CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-334 *and* 21-085/S-010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-334
Submission Date:	10/26/00
Drug:	Moxifloxacin hydrochloride (Avelox®) oral tablets
Sponsor:	Bayer Corporation West Haven, CT
Type of Submission:	New NDA (Resubmission of USSSI Indication from NDA 21-085)
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

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 deemed "approvable" pending the results of Phase IV studies.

Section 6 of NDA 21-334 contains three pharmacokinetic/pharmacodynamic studies performed as Phase IV commitments for NDA 21-085 (moxifloxacin oral tablets).

II. INDICATION AND DOSAGE

The applicant is seeking approval of moxifloxacin 400 mg once daily for 7 days for the treatment of skin and skin structure infections.

III. CLINICAL PHARMACOLOGY SYNOPSIS

What is the effect of age and gender on the pharmacokinetic parameters of moxifloxacin, in terms of AUC_{0-12} and C_{max} after a 400 mg single oral dose?

Age

- The AUC_{0-12} of moxifloxacin was not statistically different across age groups (young, middle aged, and elderly), after adjustment for body weight.
- 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} and a 34% higher C_{max} than males, which was statistically significant. This difference was lower, but persisted after adjustment for body weight (12% and 15% higher for AUC_{0-12} and C_{max}, respectively).

Reviewer's Comment: Labeling changes as a result of these findings with regard to age and gender will be addressed in the future during the review of NDA 21-277 (moxifloxacin IV).

What is the duration of QTc prolongation obtained with moxifloxacin (1) after single escalating doses up to 3-times the approved dose, (2) compared to levofloxacin and erythromycin after doses up to 2-times the approved dose, and (3) compared to sparfloxacin after single doses and dosing to steady state?

Moxifloxacin-induced changes in QTc are summarized in the following table. Data on the comparator drugs (sparfloxacin, levofloxacin, and erythromycin) are also included for comparison. Changes in QTc are reported at the time of C_{max} (i.e., T_{max}) and at the time of maximum QTc during a 12 hour interval. For reference, the approved dose of moxifloxacin is 400 mg, levofloxacin 500 mg, and erythromcyin 500 mg. Sparfloxacin is approved as a 400 mg loading dose, followed by 200 mg.

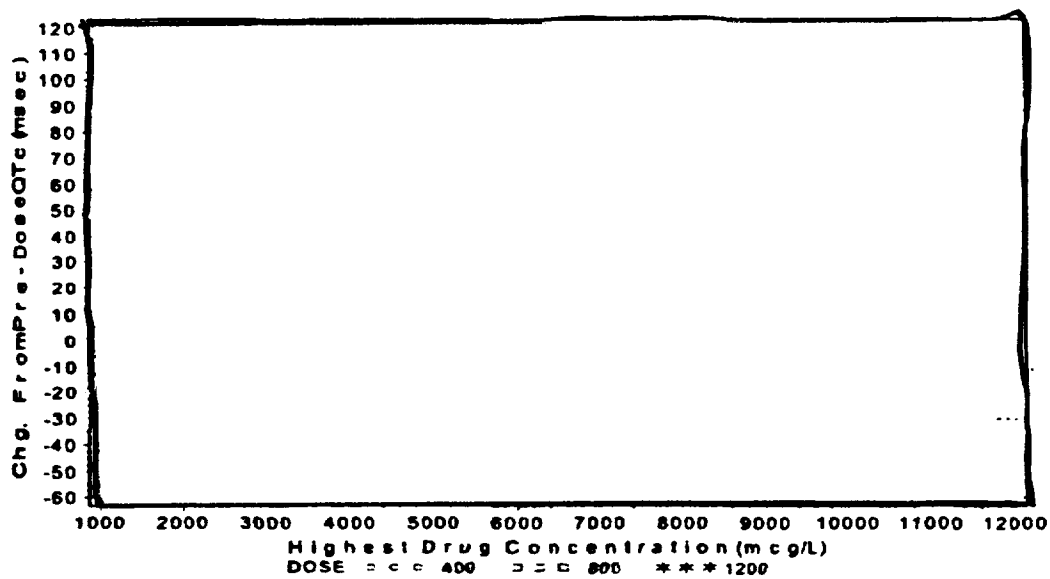
Summary of Changes in QTc Parameter by Drug and Dose

