolar macrophages remain relatively constant over time, while the serum concentrations decline readily. Therefore, the concentrations in alveolar macrophages do not correlate well with serum concentrations and the result is increasing tissue-to-serum concentrations over time.

Moxifloxacin distributes into sinus tissues where it reaches concentrations higher than in plasma. In maxillary sinus mucosa, anterior ethmoid mucosa, and nasal polyps, the concentrations were about 2.0, 2.2 and 2.6 times higher than in plasma at 3 hours after dosing, respectively, both declining at similar rate as the concentrations in plasma.

Concentrations of moxifloxacin are similar between blister fluid and plasma. It should be noted that blister fluid samples could not always be taken as planned. Therefore, pharmacokinetic estimates should be regarded only as explorative approximations.

Moxifloxacin also penetrates slowly into subcutaneous and skeletal muscle microdialysates. There is no qualitative difference between the subcutaneous and the skeletal muscle microdialysate, but the concentrations remain slightly higher in skeletal muscle compared to subcutaneous tissue during the late phases of the profile. During the terminal phase the profiles are comparable to the unbound concentrations in plasma (assuming ~ 50% protein binding). T_{max} is delayed compared to plasma most likely due to the time needed to get drug from the central compartment into the interstitial spaces.

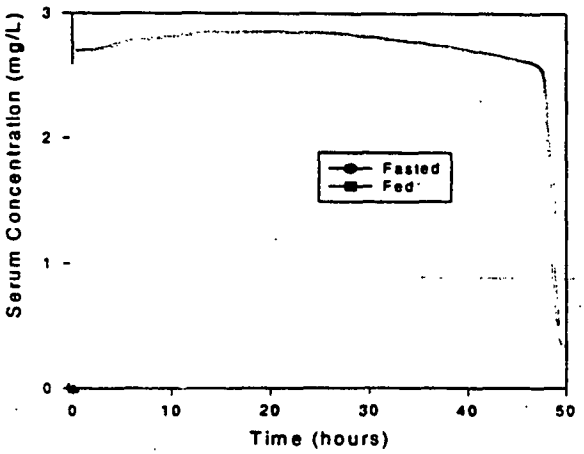
D. BIOAVAILABILITY AND BIOEQUIVALENCE

1. Bioavailability - Study Report 013; MRC-00913/100158

The study is a randomized two-period crossover study. Eighteen healthy male subjects received a single dose of 400 mg moxifloxacin (Formulation 231, the proposed commercial tablet formulation) on two separate occasions, with a one-week washout interval between each dose. One dose was administered on an empty stomach, after an overnight fast, while the other dose was given immediately following a high fat breakfast (FDA standard).

The geometric mean serum concentration profiles and pharmacokinetic parameters under fed and fasted conditions for the subjects with complete pharmacokinetic data are shown in the figure and table below.

Serum Concentrations of BAY 12-8039 Following a 400 mg Dose Given Under Fed and Fasted Conditions (n=16)



Geometric Mean (CV) [Range] Values of Pharmacokinetic Parameters after Dosing of Moxifloxacin 400 mg Oral Dose under Fed and Fasted Conditions

	N	FED	FASTED	RATIO** (Fed/Fasted)	90% CI
$AUC_{0-\infty}$ (mg·h/L)	15	37.74	38.45	0.97	0.95 - 1.00
AUC_{0-48}	16	35.34	36.61	0.96	0.93 - 0.99
C_{max} (mg/L)	16	2.50	2.80	0.88	0.78 - 0.98
T_{max} (hr)*	16	2.5			--
$t_{½}$ (hr)	15	11.7	11.5	1.01	0.97 - 1.05

* - median (range)
** - based on geometric least squares means

Administration of a single 400 mg dose of moxifloxacin to healthy male subjects under fed and fasted conditions results in similar estimates of $AUC_{0-\infty}$ (ratio 0.97; 90% confidence interval 0.95 – 1.00). The C_{max} is slightly reduced under fed conditions (ratio 0.88; 90% confidence interval 0.78 to 0.98).

These results indicate that food does not significantly alter the oral absorption of moxifloxacin from the proposed commercial tablet formulation.

2. **Influence of Dairy Products (Yogurt)** - Study Report 025; PH-27496/0157

This is a randomized, open-label study in two-way crossover design of 400 mg moxifloxacin administered as a single oral dose to 12 young healthy male subjects. In one period the medication was administered after the subject had eaten 250 gm of yogurt (about 1 cup), in the other period the subject was fasting. To compare the two treatments, ratios of moxifloxacin + yogurt to moxifloxacin alone were calculated and are shown below.

90 % Confidence Intervals for the Ratios 'Moxifloxacin + Yogurt / Moxifloxacin Alone'

	Point Estimate (Range)	90 % Confidence Interval
AUC	94 % [redacted]	[90 %; 98 %]
C_{max}	85 % [redacted]	[74 %; 98 %]

The systemic exposure to moxifloxacin as expressed by AUC is similar with comparable variability after administration of moxifloxacin in the fasted state or with 250 gm of yogurt (ratio 0.94; 90% confidence interval 0.90 to 0.98). The values for C_{max} are more variable (ratio 0.85; 90% confidence interval 0.74 to 0.98), but do not represent a statistically significant change. The mean percent change in C_{max} of moxifloxacin is −12.6% [redacted] when administration with yogurt is compared to administration of moxifloxacin alone.

Percent (%) Change in C_{max} of Moxifloxacin Alone Compared to Moxifloxacin + Yogurt

	Alone	With Yogurt	% Change
SUBJECT#	C_{max} [µg/L]	C_{max} [µg/L]	
3	2150	1560	-27.4
4	2650	2120	-20.0
5	3610	4170	15.5
6	2600	2280	-12.3
10	3850	3110	-19.2
12	1920	1680	-12.5
1	2240	2090	-6.7
2	2640	2930	11.0
7	2920	2000	-31.5
8	4780	2810	-41.2
9	2810	3780	34.5
11	3450	2040	-40.9
MEAN	**2968**	**2547.5**	**-12.6**
STD DEV	**819**	**822**	**23.2**
MIN	**1920**	**1560**	**-41.2**
MAX	**4780**	**4170**	**34.5**

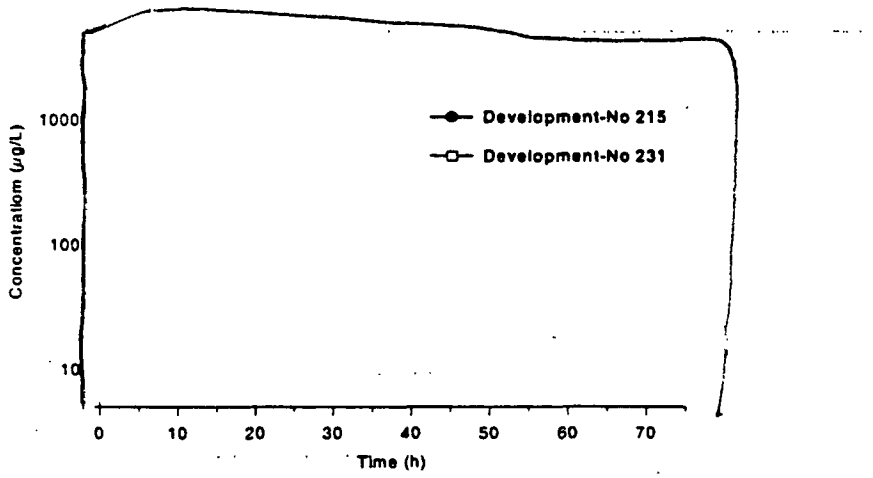
These results indicate that consumption of 1 cup of yogurt with moxifloxacin does not significantly change the rate (C_{max}) or extent (AUC) of exposure.

3. **Pivotal Bioequivalence** - Study Report 015; PH•27284/0141

This is a randomized, open-label, crossover study with two periods and two treatments in which administration of the two formulations of 400 mg moxifloxacin as a single oral dose was given to 24

healthy male subjects. The proposed commercial tablet formulation of moxifloxacin (Formulation 231) was studied relative to the clinical tablet formulation used in most clinical studies (Formulation 215). The geometric mean plasma concentration versus time curves for moxifloxacin following administration of the two formulations are nearly identical as illustrated in the figure below. The ratio of Formulation 231 (test) to Formulation 215 (reference) were calculated for AUC and C_{max} are shown in the table below.

