CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-277

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-277
Submission Dates:	11/02/00
Drug:	Moxifloxacin hydrochloride (Avelox®) 400 mg IV Infusion
Sponsor:	Bayer Corporation Bayer Pharmaceutical Division West Haven, CT
Type of Submission:	New NDA
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

EXECUTIVE SUMMARY

I. BACKGROUND

Moxifloxacin (BAY 12-8039) is a synthetic C-8-methoxy-fluoroquinolone antibiotic. The oral formulation was approved in the United States on December 10, 1999 for three indications: acute sinusitis; acute bacterial exacerbations of chronic bronchitis; and community-acquired pneumonia. A fourth indication of skin and skin structure infections was approved on April 27, 2001.

II. INDICATIONS AND DOSAGES

Moxifloxacin IV will be marketed in ready-to-use 250 mL flexibags as a sterile, preservative-free aqueous solution (0.15% NaCl) of moxifloxacin hydrochloride (400 mg).

A dosage of 400 mg a 60 minute intravenous infusion once daily is proposed for all indications previously granted to oral moxifloxacin. The proposed indications and duration of therapy are listed below.

Infection *	Daily Dose	Duration
Acute Sinusitis	400 mg	10 days
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	5 Days
Community Acquired Pneumonia	400 mg	7-14 days
Uncomplicated Skin and Skin Structure Infections	400 mg	7 days

* due to designated pathogens

III. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS SYNOPSIS

Item 6 of this submission (Human Pharmacokinetics and Bioavailability) is comprised of data from eleven Phase I studies of IV moxifloxacin, two Phase III studies of IV moxifloxacin in patients for the treatment of community-acquired pneumonia, and three pharmacokinetic/pharmacodynamic studies performed as Phase IV commitments for NDA 21-085 (moxifloxacin oral tablets).

The basic pharmacokinetic parameters, including relative bioavailability of the IV compared to the oral formulation, for moxifloxacin are characterized in single and multiple dose pharmacokinetic studies in healthy young and elderly male and female subjects and patients. Special safety studies of the effect of IV and oral administration of moxifloxacin on the QT interval were also included. In addition a tissue distribution study evaluating the penetration of moxifloxacin into subcutaneous tissues, as well as saliva, and blister fluid was included. These studies are summarized in Section X (Pharmacokinetic Summary) of this review and full study reports are included in Appendix 2, Pharmacokinetic Study Reviews.

Is the relative bioavailability of IV moxifloxacin similar to oral moxifloxacin?
The extent of exposure for IV and oral moxifloxacin was determined to be similar with a mean point estimate of the ratio of oral to IV for AUC of 86% ( ) in the mass balance study (Study Report 0139). However, the two formulations differed in terms of C_{max} (mean point estimate 69%; range ( )).

The two tables below summarize comparisons of the AUC and C_{max} ratios for the two formulations across studies. The IV formulation has a mean AUC value that is similar between the IV and oral formulations with a mean value 11% higher for the IV [redacted] compared to the oral formulation. However, the mean C_{max} is 29% higher for IV moxifloxacin (range 14% to 25% higher) compared to oral moxifloxacin.

Comparison of Moxifloxacin AUC Values Following Single IV* and Oral Doses

Study Number	Dose	IV C_{max} (mg*h/L)	Oral C_{max} (mg*/L)	Ratio (%) IV : Oral
0136	100 mg	11.708	10.752	9%
0139	400 mg	34.6	29.8	16%
0156	400 mg	39.761	35.496	12%
0145	400 mg	42.6	39.3	8%
0163	400 mg	46.333	42.331	9%

* 60 minute IV infusion

Comparison of Moxifloxacin C_{max} Values Following Single IV* and Oral Doses

Study Number	Dose	IV C_{max} (mg/L)	Oral C_{max} (mg/L)	Ratio (%) IV : Oral
0136	100 mg	1.345	1.154	16%
0139	400 mg	3.62	2.50	45%
0156	400 mg	3.647	3.189	14%
0145	400 mg	3.21	2.49	29%
0163	400 mg	4.588	3.283	40%

* 60 minute IV infusion

Are there new data, since the approval of oral moxifloxacin, on the effect of age and gender on the pharmacokinetic parameters of moxifloxacin?

The pharmacokinetics of moxifloxacin, in terms of AUC_{0-12} and C_{max}, in healthy young and elderly, male and female subjects was determined after a 400 mg single oral dose. The following conclusions were made:

Geriatrics
Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male and 8 female) and 16 young (8 male and 8 female) healthy volunteers, there were no age-related changes in moxifloxacin pharmacokinetics.

In two Phase III studies, the pharmacokinetics in elderly patients following IV infusion of 400 mg were similar to those observed in young patients.

Gender
Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 15% higher, respectively, in females compared to males. There were no

significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration.

Are there new data, since the approval of oral moxifloxacin, on the potential for drug-drug interactions with moxifloxacin?

In vivo Interactions: There was no clinically significant effect of moxifloxacin on itraconazole (and its metabolite hydroxy-itraconazole) or oral contraceptives. Itraconazole, morphine, and calcium did not affect the pharmacokinetics of moxifloxacin.

The effect of activated charcoal in conjunction with IV and oral moxifloxacin was studied to assess the impact of use of this agent in cases of moxifloxacin overdose. Administration of 40 grams of activated charcoal with a single 400 mg oral dose of moxifloxacin led to an 85% loss in absolute bioavailability of moxifloxacin. However, administration of 40 grams of activated charcoal with a single 400 mg IV dose of moxifloxacin led to only a 20% loss in absolute bioavailability of moxifloxacin. These results suggest that absorption of oral moxifloxacin is effectively prevented by activated charcoal. Administration of activated charcoal should be recommended for treatment of overdose with oral moxifloxacin early after intoxication. However, it will be of limited use after overdose with the IV formulation and therefore is not recommended in this situation.

What is the relationship between the concentration of IV moxifloxacin and QTc prolongation and how does it compare that that of oral moxifloxacin?

The relationship between moxifloxacin concentration at C_{max} (i.e., at the end of the IV infusion) and QTc prolongation was determined in Phase I (healthy volunteers) and Phase III (patients with community-acquired pneumonia) studies. These data can be compared to previously collected data from single escalating dose and multiple dose studies of oral moxifloxacin.

Concentration of Moxifloxacin at the End of Infusion and Corresponding ΔQTc Following Moxifloxacin IV Dosing

Source	Setting	Concentration at the end of infusion (mg/L) Mean ± SD [Range]	ΔQTc (msec) Mean ± SD [Range]
Phase I	Single and Multiple Doses ≤ 600 mg (N=96)	4.56 ± 2.01	15.8 ± 15.5
Phase III	Single 400 mg Dose (N=57)	4.01 ± 1.44	15.5 ± 26.6
	Multiple 400 mg Dosing (N=45)	4.38 ± 1.37	10.6 ± 31.6

Concentration of Moxifloxacin at C_{max} and Corresponding ΔQTc Following Moxifloxacin Oral Dosing

Source	Dose	Setting		C_{max} (mg/L) Mean ± SD [Range]	ΔQTc (msec) Range of Mean*
Phase I	400 mg	Single Dose	N=61	2.93 ± 0.95	
			N=48	3.3 ± 0.9	
			N=46	3.20 ± 0.62	
	400 mg	Multiple Dose (N=47)		4.0 ± 0.6	
	800 mg	Single Dose	N=61	5.26 ± 1.20	
			N=47	6.1 ± 1.5	
	1200 mg	Single Dose (N=61)		7.41 ± 1.50	

* range of change using four different definitions of baseline

As seen in the table above the concentrations of moxifloxacin and associated degree of QTc prolongation obtained following IV dosing is contained within the range of exposures and prolongation seen previously with oral moxifloxacin.

IV. GENERAL COMMENTS (NOT TO BE FORWARDED TO THE SPONSOR)

The Medical Division has determined that this NDA will be "Approvable" pending insertion of labeling information on cardiac safety in elderly patients.

V. LABELING COMMENTS

1. **Clinical Pharmacology:** The table of pharmacokinetic parameters should be separated into two tables; one with oral data and one with IV data.

2. **Clinical Pharmacology, Electrocardiogram:** The paragraph should be modified to not mention specific QT changes with oral and IV moxifloxacin.

VI. RECOMMENDATION

The information contained in Item 6 Human Pharmacokinetics and Bioavailability of NDA 21-277 for moxifloxacin IV infusion has been reviewed and was found to be acceptable.

The proposed labeling revisions to be sent to the applicant can be seen in Appendix 1.

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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) _____

cc: HFD-590: /NDA 21-277
/PM/KongY
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ
HFD-205: FOI

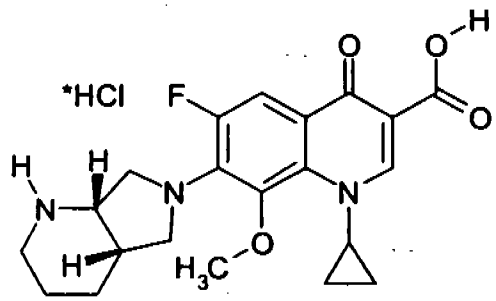
SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

VII. DRUG CHARACTERISTICS/FORMULATIONS/DISSOLUTION METHOD

Physical/Chemical Properties

Chemical name
1-Cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid hydrochloride

Structure
The molecule possesses two stereogenic centers and represents the pure S,S-enantiomer.