Drug	Dose	ΔQTc* at C_{max} (msec)	Max ΔQTc#^ (msec)
Moxifloxacin	400 mg – single dose	9.3 – 11.9 (100267) 9.2 – 16.9 (100263) 5.3 – 10.6 (100264)	26.0 – 28.6 (100267) 23.6 – 28.4 (100263) 25.3 – 30.9 (100264)
	400 mg – multiple dose	14.0 – 19.6	32.6 – 38.2
	800 mg	17.4 – 20.9 (100267) 16.3 – 19.5 (100263)	36.2 – 37.0 (100267) 28.3 – 31.5 (100263)
	1200 mg	30.2 – 35.7	42.1 – 45.8
Sparfloxacin	400 mg – single dose	12.9 – 20.2	30.6 – 35.8
	200 mg – multiple dose	21.5 – 27.0	36.9 – 42.4
Levofloxacin	500 mg	2.1 – 6.4	19.3 – 22.2
	1000 mg	7.3 – 11.8	20.8 – 21.7
Erythromycin	1000 mg	2.2 – 6.3	19.6 – 20.8

* range of change using all four definitions of baseline
# range of change using three definitions of baseline
^ Corresponding max ΔQTc on placebo is 16.0-20.2 msec (100263 and 100267)

- The regression equation for moxifloxacin was determined by compiling data from all three studies (see figure below): $\Delta QTc = 2.18 + 2.80C_{max}$

ΔQTc versus Individuals' C_{max} of Moxifloxacin Following Single Oral Doses of 400, 800, and 1200 mg



IV. RECOMMENDATION

The information contained in Item 6: Human Pharmacokinetics and Bioavailability of NDA 21-334 for moxifloxacin oral tablets has been reviewed and was found to be acceptable and adequate to support approval.

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 21-334
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ

V. STUDY 100267: 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
Study Dates: 26 April 2000 - 07 July 2000
Investigators: Larita Frazier-O'Bannon, MD; Stephen Austin, MD
Study center(s): [redacted]

OBJECTIVES

The purpose of this trial was to explore the effect of doses of 400, 800, and 1200 mg of moxifloxacin on the ECG, in particular, on the QT interval duration at C_{max}. Concurrently, plasma samples were obtained to explore the relationship between QT interval duration and drug concentration.

FORMULATIONS

- Moxifloxacin encapsulated batch M000206, tablet batch 527248C.
- Placebo capsules (microcrystalline cellulose) batch number M991202.

SUBJECTS

Demographics	*# Subjects (%) or Mean (SD)*
All Ages n (%)	62 (100)
Young n (%)	20 (32)
Middle aged n (%)	23 (37)
Elderly n (%)	19 (31)
Sex, Male n (%)	32 (58)
Weight (kg), Mean (SD)	77.8 (14.9)
Race, Caucasian, n (%)	55 (89)

STUDY DESIGN

This was a randomized, placebo-controlled, crossover study of three doses of moxifloxacin in healthy subjects. Subjects received each of the following treatments: moxifloxacin 400 mg, moxifloxacin 800 mg, moxifloxacin 1200 mg and matching placebo in random sequence. Subjects fasted overnight prior to study medication administration and continued to fast for 4 hours after dosing. A washout period of one week separated each dose.

For each of the two study centers, the following scheme was used for randomization across age groups and gender.

Group	Number of Subjects, Gender, Age
Group 1	6 males, aged 18-39 years
Group 2	6 males, aged 40-60 years
Group 3	6 males, aged >60 years
Group 4	6 females, aged 18-39 years
Group 5	6 females, aged 40-60 years
Group 6	6 females, aged >60 years

Following an overnight fast, 12 lead ECGs were performed and plasma samples obtained prior to dosing and at 1, 1.5, 2, 2.5, 3, 4, 6, and 12 following oral doses of study drug.

ANALYTIC METHODS

[redacted]

DATA ANALYSIS

The primary pharmacokinetic variables to be evaluated are the area under the concentration curve for the period 0 to 12 hours following dosing (AUC_{0-12}) and C_{max}. Additionally, both parameters were normalized with respect to body weight and dose.

A central laboratory, [redacted] provided central review of all post-screening electrocardiograms (ECG). A high-resolution scanner [redacted] was used for the analysis. In addition, a board-certified cardiologist reviewed the ECGs for the presence or absence of U-waves and T-wave abnormalities under blinded conditions.