Geometric Mean Plasma Concentration Time Curves of Moxifloxacin Following Oral Administration of 400mg Moxifloxacin (N=24)



Point Estimates and 90% Confidence Intervals for the Ratios 'Test Formulation (231) / Reference Formulation (215)'

	Point Estimate (Range)	90 % Confidence Interval
AUC	105 %	[102 %; 108 %]
C_{max}	95 %	[89 %; 102 %]

Both 90% confidence intervals for AUC and C_{max} are included in the interval [80 %; 125 %]. Thus bio-equivalence of the proposed commercial tablet formulation of moxifloxacin (Formulation 231) relative to the tablet formulation used in most clinical studies (Formulation 215) can be concluded.

E. SPECIAL POPULATIONS

1. Age and Gender - Study Report 026; D95-029/0105

This is a randomized, double blind, placebo-controlled, parallel-group study. Thirty-six (36) subjects participated in this study. Twelve (12) subjects were enrolled in each of the three groups shown below:

Group 1:	young males (18-45 years old)
Group 2:	elderly males (>65 years old)
Group 3:	elderly females (> 65 years old)

In each group 8 subjects received a single dose 200 mg of BAY 12-8039 and 4 received placebo. All 24 subjects who received moxifloxacin are valid for pharmacokinetic analysis.

Reviewer's Comment: The dose of moxifloxacin used in this study was 200 mg. The proposed dose is 400 mg.

Elderly versus Young Males

There are no statistically significant differences between young and elderly males for $AUC_{0-\infty}$ and C_{max}, as seen below. However, when normalized to dose and body weight, C_{max} is 27% higher in elderly males compared to young males. With regard to other pharmacokinetic parameters, slightly lower values for volume of distribution (↓14%) and renal clearance (↓17%) are seen in elderly males compared to young males. Neither difference reached statistical significance.

Ratio of Pharmacokinetic Parameters and 90% Confidence Intervals in Elderly Males Versus Young Males following a 200 mg Oral Dose of Moxifloxacin

Pharmacokinetic Parameter	Ratio*	90% Confidence Interval	P-value (Ratio=1)
$AUC_{0-\infty}$	1.02	0.85 - 1.23	0.839
$AUC_{0-\infty, norm}$	1.10	0.93 - 1.30	0.356
C_{max}	1.18	0.97 - 1.43	0.153
$C_{max, norm}$	1.27	1.08 - 1.49	0.020

* Ratio = Elderly Males/Young Males (Based on geometric least squares means)

Elderly Females versus Elderly Males

Pharmacokinetic results for AUC and C_{max} in elderly females and elderly males demonstrate that both parameters are higher in elderly females (by 29% and 24%, respectively), but only the difference in AUC reaches statistical significance. The higher exposure in elderly females can be explained by a lower mean weight of 20 kg compared to the elderly males (64 kg versus 84 kg). When AUC and C_{max} are normalized to dose and body weight, there are no statistically significant differences for either parameter between the two groups. With regard to other pharmacokinetic parameters, oral clearance is statistically significantly lower for elderly females compared to elderly males by 23%, but volume of distribution and half-life are not different. When oral clearance is adjusted for body weight (mean oral clearance/mean body weight) there are no differences between elderly males and females (0.128 L/h*kg for both groups). Renal clearance is not significantly different between elderly males and elderly females. Elderly women have a slightly higher percentage of renal excretion (20.8% versus 17.1%, p = 0.07) compared to elderly men.

Ratio of Pharmacokinetic Parameters and 90% Confidence Intervals in Elderly Females Versus Elderly Males following a 200 mg Oral Dose of Moxifloxacin

Pharmacokinetic Parameter	Ratio*	90% Confidence Interval	P-value (Ratio=1)
$AUC_{0-\infty}$	1.29	1.07 - 1.55	0.026
$AUC_{0-\infty, norm}$	0.98	0.82 - 1.16	0.800
C_{max}	1.24	1.02 - 1.51	0.067
$C_{max, norm}$	0.94	0.80 - 1.11	0.510

* Ratio = Elderly Females/Elderly Males (Based on geometric least squares means)

These results suggest no significant effect of age on the pharmacokinetics of moxifloxacin. However, the absence of data from young females and the dose studied (200 mg versus the 400 mg proposed dosage) makes the conclusions reached from this study questionable.

2. **Influence of Hepatic Impairment** - Study Report 028; PH-27643/0155

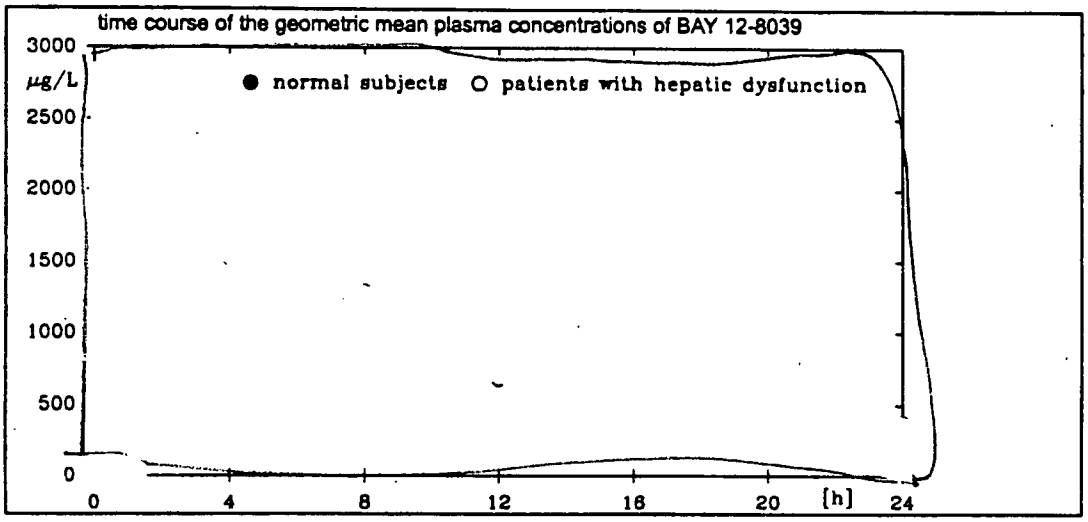
This is a multiple-center, single-dose, non-randomized, open-label, uncontrolled, parallel group trial. Age-matched (± 10 years) subjects either with (n=8) or without (n=10) hepatic function impairment received a single 400 mg dose of moxifloxacin. In the 8 patients with hepatic dysfunction, the impairment was mild (Child-Pugh Class A) in 6 and moderate (Child-Pugh Class B) in the other two patients. There were no patients with severe impairment (Child-Pugh Class C).

All 18 subjects completed the study in accordance with the protocol and are evaluable for pharmacokinetic analysis.

Moxifloxacin

The geometric mean plasma moxifloxacin concentration-time profiles are presented in the figure below.

Geometric Mean Moxifloxacin Plasma Concentrations Determined in Healthy Subjects and Patients with Hepatic Impairment Following Single Oral Administration of 400 mg Moxifloxacin



The geometric mean pharmacokinetic parameters (AUC and C_{max}) for moxifloxacin, in addition to point estimates and 90% confidence intervals (CI) of the true treatment ratios, are presented in the tables below.