$C_{21}H_{24}FN_3O_4$ *HCl

Because the correct stereochemical configuration is introduced with the starting material, no stereoselective synthesis or racemate separation is required in the synthesis of moxifloxacin.

Molecular Weight
M.W. 437.9 g/mole

Solubility
BAY 12-8039 is a pale yellow crystalline substance which is soluble in 0.1M NaOH, sparingly soluble in water and methanol, and slightly soluble in 0.1M HCl, N,N-dimethylformamide and ethanol. The drug substance is practically insoluble in dichloromethane, acetone, ethylacetate and toluene, and insoluble in t-butyl-methylether and n-heptane.

The specific rotation $[\alpha]_D^{20}$ in acetonitrile - water (1+1) is -131°.

The pK_A-values of the drug substance as determined by means of potentiometric titration are 6.38 (carboxylate function) and 9.53 (NH-function).

Formulation
Moxifloxacin IV will be available in ready-to-use 250 mL (400 mg) flexibags as a sterile, preservative-free aqueous solution of moxifloxacin hydrochloride with pH ranging from 4.1 to 4.6. The appearance of the IV solution is yellow. The inactive ingredients are sodium chloride, USP and Water for Injection, USP, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

VIII. ANALYTICAL METHODS SUMMARY

Concentrations of moxifloxacin and its conjugated metabolites (M1 and M2) were determined in plasma and urine with a [redacted] assay using fluorescence detection for the majority of studies in this NDA.

The full validation and performance reports of the assays in plasma and urine were submitted for each Phase I clinical pharmacology study. The usual lower limits of quantification (LLQ) and calibration ranges for these assays are shown below.

Substance	Plasma		Urine	
	LLQ (µg/L)	*Calibration Range (µg/L)*	*LLQ (µg/L)*	*Calibration Range (µg/L)*
BAY 12-8039 (moxifloxacin)				
M1 (BAY 30-8161)				
M2 (as BAY 12-8039)				

The performance of these assays during study sample analysis was acceptable as evidenced by QC sample precision and accuracy within ± 15%.

IX. PHARMACOKINETIC STUDIES SUMMARY

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

A BASIC PHARMACOKINETICS

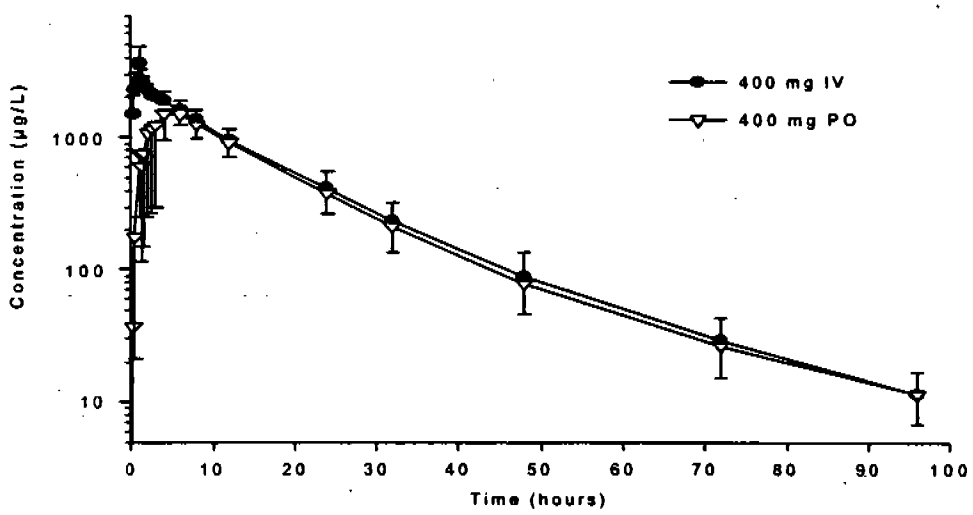
Reviewer's Comment: For a complete summary of the clinical pharmacokinetics of moxifloxacin, including disposition in special populations, please see the Biopharm review for NDA 21-085 (Moxifloxacin oral tablets).

Mass Balance - Study Report 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 % (74 - 106 %)	[81 ; 91 %]
C_{max}	69 % (51 - 94 %)	[62 ; 77 %]

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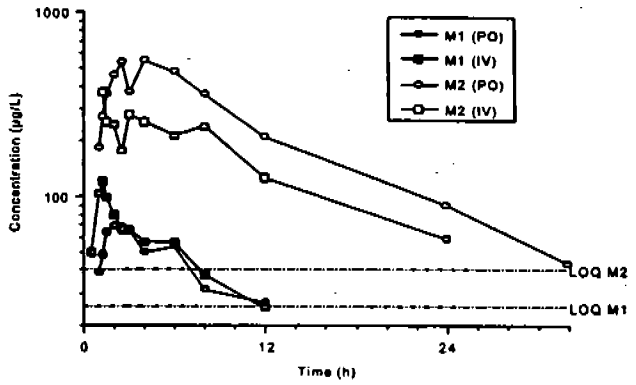
The plasma concentration of M1 (sulfate conjugate) and M2 (glucuronide conjugate) were determined in a subgroup of 8 subjects. The mean plasma concentration versus time profiles for M1 and M2 following oral and IV dosing are shown below.

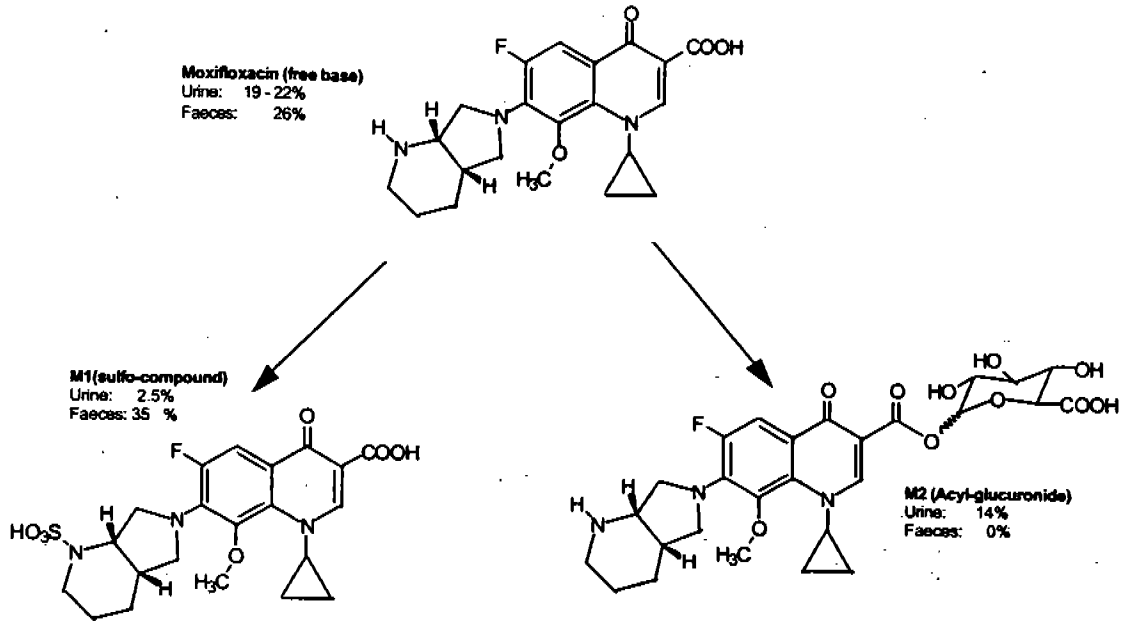
Geometric Mean Plasma Concentration Time Curves of M1 and M2 Following a Single Dose of 400 mg Moxifloxacin Given Orally or as Intravenous Infusion (N=8)



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**

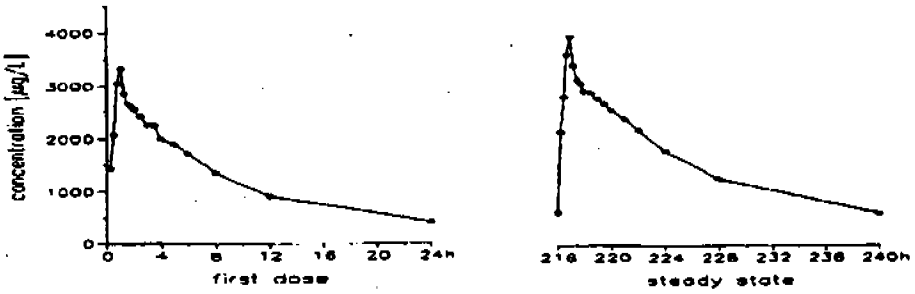
Single and Multiple Dose Pharmacokinetics – Study Report 0143

This was a single center, placebo-controlled, randomized, double blind, multiple dose, parallel group clinical trial of 400 mg BAY 12-8039 (or the respective placebo) diluted in 200 ml solution administered once daily as an intravenous (IV) infusion over 60 minutes for 10 consecutive days to 12 healthy male subjects.

Of the 12 subjects included in the study, 8 received active drug and 4 received placebo. All 8 subjects were valid for pharmacokinetic analysis.

In the figure below the geometric mean plasma concentration versus time profiles for the 400 mg IV dose on Days 1 (first dose) and 10 (steady state) are presented.

Geometric Mean Plasma Concentration-Time Profiles of BAY 12-8039 Following Once Daily Infusion of 400 mg (N=8)



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The table below presents the geometric means for most of the pharmacokinetic variables evaluated in this study.

Summary Statistics of Pharmacokinetic Variables BAY 12-8039 After a Single Dose of 400 mg IV Once Daily and on Day 10 at Steady State Geometric Mean/Standard Deviation (Range) [N=8]

Parameter	Unit	Day 1	Day 10	ratio	90% CI	R_A
$AUC_{ss,norm}$ or $AUC_{t,ss,norm}$	$[kg*h/L]^{-1}$	6430/1.12	6990/1.12	109%	104%-113%	109%/1.06
$C_{max,norm}$ or $C_{max,ss,norm}$	$[kg/L]^{-1}$	669/1.22	755/1.22	113%	100%-127%	113%/1.20
t½	h	9.87/1.16	14.7/1.17			
CL	L/h	11.5/1.13	10.6/1.13			
V_{ss}	L/kg	2.02/1.09	2.19/1.09			
$Ae_{ur,t}$	%	18.3/1.26	25.5/1.19			
CL_R	L/h	2.56/1.22	2.70/1.22			
PTF	%		218/1.33			

Accumulation of BAY 12-8039 at steady state is minimal (< 15%) and it does not appear that the drug exhibits non-linear pharmacokinetics after multiple doses.

The $t_{1/2}$ appears different on Days 1 and 10 and can be explained by the fact that concentrations were measured for 24 hours after the first dose and for 96 hours after the start of the infusion on Day 10.

The applicant noted that the drug infusions were switched off after the planned amount had been infused, as calculated by the nominal drug content of the infusion solution and the measured flow rates of the infusion pumps. Therefore, most of the infusions lasted slightly less than 60 minutes. Since the 1 hour blood sample was obtained at the correct time relative to the start of the infusion, it was often obtained a few minutes after the infuision ended. Therefore, the applicant cautions that the concentration measured in the 1 hour sample may not reflect the true C_{max} in all subjects.

Reviewer's Comment: The formulation of IV moxifloxacin used in this study was D_5W. The intended marketed formulation is in a solution of 0.16% NaCl. A single IV dose of moxifloxacin in 0.16% NaCl

infused over 30 minutes (Study Report 0132) was compared to a 30 min IV moxifloxacin infusion in D_5W (Study Report 000068) and the pharamcokinetic results were found to be similar.

B. SPECIAL POPULATIONS

Reviewer's Comment: For a complete summary of the clinical pharmacokinetics of moxifloxacin, including disposition in special populations, please see the Biopharm review for NDA 21-085 (Moxifloxacin oral tablets).

Age and Gender – Pooled Analysis of Study Reports 100263, 100264, and 100267

The AUC_{0-12} and C_{max} data from Studies 100263, 100264, and 100267 were pooled for analysis of the influence of age and gender on the pharmacokinetics of moxifloxacin following single oral doses of 400 mg.

Age

- The AUC_{0-12} [d] moxifloxacin was not statistically different between young and elderly (22.47 versus 23.95 mg*h/L), but was statistically different between middle aged and elderly (21.44 versus 23.95 mg*h/L). When normalized to body weight, there were no statistically significant differences across all three age groups (4.07, 4.29, and 4.31 kg*h/L).
- The C_{max} of moxifloxacin was statistically lower between young (2.96 mg/L) and middle aged (2.90 mg/L) and elderly (3.21 mg/L) subjects. When normalized to body weight, the difference between young subjects and the other two age groups persisted (0.54, 0.58, and 0.58 kg/L, respectively).

Gender

- Females had a 30% higher AUC_{0-12} (25.77 versus 19.82 mg*h/L) and a 34% higher C_{max} (3.50 versus 2.61 mg/L) than males, which was statistically significant. This difference was lower, but persisted after adjustment for body weight: 4.46 versus 4.0 kg*h/L for AUC_{0-12} (12% higher) and 0.61 versus 0.53 kg/L for C_{max} (15% higher).

In summary, younger subjects appear to have a lower C_{max} than older subjects, but the AUC_{0-12} is not statistically significant between age groups.

Females have a higher AUC_{0-12} and C_{max} by up to 34% than males and this difference persists after adjustment for body weight.

Pharmacokinetics in Patients (Pooled Analysis of Studies 100039 and 200036) – Study Report RH 30765

Protocol 100039 (North American study) was a randomized, double-blind, double dummy, multicenter clinical trial comparing daily 400 mg moxifloxacin IV versus (initially) trovafloxacin 200 mg IV, and later levofloxacin 500 mg IV. Patients eligible for the study were adults with community-acquired pneumonia of sufficient severity that hospitalization and IV therapy were warranted. Patients were to receive IV therapy with the study drugs for a minimum of 3 days, and depending on the clinical condition of the patient, to switch to the same daily dose of study drug orally for a 7 to 14 day course of therapy. Plasma samples for pharmacokinetic investigations were drawn from a subgroup of patients according to a sparse sampling schedule during the IV treatment phase.

Protocol 200036 (referred to as the Ex-North America study) was a randomized, open-label, multicenter, multinational study comparing 400 mg moxifloxacin IV against amoxicillin/clavulanate IV with or without clarithromycin IV, with a switch to oral therapy after a minimum of 3 days of intravenous administration. Study subject entry criteria were similar to study 100039, and the duration of therapy was also 7 to 14 days.

In both studies, plasma samples for pharmacokinetic investigations were drawn from a subgroup of patients according to a sparse sampling schedule during the IV treatment phase. Data from mulitple dose Phase I studies were provided by the sponsor as a comparison. The results are shown in the table below. The mean moxifloxacin concentration at the end of a single dose infusion was higher on Day 1 compared to Day 3 for both studies. Moxifloxacin concentrations on both days were higher and more variable than those previously reported in Phase I. The mean moxifloxacin concentration at the end of infusion in Study 200036 on both days was higher than in Study 100039, especially on Day 1. In a subgroup analysis of the Phase III data broken down by gender, female patients had higher concentrations at the end of infusion than males in both studies on both days. A population pharmacokinetic analysis was also performed by the applicant using a subgroup of patients from Study 200036, but did not add any additional information beyond the pooled analysis.

Comparison of Plasma Concentrations at the End of Infusion in Phase III Studies Compared to Phase I Studies

		Mean (±SD) Concentration [Range] in mg/L			
		N	Single Dose	N	Steady State
Phase III	100039	67	4.68 ± 3.9	67	4.53 ± 2.4
	200036	24	5.91 ± 2.8	24	4.59 ± 1.7
	Studies 100039 and 200036 Pooled	**91**	**5.01 ± 3.6**	**91**	**4.55 ± 2.2**
Phase I	Pooled analysis 1 hour infusion*	56	3.98 ± 0.9	–	
	Pooled analysis 30 minute infusion*	23	4.44 ± 1.3	–	
	Study 0154 (elderly males and females)	–		12	6.07 ± 1.3
	Study 0142 (healthy young males)	–		8	4.15 ± 0.9

* analysis performed by sponsor

C. TISSUE DISTRIBUTION

Study Reports 0145 and 0156

The sponsor conducted two tissue distribution studies to demonstrate IV and oral moxifloxacin concentrations in blister fluid, subcutaneous tissue, and skeletal muscle relative to plasma. Concentrations of moxifloxacin were shown to be similar between blister fluid and plasma. 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.

Reviewer's Comment: These studies were reviewed previously and can also be found in the Clinical Pharmacology review of NDA 21-085 (moxifloxacin oral tablets).

D. DRUG – DRUG INTERACTIONS

Reviewer's Comment: For full information regarding moxifloxacin and its potential for interaction with other studied drugs please see the Biopharm review for NDA 21-085 (Moxifloxacin oral tablets).

A significant interaction between activated charcoal and moxifloxacin was seen. This interaction may be used to the benefit of the patient in cases of moxifloxacin overdose.

a) Randomized, Open-Label, 3-Way, Cross-Over Study to Investigate the Influence of Carbo Medicinalis (Activated Charcoal) on Gastrointestinal Circulation of Moxifloxacin Following Intravenous and Oral Administration of a 400 mg Single Dose to Healthy Male Volunteers – Study Report 10089

The purpose of this study was to evaluate the possibility of using charcoal as a safety measure to remove moxifloxacin from the systemic circulation (e.g. in cases of overdose).