Geometric Means / Geometric Standard Deviations (Range) of the Pharmacokinetic Parameters of Moxifloxacin After a Single Oral Dose of 400 mg Moxifloxacin in Healthy Subjects and Patients with Impaired Hepatic Function

Parameter	Units	Healthy Subjects (N=10)	Patients with Impaired Hepatic Function (N=8)
AUC	µg*h/L	32806.6 / 1.3	25089.4 / 1.3
C_{max}	µg/L	3017.95 / 1.3	2549.96 / 1.4

Point Estimates and 90% CI of the True Mean Ratios of the Plasma C_{max} and AUC of Moxifloxacin in Patients with Impaired Hepatic Function Relative to Healthy Subjects

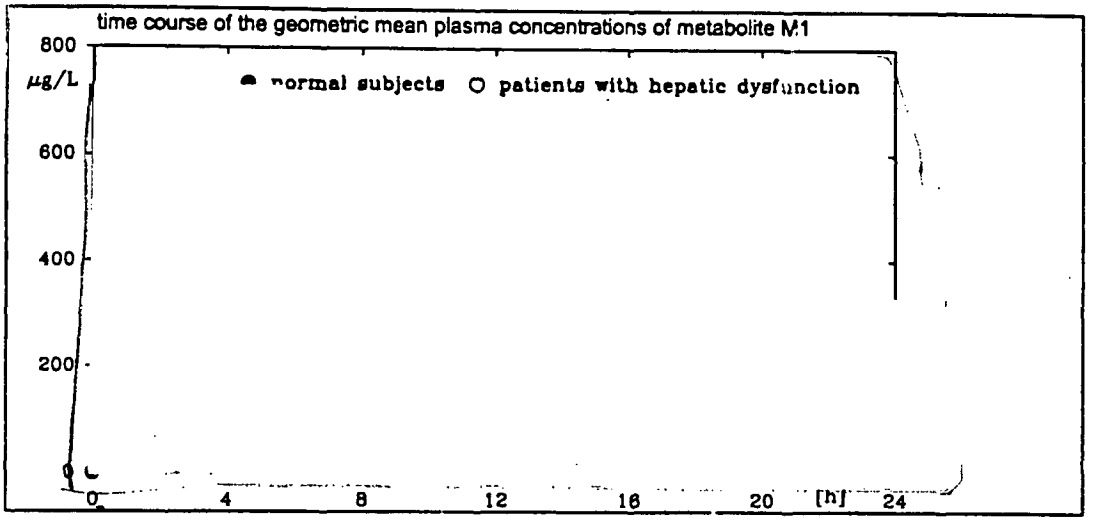
Parameter	Point Estimate (%)	90% CI
C_{max}	84.49	65.89 to 108.35
AUC	76.48	61.73 to 94.74

In comparison to the healthy subjects, the mean plasma C_{max} of moxifloxacin in patients with impaired hepatic function is approximately 16% lower. The mean total exposure, in terms of AUC, is also reduced by approximately 24% in hepatically impaired patients.

Metabolite M1

The geometric mean plasma metabolite M1 (sulfate conjugate) concentration-time profiles are presented in the figure below.

Geometric Mean Metabolite M1 Plasma Concentrations Determined in Healthy Subjects and Patients with Hepatic Impairment Following Single Oral Administration of 400 mg Moxifloxacin



The geometric mean pharmacokinetic parameters (AUC and C_{max}) for metabolite M1, in addition to point estimates and 90% confidence intervals (CI) of the true treatment ratios, are presented in the tables below.

Geometric Means / Geometric Standard Deviations (Range) of the Pharmacokinetic Parameters of Metabolite M1 After a Single Oral Dose of 400 mg Moxifloxacin in Healthy Subjects and Patients with Impaired Hepatic Function

Parameter	Units	Healthy Subjects (N=10)	Patients with Impaired Hepatic Function (N=8)
AUC	µg*h/L	1138.93 / 1.9	4974.85 / 1.6
C_{max}	µg/L	201.77 / 1.9	677.33 / 1.7

Point Estimates and 90% CI of the Plasma C_{max} and AUC of Metabolite M1 in Patients with Impaired Hepatic Function Relative to Healthy Subjects

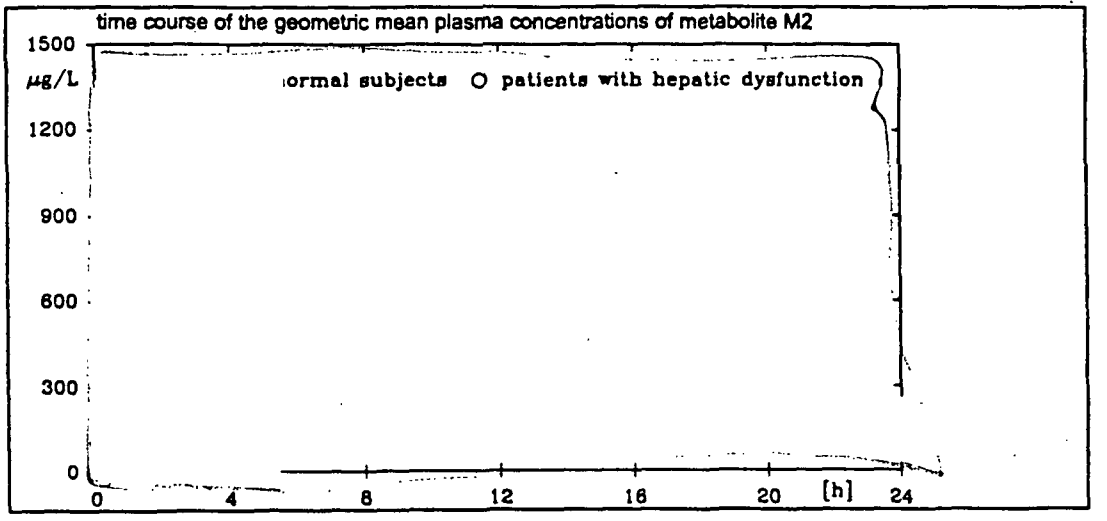
Parameter	Point Estimate (%)	90% CI
C_{max}	335.69	204.47 to 551.14
AUC	436.80	269.44 to 708.11

In comparison to the healthy subjects, the mean plasma C_{max} of metabolite M1 in patients with impaired hepatic function is increased by approximately 3-fold and individual values range up to 5.5-fold higher. The mean total exposure, in terms of AUC, is also increased by approximately 4-fold and individual values range up to 7-fold higher in hepatically impaired patients.

Metabolite M2

The geometric mean plasma metabolite M2 (glucuronide conjugate) concentration-time profiles are presented in the figure below.

Geometric Mean Metabolite M2 Plasma Concentrations Determined in Healthy Subjects and Patients with Hepatic Impairment Following Single Oral Administration of 400 mg Moxifloxacin



Reviewer's Comment: The plasma concentrations of metabolite M2 are below the LLQ for most time points in healthy subjects compared to patients with impaired hepatic function.

The geometric mean pharmacokinetic parameters (AUC and C_{max}) for metabolite M2, in addition to point estimates and 90% confidence intervals (CI) of the true treatment ratios, are presented below.

Geometric Means / Geometric Standard Deviations (Range) of the Pharmacokinetic Parameters of Metabolite M2 After a Single Oral Dose of 400 mg Moxifloxacin in Healthy Subjects and Patients with Impaired Hepatic Function

Parameter	Units	Healthy Subjects	Patients with Impaired Hepatic Function
AUC	µg*h/L	14499.3 / 2.2 *	15721.4 / 1.8
C_{max}	µg/L	889.84 / 2.9 †	1388.91 / 1.8

*quantifiable data available for 6/10 subjects

†quantifiable data available for 7/10 subjects

Point Estimates and 90% CI of the True Mean Ratios of the Plasma C_{max} and AUC of Metabolite M2 in Patients with Impaired Hepatic Function Relative to Healthy Subjects

Parameter	Point Estimate (%)	90% CI
C_{max}	156.09 †	72.47 to 336.20
AUC	108.43 *	56.42 to 208.38

† based on data from 7/10 subjects

* based on data from 6/10 subjects

In comparison to the healthy subjects, the mean plasma C_{max} in patients with impaired hepatic function is increased by approximately 1.5-fold and ranges up to 3-fold higher. The mean total exposure, in terms of AUC, is essentially unchanged, but individual values range from 50% less to 2-fold higher.

Reviewer's Comment: Comparisons of M2 parameter values between healthy subjects and patients with hepatic impairment should be done so cautiously, since data are not quantifiable for a substantial number of healthy subjects.

In summary, these results suggest no significant effect of mild hepatic impairment (Child-Pugh Class A) on the pharmacokinetics of moxifloxacin. Adjustment of the dose in patients with mild impairment of hepatic function is not necessary. There is insufficient data to make conclusions regarding patients with moderate or severe hepatic impairment (Child-Pugh Classes B and C). The clinical significance of the increases in M1 and M2 is not known.