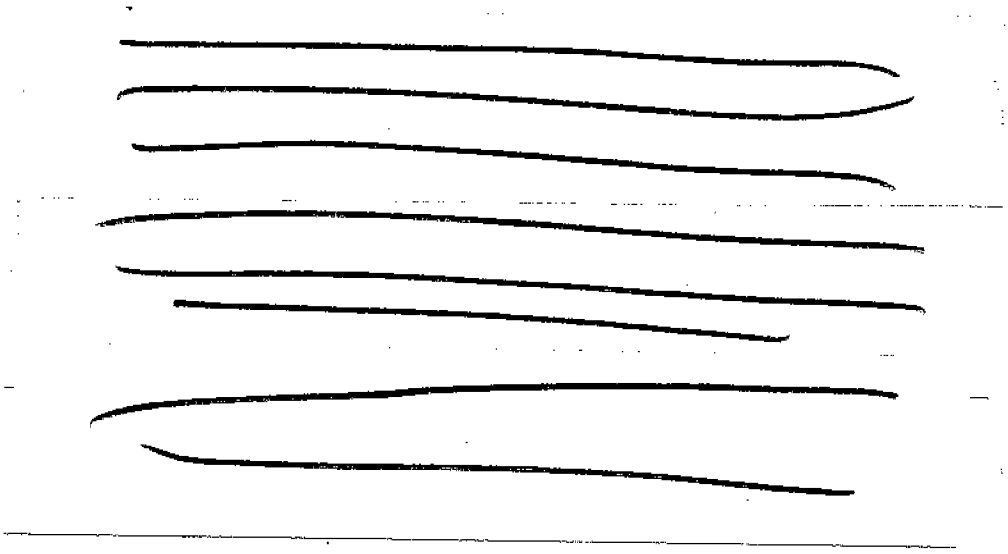
This is as a single center, open-label, uncontrolled, randomized, crossover study. Each subject received a single oral dose of 400 mg moxifloxacin (BAY 12-8039) and two IV infusions of 400 mg moxifloxacin diluted in 250 ml and administered over 60 minutes on two separate occasions. Doses of charcoal (10 grams) were given orally 15 minutes before and 2, 4, and 8 hours after the oral dose of moxifloxacin. Charcoal was also given during one of the two IV infusions at a dose of 5 grams directly before the start of the infusion, 5 grams immediately after the end of infusion and 10 grams at 2, 4, and 8 hours after the start of infusion. The other IV infusion was given alone (without charcoal) and served as a reference.

Of the 9 subjects included in the study, two dropped out prior to drug administration. The remaining 7 subjects received all three treatments and were evaluable for pharmacokinetic analysis.

Moxifloxacin

In the figure below the geometric mean moxifloxacin plasma concentration versus time profiles for all three treatment arms are presented.

Plasma Concentration-Time Profiles of Moxifloxacin Following Administration of a 400 mg Single Dose Orally With Charcoal and Intravenously With and Without Charcoal
Geometric Mean with Standard Deviation



The table below presents the geometric means for the moxifloxacin variables evaluated in this study. Following oral administration of moxifloxacin with charcoal, the AUC and C_{max} of moxifloxacin were decreased by 85% and 82%, respectively compared to the values obtained after IV administration of moxifloxacin without charcoal. The other parameters (t_{max}, $t_{1/2}$, etc.) do not appear to be affected and are similar to values obtained in other pharmacokinetic studies.

Following IV administration of moxifloxacin with charcoal, the AUC and C_{max} of moxifloxacin were decreased by 20% and 12%, respectively compared to the values obtained after IV administration of moxifloxacin without charcoal. The other parameters (t_{max}, $t_{1/2}$, etc.) do not appear to be affected and are similar to values obtained in other pharmacokinetic studies.

Pharmacokinetic Parameters of Moxifloxacin in Plasma and Urine Following Administration of a 400 mg Single Dose of Moxifloxacin Orally With Charcoal and Intravenously With and Without Charcoal
Geometric Mean/Standard Deviation (Range)

Parameter	Unit	Mono IV (N=7)	Combi IV (N=7)	Combi PO (N=7)
AUC	mg*h/L	35.5/1.15	28.5/1.13	5.40/1.92
C_{max}	mg/L	3.38/1.22	2.97/1.13	0.618/2.07
t_{max}*	h	1.00	1.00	0.75
$t_{½,24h}$	h	10.7/1.10	8.8/1.11	9.6/1.09
$t_{½,48h}$	h	11.6/1.11	11.8/1.06	10.8/1.12
$t_{½,72h}$	h	12.6/1.10	13.0/1.07	11.2/1.16
$t_{½}$	h	14.3/1.18	14.3/1.13	11.2/1.16
V_z, V_z/f	L/kg	2.61/1.25	3.24/1.18	13.4/1.86
V_{ss}	L/kg	2.01/1.14	2.28/1.15	—
CL, CL/f	L/h	11.3/1.15	14.0/1.13	74.1/1.92
CL_R	L/h	3.07/1.19	3.34/1.23	3.48/1.16
Ae_{ur}*	mg	110±22.0	95.8±15.0	24.3±23.0
Ae_{ur}*	%	27.5±5.5	23.9±3.7	6.1±5.7

*Median (Range) * arithmetic mean ± std. dev.

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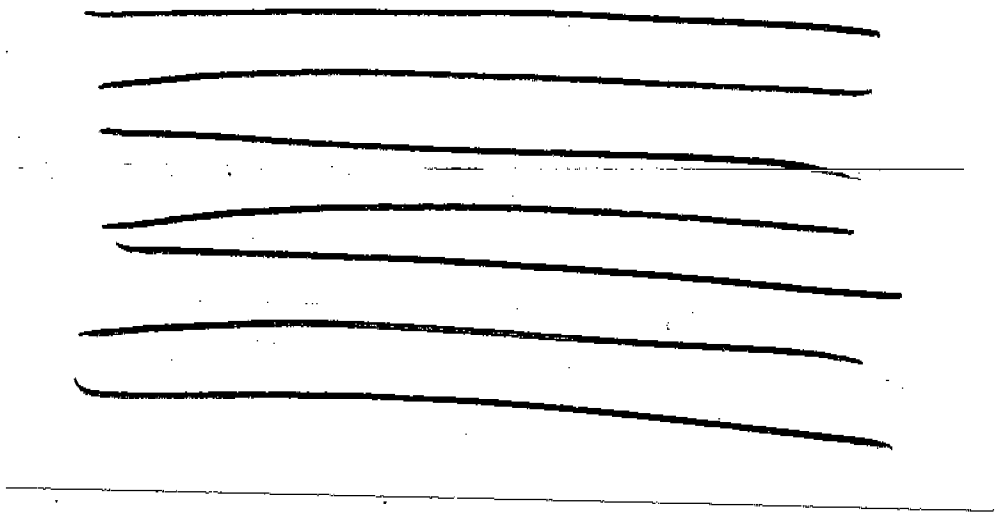
Metabolite M1 (BAY 31-8061)
In the figure below the geometric mean metabolite M1 plasma concentration versus time profiles for all three treatment arms are presented.

Plasma Concentration-Time Profiles of Metabolite M1 Following Administration of a 400 mg Single Dose of Moxifloxacin Orally With Charcoal and Intravenously With and Without Charcoal
Geometric Mean with Standard Deviation



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The table below presents the geometric means for the moxifloxacin metabolite M1 variables evaluated in this study. Following oral administration of moxifloxacin with charcoal, the C_{max} of M1 was decreased by 37% compared to the values obtained after IV administration of moxifloxacin without charcoal.

Reviewer's Comment: Since the M1 concentrations were not quantifiable in all patients, the results for certain parameters should be interpreted with caution (e.g. $AUC_{0-\infty}$ and $t_{1/2}$)

Following IV administration of moxifloxacin with charcoal, the $AUC_{(0-\infty)}$ of M1 was decreased by 22% compared to the values obtained after IV administration of moxifloxacin without charcoal. The C_{max} values were similar (8% elevated in the arm with charcoal).

Pharmacokinetic Parameters of Metabolite M1 in Plasma and Urine Following Administration of a 400 mg Single Dose of Moxifloxacin Orally With Charcoal and Intravenously With and Without Charcoal
Geometric Mean/Standard Deviation (Range)

Parameter	Unit	Mono IV (N=7)	Combi IV (N=7)	Combi PO (N=7)
AUC	mg*h/L	0.923/1.79	0.755/1.99	0.149/2.48 [2]
$AUC_{(0-tn)}$	mg*h/L	0.515/2.34	0.402/2.17	0.0957/2.61 [2]
C_{max}	mg/L	0.0916/1.60	0.0990/1.54	0.0573/1.97 [1]
t_{max}*	h	1.25	1.25	0.75 [1]
$t_{½}$	h	8.25/1.42	7.43/1.89	1.35/2.35 [2]
V_z/f	L/kg	69.4/1.49	76.2/1.45	76.3/1.20 [2]
CL_R	L/h	13.2/1.16	12.7/1.45	19.3/1.13 [3]
Ae_{ur} [4]	mg	13.5±6.4	10.3±4.7	3.6±3.0 [2]
Ae_{ur} [4]	%	2.82±1.33	2.15±0.98	0.74±0.63 [2]

*Median (Range) [1] N=6 [2] N=4 [3] N=3 [4] arithmetic mean ± std. dev.

Metabolite M2
Since only a small portion of subjects had quantifiable concentrations of M2 in all three treatment arms, no pharmacokinetic analysis was possible.

The pharmacokinetic parameters AUC, $AUC_{(0-\infty)}$, and C_{max} for moxifloxacin and metabolite M1 (BAY 21-8061) are compared statistically between treatments in the table below. Since the data obtained during the oral moxifloxacin and charcoal arm were highly variable, point estimates and confidence intervals were also calculated for the ratio of "combi IV / mono IV" (bottom half of the table below) based only on the data of the IV periods, in order to obtain a more accurate confidence interval.

Ratios (LS-Means) of "Combi IV / Mono IV"* and "Combi PO / Mono IV" with 90% Confidence Intervals for the Pharmacokinetic Parameters of Moxifloxacin and Metabolite M1**

Analyte	Ratio	Parameter	N	estimated ratio (%)	90% confidence interval
estimates based on the data of all three periods					
Moxifloxacin	Combi IV / Mono IV	AUC	7	78.19	[52.87 ; 115.62]
		$AUC_{(0-\infty)}$	7	78.06	[52.16 ; 116.83]
		C_{max}	7	84.95	[59.35 ; 121.60]
BAY 31-8061 (M1)	Combi PO / Mono IV	AUC	7	15.44	[10.44 ; 22.84]
		$AUC_{(0-\infty)}$	7	14.76	[9.86 ; 22.09]
		C_{max}	7	18.46	[12.90 ; 26.43]
estimates for 'Combi IV / Mono IV' only based on the data of the IV periods					
Moxifloxacin	Combi IV / Mono IV	AUC	7	80.37	[77.25 ; 83.63]
		$AUC_{(0-\infty)}$	7	80.33	[77.24 ; 83.54]
		C_{max}	7	86.61	[75.92 ; 98.81]
BAY 31-8061 (M1)	Combi IV / Mono IV	AUC	7	83.42	[69.74 ; 99.78]
		$AUC_{(0-\infty)}$	7	76.91	[67.43 ; 87.72]
		C_{max}	7	106.99	[101.15 ; 113.17]

* "moxifloxacin IV + charcoal" = combi IV, "moxifloxacin IV" = mono IV
** "moxifloxacin PO + charcoal" = combi PO, "moxifloxacin IV" = mono IV

In summary,

- Administration of 40 grams of charcoal with a single 400 mg oral dose of moxifloxacin led to an 85% reduction in absolute bioavailability of moxifloxacin. Concentrations of M1 were also reduced. Conclusions about the effect of charcoal on M2 are limited by the lack of quantifiable concentrations in all three treatment arms. These results demonstrate the effectiveness of activated charcoal in preventing absorption of oral moxifloxacin.

- Administration of 40 grams of charcoal with a single 400 mg IV dose of moxifloxacin led to an 20% reduction in absolute bioavailability of moxifloxacin. These results suggest that oral moxifloxacin undergoes gastrointestinal recirculation.

- Administration of activated charcoal should be recommended for treatment of overdose with oral moxifloxacin early after intoxication. However, it will be of limited use after overdose with the IV formulation and therefore is not recommended in this situation.

E. SPECIAL SAFETY STUDIES

Reviewer's Comment: All the Phase I special safety studies were previously reviewed as part of other NDAs for oral moxifloxacin. Reviews of Studies 0163, 0149, and 0154 can be found in the Clinical Pharmacology review of NDA 21-085 (original NDA, moxifloxacin oral tablets). Reviews of Studies 1000267, 100263, and 100264 can be found in the Clinical Pharmacology review of NDA 21-277 (uncomplicated skin and skin structure resubmission for moxifloxacin oral tablets).

The two Phase III studies (100036 and 200039) contain new data and are presented here for the first time.

Phase I Studies of IV Moxifloxacin

a) Effect of Single Oral or Intravenous Doses of Moxifloxacin (BAY 12-8039) on QT interval – Study Report 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					
MAX					

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 Fridericia's cubic root formula QTcF. The QT was also corrected for heart rate by Bazett's formula (QTc or QTcB).

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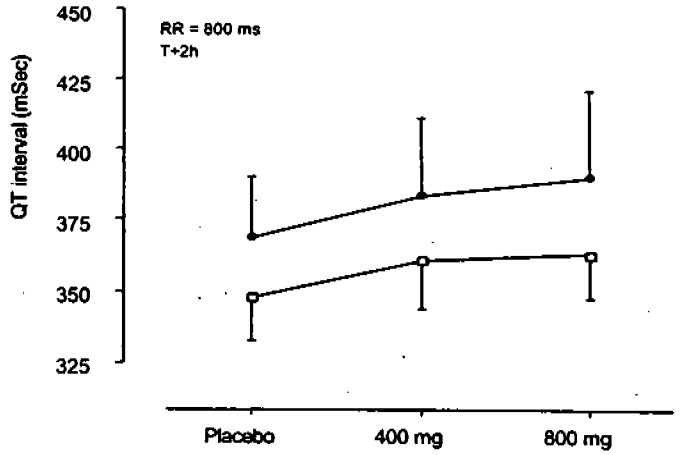
A possible gender influence on the QTc changes was investigated in this study. Mean calculated QT interval values 2 hours post-oral dosing (expected C_{max}) for RR = 800 msec (heart rate = 75 bpm) in males and females are shown graphically below.

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 Fridericia's 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.

b) Pharmacokinetics of Intravenously Administered Moxifloxacin (BAY 12-8039) and the Influence of Different Rates of Infusion on the QTc Interval - Study Report 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 (see table below).

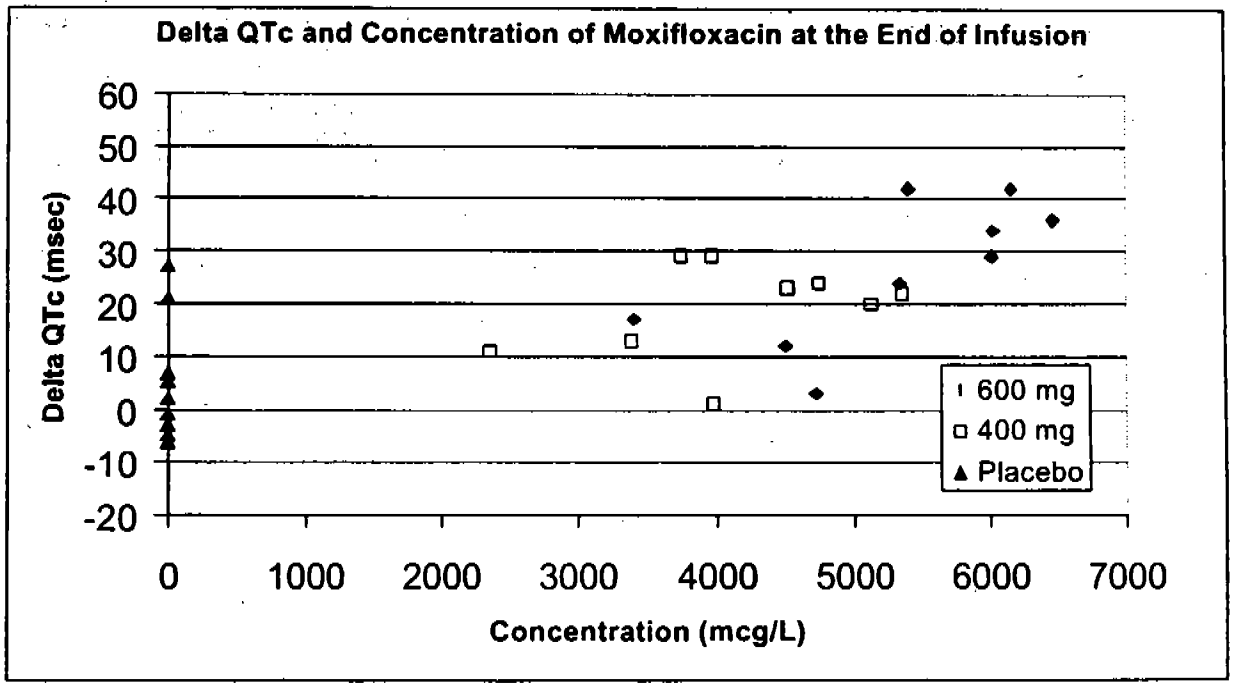
Geometric Means / Geometric SD (Range) of Moxifloxacin Pharmacokinetic Parameters in Plasma Following a Single Intravenous Infusion of 400 mg over 33 minutes and 600 mg Moxifloxacin Over 100 minutes

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.

c) Pharmacokinetics, Pharmacodynamics and Safety of an Intravenous Infusion of 400 mg BAY 12-8039 (Moxifloxacin) in Healthy Young and Elderly Volunteers - Study Report 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).