Reviewer's Comment: The applicant has included only two patients with Child-Pugh Class B in this study. This number is too small to draw any conclusions regarding the effect of moderate hepatic dysfunction on the pharmacokinetics of moxifloxacin. The applicant was requested to provide the safety profile for patients with a Child-Pugh Class of B or C compared to normals enrolled in the Phase III trials, but they were unable to provide the information as requested. Therefore, in the label moxifloxacin will be contraindicated in patients with moderate to severe hepatic impairment.

3. Influence of Renal Impairment - Study Report 027; PH 27642/0148

This was a single-center, single-dose, non-randomized, open-label, non-controlled, parallel group trial. A single 400 mg dose of moxifloxacin was given to age-matched (± 10 years) subjects, aged between 18 and 75 years, and either with or without renal function impairment. Renal function was determined by creatinine clearance, which was obtained from a 24-hour urine collection within 1 week before dosing. The following four groups of subjects were defined as follows:

Group 1: CL_{CR} > 90 mL/min (n=8)
Group 2: CL_{CR} > 60 and ≤ 90 mL/min (n=31)
Group 3: CL_{CR} > 30 and ≤ 60 mL/min (n=7)
Group 4: CL_{CR} ≤ 30 mL/min (n=4) [not on dialysis from recruitment up to the end-of-study evaluation]

Results
All 32 subjects completed the study in accordance with the protocol and are evaluable for pharmacokinetic analysis.

Moxifloxacin
The point estimates and 90% confidence intervals (CI) of the true treatment ratios, are presented in the table below for moxifloxacin.

Point Estimate (%) and 90% CI of the True Mean Ratios for the Various Groups of the Plasma C_{max} and AUC of Moxifloxacin

Parameter	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
	PE	90% CI	PE	90% CI	PE	90% CI
AUC	103.1	82.6 to 1.29	113.6	88.0 to 146.6	101.3	81.5 to 149.2
C_{max}	105.0	80.9 to 136.3	77.6	57.5 to 104.8	80.5	56.4 to 114.9

The mean C_{max} of moxifloxacin was reduced by 22% and 20% in the patients with moderate (CL_{CR} > 30 and ≤ 60 mL/min) and severe (CL_{CR} ≤ 30mL/min) renal impairment, respectively. The mean AUC was also increased by 14% in the moderately impaired patients and unchanged in the severely impaired. The lower range of the 90% confidence intervals for the AUC and C_{max} in Group 4 < 80%. The clinical significance of this reduction is unknown.

Metabolite M1

The point estimates and 90% confidence intervals (CI) of the true treatment ratios, are presented in the table below for metabolite M1 (sulfate conjugate).

Point Estimate (%) and 90% CI of the True Mean Ratios for the Various Groups of the Plasma C_{max} and AUC of Metabolite M1

Parameter	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
	PE	90% CI	PE	90% CI	PE	90% CI
AUC	75.4	49.4 to 115.1	173.4	106.5 to 282.4	112.7	63.3 to 200.7
C_{max}	74.2	53.6 to 102.8	111.2	76.4 to 161.8	79.4	50.9 to 123.7

For metabolite M1, the overall exposure in terms of mean AUC is increased approximately 1.7-fold and (ranges up to 2.8-fold) between healthy subjects (Group 1) and moderately renally impaired patients (Group 3: $CL_{CR} > 30$ and ≤ 60 mL/min). The mean C_{max} remains essentially unchanged in all four groups.

Metabolite M2

The point estimates and 90% confidence intervals (CI) of the true treatment ratios, are presented in the table below for metabolite M2 (glucuronide conjugate).

Point Estimate (%) and 90% CI of the True Mean Ratios for the Various Groups of the Plasma C_{max} and AUC of Metabolite M2

Parameter	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
	PE	90% CI	PE	90% CI	PE	90% CI
AUC	135.5	91.0 to 201.8	182.5	117.1 to 284.4	282.3	167.0 to 477.3
C_{max}	109.1	69.9 to 170.1	95.4	57.6 to 157.8	140.3	77.3 to 254.6

For metabolite M2, the overall exposure in terms of mean AUC is increased approximately 2.8-fold (and ranges up to 4.8-fold) between healthy subjects (Group 1) and severely renally impaired patients (Group 4: $CL_{CR} \leq 30$ mL/min). In addition, there is a trend for higher mean C_{max} values in all degrees of renal impairment (Groups 2, 3, and 4).

In summary, these results make it difficult to conclude the effect of renal impairment on the pharmacokinetics of moxifloxacin.

Reviewer's Comment: Since this study did not provide a clear answer regarding the effect of renal impairment on the pharmacokinetics of moxifloxacin, the sponsor was requested to provide the efficacy profile (i.e. microbiologic and/or clinical success rates) for each indication for patients with a creatinine clearance of (1) < 30 mL/min, (2) >30 but < 60 mL/min, and (3) ≥ 60 mL/min enrolled in the Phase III trials. The resulting analysis showed similar clinical cure rates regardless of renal function. Therefore, the label will reflect that no dosage adjustment is necessary for moxifloxacin in renal impairment.

F. DRUG – DRUG INTERACTIONS

1. No significant interaction of the following co-administered drugs on the pharmacokinetics of moxifloxacin was shown:

- Theophylline 400 mg po Q12 hours x 3 days (with morning doses on Days 1 and 5) + moxifloxacin 200 mg po Q12 hours x 3 days (with morning doses on Days 1 and 5) (Study Report 017; R 7060/0107)

  Moxifloxacin was dosed at 200 mg every twelve hours in this study. The proposed dosing regimen for marketing will be 400 mg once daily.

- Digoxin 0.6 mg po as a single dose + moxifloxacin 400 mg po Qd x 2 days (Study Report 021; PH 27388/0142)

- Probenecid 500 mg po BID x 2 days + moxifloxacin 400 mg po as a single dose (Study Report 020; PH 26980/0135)

- Ranitidine 150 mg po BID x 3 days + moxifloxacin 400 mg po as a single dose (Study Report 018; PH 26603/0117)

2. No significant interaction of moxifloxacin on the pharmacokinetics of the following co-administered drugs was shown:

- Moxifloxacin 200 mg po Q12 hours x 3 days + theophylline 400 mg po Q12 hours x 3 days (Study Report 017; R 7060/0107)

  Moxifloxacin was dosed at 200 mg every twelve hours in this study. The proposed dosing regimen for marketing will be 400 mg once daily.

- Moxifloxacin 400 mg po Qd x 8 days + warfarin 25 mg po as a single dose on the fifth day (Study Report 024; R 7185/0151)

- Moxifloxacin 400 mg po Qd x 5 days + glyburide 2.5 mg po Qd for two weeks pretreatment and for 5 days concurrently (Study Report 022; MMRR 1455/0144 (D97-012-01))

No clinically significant interaction with warfarin or glyburide was determined by either the pharmacokinetic or pharmacodynamic results.

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

Effect of Moxifloxacin on Digoxin - Study Report 021; PH 27388/0142

This study is a placebo-controlled, randomized, three-period crossover, partially blinded (two treatments double blind, one treatment non-blind) study.

The following administrations were carried out in one of the three study periods:

Treatment A: moxifloxacin 400 mg po Qd x 2 days + β-acetyldigoxin 0.6 mg po as a single oral dose on Day 1

Treatment B: Placebo (for moxifloxacin) po Qd x 2 days + β-acetyldigoxin 0.6 mg as a single oral dose on Day 1

Treatment C: moxifloxacin 400 mg po Qd x 2 days

To compare the two treatments, ratios of moxifloxacin + digoxin to digoxin alone for the parameters $AUC_{(0\text{-}24h)}$, C_{max}, and C_{24h} were calculated and are summarized below. Estimates of differences for the parameter $Ae_{ur(0\text{-}24h)}$ are also included. Using ANOVA, no statistically significant difference between the two treatments is found with respect to $AUC_{(0\text{-}24h)}$. However, with respect to C_{max}, C_{24h} and $Ae_{ur(0\text{-}24h)}$, statistically significant treatment differences were found: C_{max} is approximately 50% higher and ranges up to 2-fold higher, trough concentrations (C_{24h}) are 18% lower, and the difference in renal excretion is 4% higher for digoxin when given in combination with moxifloxacin as compared to when given alone.