Phase IV Studies for Oral Moxifloxacin

a) A Randomized, Double Blind, Four-Way Crossover, Ascending Single-Dose Trial of Moxifloxacin 400 mg, 800 mg, and 1200 mg, Orally and Placebo: Effect on the QTc Interval – Study Report 100267

This was a randomized, placebo-controlled, crossover study of three doses of moxifloxacin in healthy subjects male and female subjects from 18 to > 60 years. Subjects received each of the following treatments: moxifloxacin 400 mg, moxifloxacin 800 mg, moxifloxacin 1200 mg and matching placebo in random sequence. The relationship between QT interval duration and dose and plasma concentration of moxifloxacin was explored in various ways.

Sixty-two (62) subjects were randomized and received one or more doses of study drug. All are presented in the analysis of safety. Sixty-one (61) of 62 subjects were valid for pharmacokinetics and pharmacodynamics.

The table below presents the mean (SD) pharmacokinetic data for moxifloxacin obtained after each dose.

Mean (SD) Pharmacokinetic Parameters for a Single Dose of Moxifloxacin 400 mg, 800 mg, and 1200 mg

Dose	AUC_{0-12} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)				Ratio of Observed:Expected*	
(mg)	n	Mean	SD	n	Mean	SD	n	Max - Min	Mean	SD	AUC_{0-12} (%)	C_{max} (%)
400	61	22.08	5.06	61	2.93	0.95	61	[redacted]	2.08	0.81	–	–
800	61	42.01	9.34	61	5.26	1.20	61	[redacted]	2.97	1.23	95.1	89.8
1200	61	62.25	12.62	61	7.41	1.50	61	[redacted]	3.53	1.29	94.0	84.3

* from linear extrapolation of the 400 mg data

The ΔQTc at C_{max} was calculated using four different definition of baseline and the results are shown below.

1. t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the pre-dose (t=0) value on the corresponding day of treatment (i.e. t=0 as baseline).

Mean (SD) ΔQTc at C_{max} Using t=0 as Baseline (N=61)

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg	11.9	16.0	13.9	13.2
Moxi 800 mg	17.4	17.0	17.0	15.1
Moxi 1200 mg	30.2	21.5	26.9	16.2

For each of the determinations of ΔQTc on active drug a corresponding value on placebo is available. It should be noted that the placebo value was obtained varied according to the timing of C_{max}. For the 400 mg moxifloxacin data the mean (SD) ΔQTc (Bazett's) for the corresponding placebo was 0.7 (16.1) msec; for the 800 and 1200 mg data the values were –1.4 (17.1) and –0.4 (18.1) msec, respectively.

2. Average t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the average of the pre-dose (t=0) values across all four treatment periods (i.e. average t=0 as baseline).

Mean (SD) ΔQTc at C_{max} Using Average t=0 as Baseline (N=61)

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg	9.3	14.8	11.7	12.9
Moxi 800 mg	18.0	14.7	17.6	13.7
Moxi 1200 mg	33.8	18.5	29.3	14.5

3. Corresponding time on placebo day as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the value obtained on placebo at the corresponding time of C_{max} for each of the moxifloxacin treatments (i.e. corresponding time on placebo day as baseline).

Mean (SD) ΔQTc at C_{max} Using Corresponding Time on Placebo Day as Baseline (N=61)

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg	10.1	19.7	9.5	16.3
Moxi 800 mg	20.9	19.4	17.6	16.5
Moxi 1200 mg	35.7	22.1	29.3	16.6

4. Average on placebo day as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using an average of all values collected over the entire 12-hour interval following placebo administration (i.e. average on placebo day as baseline).

Mean (SD) ΔQTc at C_{max} Using Average on Placebo Day as Baseline (N=61)

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg	9.4	14.8	11.4	12.9
Moxi 800 mg	18.1	15.1	17.3	14.7
Moxi 1200 mg	33.9	18.6	29.0	14.9

In addition, to the ΔQTc at C_{max}, the maximal change in QTc from baseline (max ΔQTc) was analyzed. The table below summarizes the results using various definitions of baseline.

Summary - Mean (SD) Max ΔQTc Using Different Definitions of Baseline (N=61)

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
t=0 as baseline	20.2	13.9	14.7	11.7
Moxi 400 mg	28.6	14.4	24.2	11.9
Moxi 800 mg	36.2	15.6	29.0	12.4
Moxi 1200 mg	42.1	17.4	36.2	12.7
average t=0 as baseline				
Placebo	18.7	11.0	14.0	9.7
Moxi 400 mg	26.0	12.3	22.0	10.8
Moxi 800 mg	36.8	13.6	29.5	11.8
Moxi 1200 mg	45.7	15.6	38.6	11.8
average on placebo day as baseline				
Placebo	18.9	7.7	13.7	5.1
Moxi 400 mg	26.2	12.6	21.7	11.2
Moxi 800 mg	37.0	14.8	29.2	13.5
Moxi 1200 mg	45.8	16.2	38.3	13.1

The concentration-effect relationship was obtained for ΔQTc versus C_{max}. Change in QTc was defined using the pre-dose (t=0) value as baseline. All moxifloxacin doses were included. The resulting equation of the line is described as: $\Delta QTc = -0.83 + 3.97C_{max}$. The intercept of this line was not significantly different from zero, but the slope was statistically significant ($p<0.001$).

In summary,

- Over the range 400 to 1200 mg of moxifloxacin, C_{max} and AUC_{0-12} appeared proportional to dose.
- There was a dose- and concentration-related increase in the effect of moxifloxacin on ΔQTc, regardless of how baseline QTc was determined.
- No significant effects of age or sex on QT findings were established in this study.

b) A Randomized, Six-Way Crossover Comparison of Single Oral Doses of Moxifloxacin 400 mg and 800 mg, Levofloxacin 500 mg and 1000 mg, Erythromycin 1000 mg, and Placebo on the QTc Interval – Study Report 100263

This was a single blind, randomized, six-period, crossover study in healthy male and female subjects between 18 and > 60 years of age. Subjects received each of the following treatments: moxifloxacin 400 mg, moxifloxacin 800 mg, levofloxacin 500 mg, levofloxacin 1000 mg, erythromycin ethylsuccinate 1600 mg (equivalent to 1000 mg erythromycin base), and matching placebo in random sequence. The relationship between QT interval duration and dose and plasma concentration of moxifloxacin was explored in various ways.

Of the 49 subjects randomized to the study, 47 completed the study. The table below presents the mean (SD) pharmacokinetic data for moxifloxacin, levofloxacin, and erythromycin obtained after each dose. AUC_{0-12} and C_{max} for the moxifloxacin and levofloxacin periods showed approximately proportional increases with doubling of dose. Erythromycin was notably different from the other drugs in two respects. First, erythromycin AUC_{0-12} exhibited greater between-individual variability (CV 73%) than either

moxifloxacin or levofloxacin. Additionally, T_{max} was earlier for erythromycin than was the case for the other drugs; it was usual for the first concentration time point to have the highest value (i.e. 1 hour after dosing).

Mean (SD) Pharmacokinetic Parameters for a Single Dose of Moxifloxacin 400 mg and 800 mg, Levofloxacin 500 mg and 1000 mg, and Erythromycin 1000 mg

	AUC_{0-12} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)			
Dose (mg)	n	Mean	SD	n	Mean	SD	n	Mean	SD	Max - Min
Moxi 400	48	23.3	5.7	48	3.3	0.9	48	2.0	0.8	
Moxi 800	47	46.9	11.1	47	6.1	1.5	47	2.4	1.1	
Levo 500	47	41.5	10.8	47	6.7	1.9	47	1.5	0.6	
Levo 1000	47	89.1	22.5	47	13.4	3.5	47	1.5	0.6	
Erythro 1000	48	7.3	5.3	48	1.5	0.8	48	1.3	0.4	

The ΔQTc at C_{max} was calculated using four different definition of baseline and the results are shown below.

1. t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the pre-dose (t=0) value on the corresponding day of treatment (i.e. t=0 as baseline). For each of the determinations of ΔQTc on active drug a corresponding value on placebo is available. It should be noted the placebo value that was obtained varied according to the timing of C_{max}.

Mean (SD) ΔQTc at C_{max} Using t=0 as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg n=48	9.2	14.5	8.5	12.6
Matched placebo	-4.6	16.0	-2.3	12.6
Moxi 800 mg n=47	19.5	17.5	16.	14.4
Matched placebo	-4.3	14.1	-2.1	12.2
Levo 500 mg n=47	5.1	14.0	2.9	11.0
Matched placebo	-5.1	14.9	-3.3	12.8
Levo 1000 mg n=47	7.3	14.8	4.1	11.6
Matched placebo	-5.3	14.4	-2.9	11.5
Erythro 1000 mg n=48	3.4	14.2	3.8	12.5
Matched placebo	-4.8	15.7	-3.1	12.9

The change in QTc with the 800 mg dose of moxifloxacin was approximately twice that associated with 400 mg. Relatively smaller increases in QTc were observed with levofloxacin (at either dose) and erythromycin.

2. Average t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the average of the pre-dose (t=0) values across all four treatment periods (i.e. average t=0 as baseline).

Mean (SD) ΔQTc at C_{max} Using Average t=0 as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg n=48	13.1	14	11.7	11.6
Moxi 800 mg n=47	16.3	13.7	13.0	12.6
Levo 500 mg n=47	2.1	13.0	0.7	11.0
Levo 1000 mg n=47	7.3	15.5	4.6	12.7
Erythro 1000 mg n=48	2.2	12.2	3.0	11.3

3. Corresponding time on placebo day as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the value obtained on placebo at the corresponding time of C_{max} for each of the moxifloxacin treatments (i.e. corresponding time on placebo day as baseline).

Mean (SD) ΔQTc at C_{max} Using Corresponding Time on Placebo Day as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg n=48	16.9	18.6	13.9	15.0
Moxi 800 mg n=47	19.5	17.3	14.8	15.2
Levo 500 mg n=47	6.4	19.7	3.9	17.0
Levo 1000 mg n=47	11.8	19.1	7.5	15.5
Erythro 1000 mg n=48	6.3	17.1	6.0	14.5

4. Average on placebo day as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using an average of all values collected over the entire 12-hour interval following placebo administration (i.e. average on placebo day as baseline).

Mean (SD) ΔQTc at C_{max} Using Average on Placebo Day as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg n=48	14.0	16.6	14.1	13.1
Moxi 800 n=47	17.1	16.1	15.2	13.9
Levo 500 mg n=47	3.3	16.4	3.2	13.1
Levo 1000 mg n=47	8.2	18.7	7.0	14.7
Erythro 1000 mg n=48	3.2	13.1	5.4	11.6

In addition, to the ΔQTc at C_{max}, the maximal change in QTc from baseline (max ΔQTc) was analyzed. The table below summarizes the results using various definitions of baseline.

Summary - Mean (SD) Max ΔQTc Using Different Definitions of Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
t=0 as baseline				
Placebo n=48	16.0	14.3	9.5	10.5
Moxi 400 mg n=48	23.6	15.0	17.8	12.2
Moxi 800 mg n=47	31.5	16.6	25.6	13.1
Levo 500 mg n=48	22.2	14.2	13.3	11.6
Levo 1000 mg n=48	20.9	12.1	12.6	8.4
Erythro 1000 mg n=48	20.8	13.3	14.1	10.1
average t=0 as baseline				
Placebo n=48	16.9	10.5	9.5	8.2
Moxi 400 mg n=48	27.5	12.1	21.0	10.3
Moxi 800 mg n=47	28.3	10.4	22.1	11.0
Levo 500 mg n=48	19.3	12.2	11.1	11.0
Levo 1000 mg n=48	20.8	13.5	12.9	10.8
Erythro 1000 mg n=48	19.6	11.5	13.3	9.0
average on placebo day as baseline				
Placebo n=48	17.8	7.8	119	4.8
Moxi 400 mg n=48	28.4	15.3	23.4	11.9
Moxi 800 mg n=47	29.1	11.8	24.3	11.3
Levo 500 mg n=48	20.2	16.0	13.4	13.3
Levo 1000 mg n=48	21.7	17.2	15.3	12.8
Erythro 1000 mg n=48	20.6	13.5	15.6	10.8

The concentration-effect relationship was obtained for ΔQTc versus C_{max}. Change in QTc was defined using the pre-dose (t=0) value as baseline. Equations describing the moxifloxacin and levofloxacin data are as shown below. The p-values indicate the difference of the slopes from zero.

For moxifloxacin (using the 400 and 800 mg data): $\Delta QTc \text{ (from t=0)} = -2.35 + (0.003498)C_{max}$ (p=0.005)

For levofloxacin (using the 500 and 1000 mg data): $\Delta QTc \text{ (from t=0)} = -0.38 + (0.6544)C_{max}$ (p=0.11)

In summary,

- Of the three drugs tested, moxifloxacin had the greatest effect on the ECG at its therapeutic dose.
- Single doses of moxifloxacin caused a dose- and concentration- related increase in QT interval duration, but only when ΔQTc was calculated using t=0 as the baseline value
- There is a more clearly defined concentration effect relationship for moxifloxacin than for levofloxacin.
- Levofloxacin and erythromycin produced lesser increases in QTc than moxifloxacin.
- No significant effects of age or sex on QT findings were established in this study.

c) A Ten Day Multiple Dose, Randomized, Crossover Study of 400 mg Moxifloxacin and 200 mg Sparfloxacin: Comparison of the Effects of Single-Dose and Steady State Dosing on the QTc Interval, and on Moxifloxacin and Moxifloxacin Metabolite Pharmacokinetics in Adult Male and Female Subjects – Study Report 100264

This was a randomized, 2-period crossover study in healthy adult male and female subjects between 18 and > 60 years of age. Each subject received each of two treatments, comprising moxifloxacin 400 mg orally once daily for 10 days and sparfloxacin 400 mg orally as a loading dose on Day 1 followed by 200 mg orally once daily on Days 2 through 10. The relationship between QT interval duration and dose and plasma concentration of moxifloxacin and sparfloxacin was explored in various ways.

Forty-eight subjects were valid for safety analysis. Two subjects were withdrawn for adverse events. The following four tables below present the mean (SD) pharmacokinetic data for moxifloxacin, metabolite M1, metabolite M2, and sparfloxacin, respectively.

Mean (SD) Pharmacokinetic Parameters for Moxifloxacin on Days 1 through 10

	AUC_{0-24} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)			$C_{pre-dose}$ (mg/L)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Day 1	46	34.9	5.7	46	3.2	0.6	46	1.9	0.8	-	-	-
Day 2	-	-	-	-	-	-	-	-	-	47	0.61	0.18
Day 8	-	-	-	-	-	-	-	-	-	47	0.84	0.28
Day 9	-	-	-	-	-	-	-	-	-	47	0.86	0.25
Day 10	47	50.1	8.1	47	4	0.6	47	2	0.8	47	0.89	0.24

Mean (SD) Pharmacokinetic Parameters for Moxifloxacin Metabolite (M1) on Days 1 Through 10

	AUC_{0-24} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)			$C_{pre-dose}$ (µg/L)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Day 1	45	1.3	0.5	45	0.2	0.1	45	1.3	0.6	-	-	-
Day 2	-	-	-	-	-	-	-	-	-	47	20.59	10.48
Day 8	-	-	-	-	-	-	-	-	-	47	24.57	12.14
Day 9	-	-	-	-	-	-	-	-	-	47	24.06	10.77
Day 10	47	1.5	0.6	47	0.2	0.1	47	1.3	0.5	47	24.55	10.82

Mean (SD) Pharmacokinetic Parameters for Moxifloxacin Metabolite (M2) on Days 1 Through 10

	AUC_{0-24} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)			$C_{pre-dose}$ (µg/L)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Day 1	46	6.1	2.9	4.6	0.7	0.3	46	2.4	1.3	-	-	-
Day 2	-	-	-	-	-	-	-	-	-	47	91.2	60.2
Day 8	-	-	-	-	-	-	-	-	-	47	112.4	70.6
Day 9	-	-	-	-	-	-	-	-	-	47	122.6	65.0
Day 10	47	7.6	3.6	47	0.8	0.3	47	2.9	3.9	47	128.3	70.1

Mean (SD) Pharmacokinetic Parameters for Sparfloxacin on Days 1 through 10

	AUC_{0-24} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)			$C_{pre-dose}$ (mg/L)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Day 1	47	20.3	5.1	47	1.3	0.4	47	4.7	2.5	-	-	-
Day 2	-	-	-	-	-	-	-	-	-	47	0.59	0.18
Day 8	-	-	-	-	-	-	-	-	-	45	0.50	0.17
Day 9	-	-	-	-	-	-	-	-	-	45	0.49	0.16
Day 10	45	20.7	4.6	45	1.3	0.3	45	3.2	1.4	45	0.50	0.14

The ΔQTc at C_{max} was calculated using four different definition of baseline and the results are shown below.

1. t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the pre-dose (t=0) value on the corresponding day of treatment (i.e. t=0 as baseline).

Mean (SD) ΔQTc at C_{max} Using t=0 as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg Day 1 n=46	10.6	13.7	12.3	11.3
Moxi 400 mg Day 10 n=47	19.6	15.4	16.5	14.1
Spar 400 mg Day 1 n= 47	20.2	17.1	18.3	15.2
Spar 200 mg Day 10 n= 45	27.0	17.3	23.9	14.9

2. Average t=0 (using Day –1 and Day 1 from both study periods) as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the average of the pre-dose (t=0) values on Day –1 and Day 1 (i.e. average t=0 as baseline).