Reviewer's Comment: Although it appears that moxifloxacin increases the C_{max} of digoxin, therapeutic drug monitoring for digoxin is based upon trough concentrations, which do not appear appreciably changed by the presence of moxifloxacin. The sponsor has completed a chronic digoxin-moxifloxacin

interaction study (Study #0036) to examine the effects of 400mg moxifloxacin once daily for 14 days on steady state digoxin pharmacokinetics. This study was submitted to the IND for moxifloxacin. The sponsor's conclusion from this follow-up study is that C_{max} of digoxin increases, but not C_{min}.

Estimates (LS-Means) of Ratios (Moxifloxacin + Digoxin to Digoxin Alone) with 90 % Confidence Intervals for Primary Pharmacokinetic Parameters (Total Study Population, N=11)

Parameter	Estimated Ratio (%)	90 % Confidence Interval
$AUC_{(0\text{-}24h)}$	107.5	[96.1 ; 120.3]
C_{max}	149.6	[109.7 ; 204.1]
C_{24h}	81.8	[71.3 ; 93.8]
$Ae_{ur(0\text{-}24h)}$ *	4.2	[2.0 ; 6.4]

* Estimates of differences

Effect of Antacids on Moxifloxacin
Maalox® 70 + moxifloxacin - Study Report 019; PH 26911/0123

This is a randomized, open-label, four-way crossover study in 12 healthy male subjects with single dose administration of 400 mg moxifloxacin (8 x 50 mg tablets) alone or with 10 mL oral suspension of Maalox® 70 at different dosing times. Subjects were randomly assigned to receive a different order of the following four treatments:

Treatment A: 400 mg moxifloxacin (8 x 50 mg tablets) alone
Treatment B: 400 mg moxifloxacin (8 x 50 mg tablets) simultaneously with 10 mL Maalox® 70.
Treatment C: 400 mg moxifloxacin given 4 hours after the administration of 10 mL Maalox® 70.
Treatment D: 400 mg moxifloxacin given 2 hours before the administration of 10 mL Maalox® 70.

Reviewer' Comment: The recommended dose of Maalox® Suspension, which it the comparable liquid form of this antacid in the US, is 30 mL. See the following table for a comparison of the aluminum and magnesium content per dose of Maalox® Suspension and Maalox® 70.

Drug Product	*Aluminum Hydroxide (mg)*	*Magnesium Hydroxide (mg)*
Maalox® Suspension per 30 mL	*1350*	*1200*
Maalox® 70 per 10 mL	*900*	*600*

The dose of antacids used in this study contains less aluminum and magnesium hydroxide than the dose expected to be used in the clinical setting.

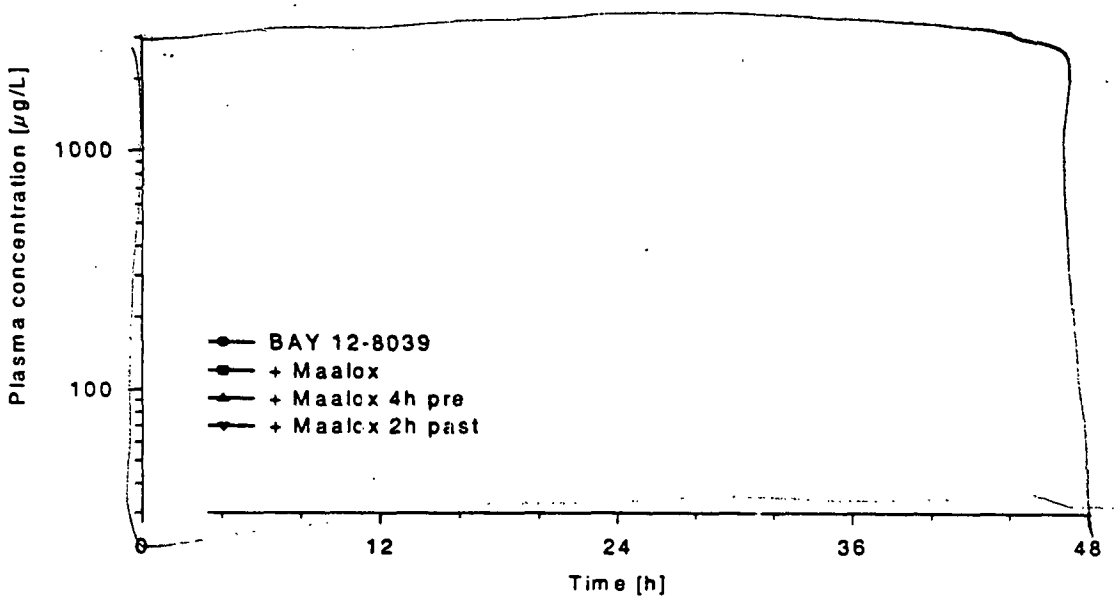
Each subject received 400 mg moxifloxacin in the fasted state.

After the initial administration of Maalox® 70, the antacid was to be given another 5 times for Treatments B, C, and D, each time 1 hour after the forthcoming mealtimes. The study was conducted in four periods with one "Pre-day" and one "Profile day" with administration of moxifloxacin followed by an observation period of 48 hours each. The washout phase between different periods was at least 7 days.

The geometric mean plasma concentration-time profiles for moxifloxacin when administered alone or in combination with Maalox® 70 are shown in the figure below. The pharmacokinetic parameters for moxifloxacin are also summarized in the table below.

Reviewer's Comment: For clarification of the legend on the following figure: "BAY 12-8039" refers to Treatment A (Moxifloxacin alone), "+ Maalox" refers to Treatment B (Moxifloxacin given simultaneously with Maalox), "+ Maalox 4 h pre" refers to Treatment C (Moxifloxacin 4 hours post-Maalox), and "+ Maalox 2 h past" refers to Treatment D (Moxifloxacin 2 hours pre-Maalox).

Geometric Mean Plasma Concentration Time Curves of Moxifloxacin Following Single Oral Dose Administration of Moxifloxacin Alone and in Combination with Maalox 70® (N=12)



Point Estimates and 90% CIs for the Ratios of Moxifloxacin + Maalox 70®/Moxifloxacin Alone for Various Moxifloxacin Pharmacokinetic Parameters (N=12)

Parameter	Ratio*	Geometric mean ratio (%)	90 % confidence interval
AUC	D / A	73.76	[65.22 ; 83.41]
	B / A	40.73	[36.02 ; 46.06]
	C / A	77.36	[68.41 ; 87.48]
C_{max}	D / A	92.49	[77.42 ; 110.50]
	B / A	38.74	[32.43 ; 46.28]
	C / A	98.97	[82.85 ; 118.24]

A = moxifloxacin alone
B = moxifloxacin simultaneously Maalox® 70.
C = moxifloxacin given 4 hours after the administration Maalox® 70.
D = moxifloxacin given 2 hours before the administration of Maalox® 70.

*Reviewer's Comment: When individual AUC values obtained in Treatment A (moxifloxacin alone) are compared to Treatments C and D (moxifloxacin 4 hour after and 2 hours before Maalox 70®, respectively), 6/12 subjects in Treatments C and D had lower AUC values than the lowest AUC (27.7 mg*h/L) obtained in Treatment A.*

The data clearly indicate that concomitant dosing of moxifloxacin simultaneously with an antacid containing magnesium and aluminum (Maalox® 70) leads to impaired absorption and a clinically significant reduction in the plasma concentrations of moxifloxacin. The AUC of moxifloxacin is also substantially reduced when moxifloxacin is given 2 hours before or 4 hours after Maalox® 70.

Reviewer's Comment: The wording in the proposed label would allow administration of moxifloxacin 2 hours before or 4 hours after antacids. Since the applicant has not shown that the reduction in exposure

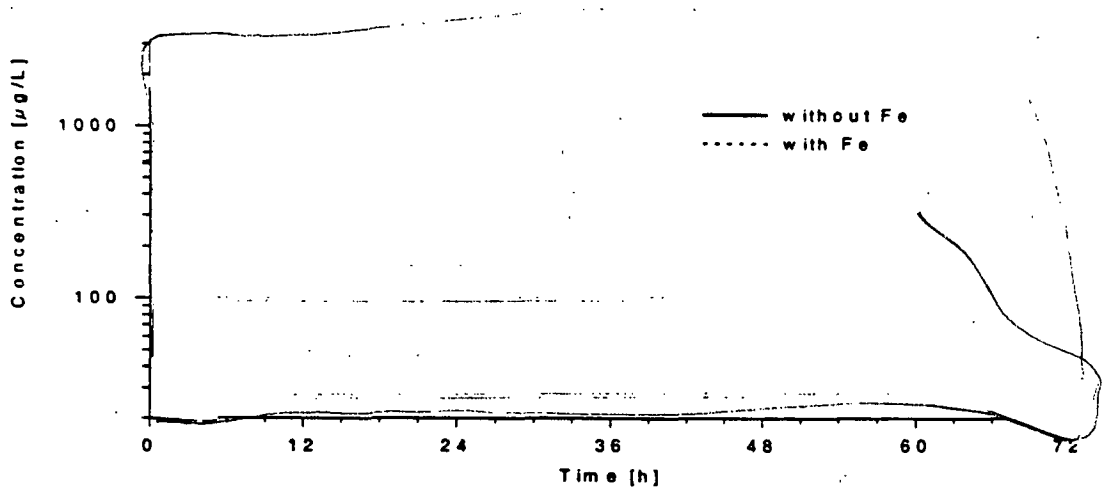
is insignificant, this proposed wording is not acceptable. As a result, the wording in the label will be changed to state that moxifloxacin should be given at least 4 hours before or 8 hours after antacids.

Iron Study Report 023 - Study Report 023, PH 27392/0146

Twelve (12) healthy young male subjects were enrolled in this randomized open-label, two-period, crossover study. Subjects were randomized to receive a single oral dose of 400 mg moxifloxacin on Day 1 alone or combined with a dose of iron as ferrous sulfate (Eryfer® 100) on Day 1. In the combination treatment arm, a second dose of iron was given on Day 2.

The geometric mean plasma concentration-time profiles for moxifloxacin when administered alone or in combination with iron are shown in the figure below. To compare the two treatments, ratios of moxifloxacin + iron / moxifloxacin alone (test/reference) for AUC and C_{max} were calculated and are also summarized in the table below.

Geometric Mean Plasma Concentration Time Curves of Moxifloxacin Following Single Dose Administration of 400 mg Moxifloxacin with and without Concomitant Administration of Iron (n=12)



Point Estimates and 90% Confidence Intervals for the Ratio of Moxifloxacin + Iron/Moxifloxacin Alone for Moxifloxacin Pharmacokinetic Parameters (N=2)

	Point Estimate (range, %)	90% Confidence Interval (%)
AUC	61	54 - 69
C_{max}	41	34 - 49

The AUC and C_{max} of moxifloxacin are decreased by 39 % and 59%, respectively, following concomitant administration with iron. Not only extent, but also rate of absorption is decreased. The time to reach peak concentrations (T_{max}) increases almost 3-fold. Renal excretion is decreased by 39%, which also supports the finding of decreased absorption of moxifloxacin with concomitant iron.

Pharmacokinetic results from plasma and urine demonstrate a significant decrease in absorption of moxifloxacin when administered concomitantly with iron. Therefore, concomitant administration of moxifloxacin and iron preparations should be avoided.

Reviewer's Comment: In the proposed label, it will be stated that iron should be administered at least 4 hours before or 8 hours after moxifloxacin to be consistent with the dosing recommendations for antacids.

F. SPECIAL SAFETY STUDIES

1. **Phototoxicity Study** - Study Report 043; PH 26490/0108

This is a randomized, double blind, placebo- and active- controlled study. Following pre-study screening, including phototesting, 32 subjects (8 per treatment group) received 200 mg moxifloxacin, 400 mg moxifloxacin, 400 mg lomefloxacin, or placebo once daily for seven days. From Days 5 to 7 of the study, phototesting to assess the subject's minimal erythema dose (MED) was performed using a range of wavebands chosen to represent the UVB (280-315 nm), UVA (315-400 nm), and visible radiation (>400 nm) spectrum.

Moxifloxacin at a dose of 200 mg or 400 mg failed to produce phototoxicity when tested in with a range of wavebands covering the UVA, UVB and visible radiation spectrum. A dose-dependent phototoxicity for the two tested moxifloxacin dosages could not be demonstrated.

The lomefloxacin positive control revealed a statistically significant decrease in the 24-hours MED for the wavelengths 335±30 nm and 365±30 nm when compared with both doses of moxifloxacin and placebo groups. The MEDs for both moxifloxacin dose groups for these wavelengths were similar to placebo. No phototest change was established for any of the four treatment groups in wavelengths 305±5 nm, 400±30 nm and 430±30 nm in this study.

On the basis of these data, moxifloxacin appears to produce little or no phototoxicity.

Reviewer's Comment: In the label for moxifloxacin there will be a class labeling statement similar to other quinolones that states: Photoxicity has been reported in patients receiving quinolones. Although there was little or no photoxicity seen with moxifloxacin at the recommended dose, care should be taken to avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds) while taking moxifloxacin and to discontinue if phototoxicity (e.g., sunburn-like reaction or skin eruptions) occurs.

2. **Effect of Single Oral or Intravenous Doses of Moxifloxacin (BAY 12-8039) on QT Interval** - Study Report 041; PH-27956/0163

This is as a single center, placebo-controlled, randomized, double blind, crossover clinical trial of three periods (moxifloxacin 400 mg, moxifloxacin 800 mg, or placebo as a single oral dose). The fourth, and final, study period was conducted as an open-label, single IV administration of 400 mg moxifloxacin over 60 minutes. Twenty (20) healthy male and female subjects were enrolled.

The pharmacokinetics of moxifloxacin after a single 400 mg oral dose in young females versus young males is shown below.

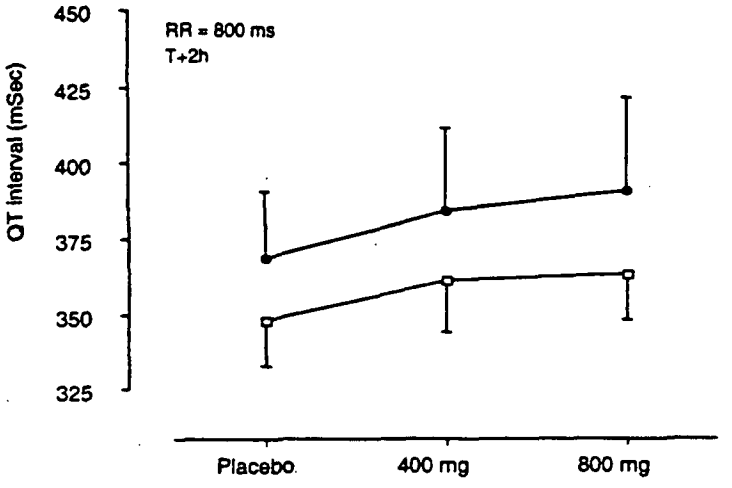
FEMALES			**MALES**		
Subject #	AUC (mcg*h/L)	Cmax (mcg/L)	Subject #	AUC (mcg*h/L)	Cmax (mcg/L)
3	51300	2880	5	36000	3880
10	38000	3260	16	36100	2100
115	68600	4490	9	37800	3730
107	47600	3280	17	27600	3570
2	45800	3330	12	38300	2720
18	54800	2740	13	41900	3740
6	44300	3850	1	38600	2810
11	37200	3320	4	39900	3360
14	53700	3400	8	40200	3440
MEAN	**49033.3**	**3394.4**	**MEAN**	**37377.8**	**3261.1**
STD DEV	**9615.7**	**517.4**	**STD DEV**	**4129.7**	**593.1**
MIN	**37200**	**2740**	**MIN**	**27600**	**2100**
MAX	**68600**	**4490**	**MAX**	**41900**	**3880**

The mean AUC is approximately 30% higher in young females compared to young males. There is no significant difference in the mean C_{max}.