Mean (SD) ΔQTc at C_{max} Using Average t=0 as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg Day 1 n=46	8.7	12.2	10.4	9.8
Moxi 400 mg Day 10 n=47	17.6	14.0	14.6	12.7
Spar 400 mg Day 1 n= 47	19.3	14.2	16.7	13.5
Spar 200 mg Day 10 n= 45	25.9	15.6	22.1	14.1

3. Corresponding time on Day -1 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using the value obtained with placebo administration on Day -1 at the corresponding time of C_{max} for both of the treatments (i.e. corresponding time on Day -1 as baseline).

Mean (SD) ΔQTc at C_{max} Using Corresponding Time on Day -1 as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg Day 1 n=46	9.4	14.4	6.8	10.7
Moxi 400 mg Day 10 n=47	17.4	17.2	10.7	13.7
Spar 400 mg Day 1 n= 47	12.9	16.1	11.0	14.0
Spar 400 mg Day 10 n= 45	22.3	15.3	16.4	14.5

4. Average on Day -1 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown using an average of all values collected following placebo administration on Day –1 (i.e. average of Day –1 as baseline).

Mean (SD) ΔQTc at C_{max} Using Average of Day -1 as Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
Moxi 400 mg Day 1 n=46	5.3	11.3	6.3	8.9
Moxi 400 mg Day 10 n=47	14.0	13.2	10.5	11.4
Spa. 400 mg Day 1 n= 47	15.0	12.4	11.7	11.5
Spa. 200 mg Day 10 n= 45	21.5	12.7	17.1	11.6

In addition, to the ΔQTc at C_{max}, the maximal change in QTc from baseline (max ΔQTc) was analyzed. The table below summarizes the results using various definitions of baseline.

Summary - Mean (SD) Max ΔQTc Using Different Definitions of Baseline

	ΔQTc Bazett's correction		ΔQTc Freidericia's correction	
	Mean	SD	Mean	SD
t=0 as baseline				
Moxi Day 1 n=47	30.9	12.3	26.3	11.1
Moxi Day 10 n=47	38.2	12.5	28.8	12.0
Spar Day 1 n=47	35.8	14.4	31.1	11.1
Spar Day 10 n=45	42.4	16.8	33.2	14.4
average t=0 as baseline				
Moxi Day 1 n=47	28.9	10.8	24.4	9.7
Moxi Day 10 n=47	36.2	11.0	26.9	10.0
Spar Day 1 n=47	34.9	12.1	29.4	10.3
Spar Day 10 n=45	41.3	13.9	31.4	12.8
average on Day -1 as baseline				
Moxi Day 1 n=47	25.3	8.4	20.3	7.1
Moxi Day 10 n=47	32.6	9.7	22.8	8.1
Spar Day 1 n=47	30.6	8.8	24.4	8.0
Spar Day 10 n=45	36.9	10.1	26.4	9.7

The concentration-effect relationship was obtained for ΔQTc versus C_{max}. Change in QTc was defined using the pre-dose (t=0) value as baseline. Intercepts, slopes and p-values for the regression lines (for the difference of the slope from zero) are provided in the table below.

Regression Equations (Bazett)
QTc = Intercept + Slope*C_{max}

	Intercept	Slope	p-value[#]
Spar Day 1	402	5.59	0.54
Moxi Day 1	372	0.0087	0.18
Spar Day 10	391	19.14	0.046
Moxi Day 10	372	0.0088	0.12

[#]The p-values indicate the difference of the slopes from zero.

In summary,

- Mean moxifloxacin AUC_{0-24} on Day 10 was 40% greater than the Day 1 value, and the mean C_{max} increased 25% from 3.2 mg/L to 4.0 mg/L.

- The concentrations of the sulfate (M1) and glucuronide (2) metabolites were less than 4% and 22% of the parent drug and did not increase as a proportion of parent drug during 10 days of dosing.

- The pharmacokinetics of moxifloxacin and its metabolites showed no consistent relationship to age or gender.

- The effect of sparfloxacin on QTc consistently exceeded that of moxifloxacin.

- For both drugs, the effect on QTc on Day 10 was greater than on Day 1.

- No significant effects of age or sex on QT findings were established in this study.

Correlation of QTc Changes with Plasma Concentrations of Moxifloxacin Data Obtained from Phase III Studies, 100039 and 200036.

Protocols 100039 and 200036 were designed to study sequential intravenous (IV) followed by oral therapy with moxifloxacin in comparison to other antibiotics recommended for treatment of community acquired pneumonia.

Protocol 100039 (North American study) was a randomized, double-blind, double dummy, multicenter clinical trial comparing daily 400 mg moxifloxacin IV versus (initially) trovafloxacin 200 mg IV, and later levofloxacin 500 mg IV. Patients eligible for the study were adults with community-acquired pneumonia of sufficient severity that hospitalization and IV therapy were warranted. Patients were to receive IV therapy with the study drugs for a minimum of 3 days, and depending on the clinical condition of the patient, to switch to the same daily dose of study drug orally for a 7 to 14 day course of therapy. The blinded administration of the intravenous drugs necessitated that each patient receives two one-hour infusions, placebo and study drug, in randomized order. The principal ECG data gathered in this study were ECG recordings obtained prior to the first infusion of study drug, after the first infusion of study drug (Both on Day 1 of the study), and before and after the third infusion of the study medications (Day 3). Blood sampling for moxifloxacin plasma concentrations was performed in most patients after the first and third infusions of drug, at the time of the ECG recordings. Data from the Day 3 time point were pooled with the data from Protocol 200036, and data from the Day 1 time point were analyzed separately.

Protocol 200036 (referred to as the Ex-North America study) was a randomized, open-label, multicenter, multinational study comparing 400 mg moxifloxacin IV against amoxicillin/clavulanate IV with or without clarithromycin IV, with a switch to oral therapy after a minimum of 3 days of intravenous administration. Study subject entry criteria were similar to study 100039, and the duration of therapy was also 7 to 14 days. The ECG data collected during this protocol included a pre-treatment ECG, and an ECG within 30 minutes of the end of drug infusion on Day 3. Some patients had blood sampling for determination of moxifloxacin concentrations at the time of the Day 3 ECG recording. Both studies had the option of performing additional ECGs while patients were on oral therapy.

The patients analyzed were those with paired-valid ECGs on Day 1 or Day 3 in whom blood samples were obtained at the end of infusion on the appropriate day. The contribution of patients to the analysis by Study number is found in the table below. Data were not collected on Day 1 for Study 200036 and are limited on Day 3 because fewer patients had blood sampling, and most of the blood sampling was performed on Day 2, without a simultaneous ECG.

	Day 1	**Day 3**
Study 100039*	N=58	N=45
Study 200036	--	N=8
TOTAL	**58**	**53**

*For Study 100039, the infusions of placebo and active drug on each day were randomized, so data for this analysis were only taken from those patients who received active drug in the second infusion, immediately prior to blood sampling and ECG measurement.

The change in QTc on Days 1 and 3 as well as the corresponding concentrations of moxifloxacin for Study 100039 are shown in the table below.

Study 100039	Day 1 (N=57)	Day 3 (N=45)
Δ QTc	15.5 ± 26.6 msec [-6.74 to 78.4 msec]	10.6 ± 31.6 msec [-109.9 to 65.4 msec]
Moxifloxacin concentration	4.01 ± 1.44 mg/L* [1.84 to 7.84 mg/L]	4.38 ± 1.37 mg/L [1.66 to 7.59 mg/L]

* Excluding one patient with a moxifloxacin concentration of 28.5 mg/L obtained 17 minutes after the end of infusion on Day 1. The ΔQTc in this patient was 9 msec.

There was no statistically significant correlation between the plasma concentration of moxifloxacin and the QTc or the change in QTc on Days 1 and 3. The slope of the regression line was not statistically different from zero. Analyses of each study separately also found no statistically significant association between moxifloxacin plasma concentrations and the QTc or the change in QTc.

Study 100039 recorded the start and stop times of both the placebo and active drug infusions, and permitted analysis of the change in QTc by duration of infusion. The table below displays the change in mean QTc by order of infusion (Placebo/Active vs. Active/Placebo) on Day 3 and Day 1 of moxifloxacin or comparator therapy.

Reviewer's Comment: Patients were included in this analysis with or without plasma drug concentrations obtained. Therefore, the sample size is larger and includes all patients with paired valid ECGs.

Change in Mean QTc by Order of Infusion, Day 3 and Day 1
(Study 100039)

Day	Order of Infusion	Drug	n	ΔQTc ± S.D. msec
3	PLA/Active	Moxifloxacin	71	7 ± 30
		Comparator	74	-3 ± 26
	Active/PLA	Moxifloxacin	83	0 ± 26
		Comparator	92	-4 ± 25
1	PLA/Active	Moxifloxacin	85	14 ± 26
		Comparator	82	0 ± 25
	Active/PLA	Moxifloxacin	90	5 ± 20
		Comparator	102	2 ± 20

In summary, the mean ΔQTc (QTc at the end of infusion subtracted from predose) was similar on Days 1 and 3 and the mean moxifloxacin concentration obtained at the end of infusion was similar on Days 1 and 3.

31 page(s) of revised draft labeling has been redacted from this portion of the review.