ECGs were obtained at rest and during the course of a 20-minute exercise tolerance test (ETT) at 2 hours after dosing, to correspond with the expected C_{max} of moxifloxacin. The ETT involved successive load levels until a heart rate of 160 bpm was reached. For the resting ECGs, QT was corrected for heart rate by [redacted] cubic root formula QTcF. The QT was also corrected for heart rate by [redacted] formula (QTc or QTcB).

A possible gender influence on the QTc changes was investigated in this study. Mean calculated QT interval values 2 hours post-oral dosing (expected C_{max}) for RR = 800 msec (heart rate = 75 bpm) in males and females are shown graphically below.

Mean Calculated* QT Interval Duration (msec) in Male (squares) and Female (dots) Subjects 2 Hours After Administration of Placebo, 400 mg and 800 mg of Moxifloxacin (RR=800 msec)



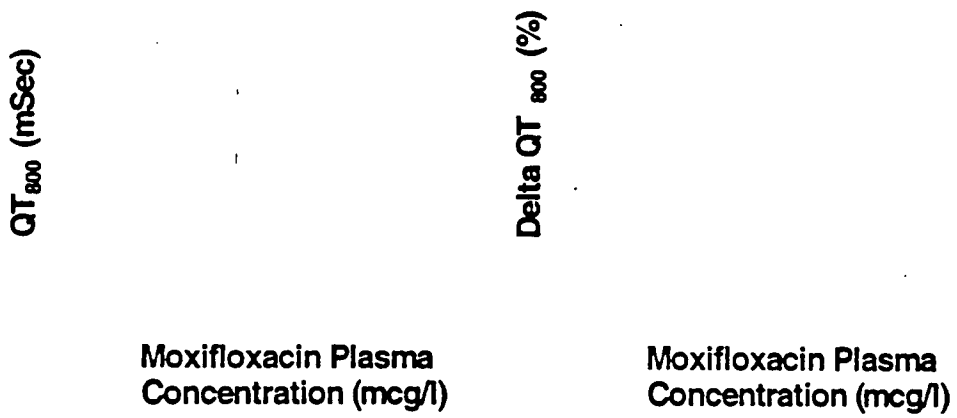
(*) QT = A-B* exp (-C*RR) (where A, B, C are the regression parameters)

The calculated QT interval values are higher in female subjects, as compared to male subjects, for all tested doses and RR intervals. The difference can be accounted for by the fact that females have physiologically higher baseline values. Therefore, there was no indication of any significant difference of the QT prolonging effect of moxifloxacin due to gender.

Moxifloxacin showed no relevant reverse-rate dependence with either oral dose (400 mg or 800 mg) and had no effect on heart rate at rest. Both of these parameters, if positive, are known predictors of *Torsades de Pointes*.

A correlation was established between the calculated QT interval change and the moxifloxacin plasma concentration at 2 hours post-dosing (the expected C_{max}) for RR = 800 msec as shown below.

Relationship Between Calculated* QT Interval Duration and Moxifloxacin Plasma Concentration at C_{max} (RR=800 msec)



(*) QT = A-B* exp (-C*RR) (where A, B, C are the regression parameters)

Since outlying abnormal values (QTcB > 450 msec for male or QTcB > 470 msec for female) are considered to be more important than mean values for the assessment of a potential proarrhythmic effect, an additional descriptive analysis was performed focusing on all resting ECGs that were recorded after study drug intake regardless of time post-dosing. No male subject developed a QTcB value above 450 msec, while, among the female subjects, two had a QTcB value above 470 msec. Corrected by formula, these two values remained < 470 msec.

A change in QTc values (as compared to baseline) above 60 msec is considered to determine a potential increase risk to induce *Torsades de Pointes*. Changes in QTcB values above 60 msec were recorded in 17 out of 806 (2.1 %) resting ECGs recorded after study drug intake: 1 after 400 mg oral, 12 after 800 mg oral, and 4 after 400 mg IV administration of moxifloxacin. A change in QTcF above 60 msec was observed in 7 out of 806 ECG tracings and all occurred after 800 mg of oral moxifloxacin.

Although the data are limited, it does appear that there is a relationship between the concentration of moxifloxacin and the increase in QTc interval.

3. **Pharmacokinetics of Intravenously Administered Moxifloxacin (BAY 12-8039) and the Influence of Different Rates of Infusion on the QTc Interval** - Study Report 042; PH-27691/0149

This is a single center, single dose, crossover, randomized; single-blind trial comprised of three periods and three treatment groups. Twelve (12) healthy male subjects were given a single IV dose of 400 mg moxifloxacin (infused at 12 mg/min), 600 mg moxifloxacin (infused at 6 mg/min), and placebo in a randomized fashion.

Complete pharmacokinetic data are available for 10 patients, but all 12 are included in the safety (QT) population.

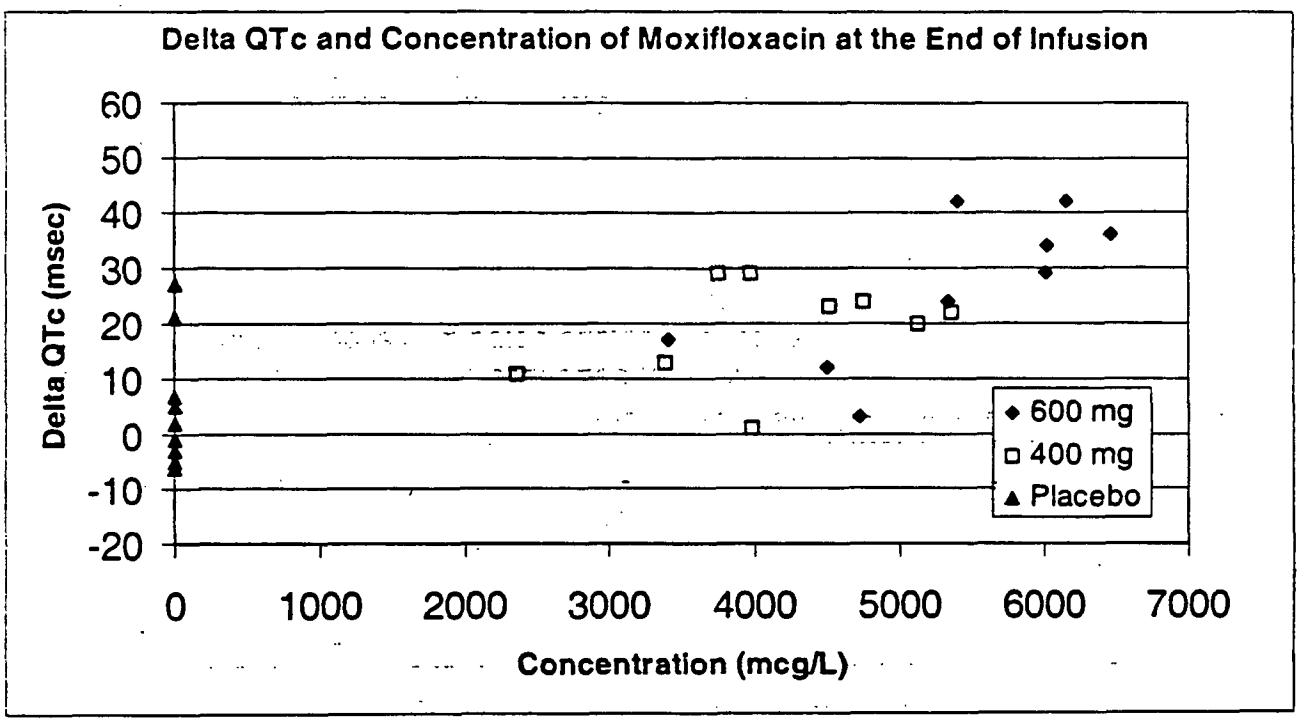
Geometric Means / Geometric SD (Range) of Moxifloxacin Pharmacokinetic Parameters in Plasma Following a Single Intravenous Infusion of 400 mg over 33 minutes and 600 mg Moxifloxacin Over 100 minutes

Parameter	Unit	Moxifloxacin 400 mg IV 33 minute infusion (N=9)	Moxifloxacin 600 mg IV 100 minute infusion (N=9)
AUC	mg*h/L	42.9 / 1.12	67.8 / 1.18
AUC_{norm}	kg*h/L	8.52 / 1.16	8.75 / 1.21
C_{max}	mg/L	4.28 / 1.23	5.25 / 1.22
$C_{max, norm}$	µg/L	0.85 / 1.34	0.68 / 1.25
T_{max}^{*}	h	0.5	1.67
MRT	h	15.0 / 1.14	16.0 / 1.22
$T_{1/2}$	h	13.5 / 1.22	14.2 / 1.18
V_{ss}	L/kg	1.75 / 1.17	1.83 / 1.13
CL	L/h	9.32 / 1.12	8.86 / 1.18

*Median (Range)

The pharmacokinetics of moxifloxacin are similar for both treatments with AUC_{norm} estimates indicating dose proportionality for a 400 and 600 mg IV infusion. Administration of the 400 mg dose of moxifloxacin results in peak concentrations that are slightly lower (by 18 %) compared those achieved with the 100 minute infusion of 600 mg moxifloxacin. However, when normalized to dose and body weight, the C_{max} values are higher for the 400 mg dose group.

There appears to be a weak correlation between the moxifloxacin concentration at the expected C_{max} (end of the infusion) and the change in QTc (ΔQTc) compared to placebo (seen below in the figure and in the table).



Categorical Changes in the ΔQTc* at the End of Infusion (N=12)

Treatment (study time)	Δ QTc ≤ 20 msec	Δ QTc > 20 msec	Δ QTc ≤ 30 msec	Δ QTc 31 - 60 msec	Δ QTc > 60 msec
Placebo +	# 1, # 2, # 5, # 10, # 11, # 12, # 204	# 3, # 9	# 1, # 2, # 3, # 5, # 9, # 10, # 11, #12, # 204	-	-
400 mg (30 min)	# 1, # 4, # 6, # 7, # 11, # 12	# 2, # 3, # 5, # 10, # 204	# 1, # 2, # 3, # 4, # 5, # 6, # 7, # 10, # 11, # 12, # 204	-	-
600 mg (1 h 40 min)	# 1, # 2, # 5	# 3, # 6, # 9, # 10, # 12, # 204	# 1, # 2, # 5, # 10, # 12	# 3, # 6, # 9, # 204	-

* ΔQTc = QTc at the end of infusion minus QTc at baseline
+ QTc values at 30 min and 1 h 40 min were reviewed and the highest of the two values was selected

For placebo treatment, all ΔQTc values are below 30 msec. With two exceptions they are even below 20 msec. At the end of a 400-mg moxifloxacin infusion over 30 minutes, there is no ΔQTc exceeding 30 msec, but half of the subjects display values between 20 and 30 msec. In the 600 mg infusion group, some ΔQTc values range up to 31- 60 msec at the end of a 100 minute infusion. None of the QTc values exceeded the normal range, and none of the ΔQTc values was greater than 60 msec. There were no clinical signs or symptoms associated with the QTc changes.

This study demonstrates a concentration-dependent effect of moxifloxacin on the QTc when given as a single intravenous infusion. Unfortunately, the relationship between the infusion rate of moxifloxacin and the ΔQTc interval can not be determined from this study, since the sponsor used two different doses of moxifloxacin and the infusion rate for the lower dose was faster than the infusion rate for the higher dose.

4. **Pharmacokinetics, Pharmacodynamics and Safety of an Intravenous Infusion of 400 mg BAY 12-8039 (Moxifloxacin) in Healthy Young and Elderly Volunteers** - Study Report 036; D97-021/0154

This is a randomized, double blind, placebo-controlled, parallel group study, comprised of two stages. Stage I consisted of a single 15 minute infusion of 400 mg moxifloxacin (n=6) or placebo (n=3) to young male subjects. Stage II consisted of a single 15 minute infusion of 400 mg moxifloxacin (n=12) or placebo (n=6) followed by four daily 60-minute infusions to healthy elderly male and female subjects.

The table below provides a summary of the pharmacokinetic parameters for the 6 subjects in Stage I and the 12 subjects in Stage II who received moxifloxacin.

Geometric Mean (Approximate % CV) Pharmacokinetic Parameters In Plasma Following IV Doses of 400 mg Moxifloxacin

Variable	Stage I: Young Males (N=6)	Stage II: Elderly Males and Females (N=12)	
	Day 1	*Day 1*	*Day 5*
$AUC_{0-\infty}$ (mg*h/L)	36.30 (11.0%)	38.59 (21.4%)	NA
$AUC_{0-\infty\ norm}$ (kg*h/L)	7.14 (19.2%)	7.71 (17.6%)	NA
AUC_{0-24} (mg*h/L)	30.14 (6.6%)	32.90 (20.8%)	47.37 (19.6%)
$AUC_{0-24\ norm}$ (kg*h/L)	5.93 (16.0%)	6.57 (15.7%)	9.47 (19.1%)
C_{max} (mg/L)	6.63 (29.5%)	6.62 (27.1%)	5.94 (21.4%)
$C_{max\ norm}$ (kg/L)	1.30 (34.3%)	1.32 (30.4%)	1.19 (19.1%)
T_{max} (h)	0.25 (0.0%)	0.26 (20.0%)	1.00 (0.0%)
$T_{1/2}$ (h)	9.31 (16.5%)	8.63 (14.6%)	10.06 (15.5%)

Although this is not a comparative study, Day 1 pharmacokinetic results (i.e. following the 15-minute infusion) are similar between young males (Stage I) and elderly males and females (Stage II).

Day 5 results for the elderly subjects reflect the longer infusion time with approximately 10% lower mean values for C_{max} and $C_{max\ norm}$ and a longer time to maximum concentration (T_{max}) as compared to Day 1 results. The AUC_{0-24} is higher on Day 5 as compared to Day 1 with a ratio of 1.44. Values for $T_{1/2}$ are also slightly increased on Day 5 (17%) as compared to Day 1 in this elderly population.

The table below provides a summary of the change in QTc (ΔQTc) by treatment group for both stages of the study.

ΔQT_c Interval (msec) [LS Means (SE)] in All Subjects Following 400 mg IV Moxifloxacin Infused over 15 Minutes (Day 1) or 1 Hour (Day 5)

Stage	Day	Change[1]	Moxifloxacin	Placebo	p-value[2]
I	Day 1	Pre-dose Day 1 to 0.25 hours	25.7 (10.6)	19.3 (15.0)	0.740
II	Day 1	Pre-dose Day 1 to 0.25 hours	17.8 (3.3)	-1.8 (4.7)	0.003
	Day 5	Pre-dose Day 1 to 1 hour	5.1 (3.5)	-13.7 (5.0)	0.007
	Day 5	Pre-dose Day 5 to 1 hour	13.6 (3.0)	-2.0 (4.2)	0.008

[1] 0.25 hours is the end of a 15 minute infusion; 1 hour is the end of a 60 minute infusion
[2] From ANOVA with term for treatment

Administration of moxifloxacin at a dose of 400 mg IV is associated with increases in the QT_c interval. In the young male subjects receiving moxifloxacin (Phase I) the ΔQT_c interval following the rapid infusion (15 minutes) is of similar magnitude as that observed in the elderly subjects (Phase II, Day 1). Although the change in young subjects treated with moxifloxacin was not statistically different from that seen in the placebo group (Phase I), it should be noted that the placebo group consists of only three subjects and one has a ΔQT_c interval of 65 msec.

In elderly subjects (Phase II), administration of moxifloxacin at a dose of 400 mg IV is associated with statistically significant increases in the QT_c interval compared to placebo at the end of a 15-minute single infusion and at the end of the fourth of four daily 60-minute infusions. Although not compared statistically, there appears to be little difference in the ΔQT_c interval between the 15-minute rapid infusion and the longer 60-minute infusion in elderly subjects. In addition, the magnitude of change appears to be similar between young and elderly subjects after a single 15-minute infusion. No statistical comparisons were performed between Stage I and Stage II or between dosing days.

Limitations of this study in predicting the association between moxifloxacin infusion rate or age and ΔQT_c include: parallel rather than cross-over study design, too many variables in the analysis (age, infusion rate, single versus multiple dose), and unequal number of subjects in Stage I (young) versus Stage II (old).

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