The absolute value of QTc (either Bazett's or Freidericia's correction) was examined by dose and by time.

The relationship between QT interval duration and dose and plasma concentration of moxifloxacin was explored in various ways. Four different definitions of baseline values were used in order to express the drug effect as a change from baseline. Baseline was defined as:

1. the pre-dose (t=0) value on the corresponding day of treatment **(t=0 as baseline)**

2. an average of the pre-dose (t=0) values across all four treatment periods **(average t=0 as baseline)**

3. the value obtained on placebo at the corresponding time of C_{max} for each of the moxifloxacin treatments **(corresponding time on placebo day as baseline)**

4. an average of all values collected over the entire 12-hour interval following placebo administration **(average on placebo day as baseline)**

In order to characterize each subject's exposure to a given dose with a single value

- the effect at C_{max} was analyzed
- the maximal change in QTc from baseline was analyzed (independent of the maximum drug concentration)

All primary and the secondary variables were analyzed using an analysis of covariance (ANCOVA). An ANCOVA with terms for sequence, subjects within sequence, period, treatment and pre-dose baseline was performed. Treatment groups were compared in pairwise fashion – the primary comparisons were moxifloxacin and placebo. Comparison contrasts to test for a linear trend in dose were performed. An ANCOVA with terms for sequence, subjects within sequence, period, treatment, pre-dose, age, gender, age*gender and treatment*age and a separate model including terms for sequence, subjects within sequence, period, treatment, baseline, age, gender, age*gender and treatment*gender were used to test whether the comparison of moxifloxacin to placebo is independent of age or gender.

The following presentations of the data were also prepared to examine the relationship between the QTc and the drug concentration:

- Plot of change in QTc at C_{max} from the corresponding time on the placebo day versus drug concentration at T_{max},
- Plot of all changes in QTc versus all concentrations.
- Plot of change in QTc at C_{max} from the t=0 value versus drug concentration (at C_{max}).

No adjustments for multiple tests were to be performed.

Reviewer's Comment: The sponsor initially proposed in the protocol to examine the relationship between AUC_{0-12} for ΔQTc versus AUC_{0-12}. The sponsor noted that after further consideration of the analytic plans they felt that presentation of the effect data (the ECG changes) in relation to moxifloxacin AUC was unlikely to provide additional insight into the PK/PD relationship.

Supplementing the analysis of changes in mean values of QT, the number of subjects in which "outlier" QT values or changes in value occurred is presented. The threshold values used for the analyses are those proposed by the EMEA. An outlier was defined as an abnormal value or change at any time during the day.

RESULTS

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) subjects completed all four periods of the study; one subject was withdrawn from the study having received only one dose of study drug (moxifloxacin 800 mg). The reason for withdrawal of this subject was a protocol violation (high plasma creatine kinase). This was in the plasma sample obtained at the predose sampling time on the first day of the study. All other subjects completed the study as planned. Thus 61 of 62 subjects were valid for pharmacokinetics and pharmacodynamics.

Table 1 below presents the mean (SD) pharmacokinetic data for moxifloxacin obtained after each dose

Table 1
Mean (SD) Pharmacokinetic Parameters for a Single Dose of Moxifloxacin 400 mg, 800 mg, and 1200 mg

Dose (mg)	AUC_{0-12} (mg*h/L) n	Mean	SD	C_{max} (mg/L) n	Mean	SD	T_{max} (h) n	Max - Min	Mean	SD	Ratio of Observed:Expected* AUC_{0-12} (%)	C_{max} (%)
400	61	22.08	5.06	61	2.93	0.95	61	3	2.08	0.81	--	--
800	61	42.01	9.34	61	5.26	1.20	61	5	2.97	1.23	95.1	89.8
1200	61	62.25	12.62	61	7.41	1.50	61	5	3.53	1.29	94.0	84.3

* from linear extrapolation of the 400 mg data

Plots of Change in Bazett QTc from t=0, median and distribution
See Figure 1, attached at end of this report. The distribution of QT data is provided by graphs showing the 5th, 25th, 75th, and 95th percentiles and the median values of ΔQTc using the pre-dose (t=0) value as baseline.

Reviewer's Comment: It is also possible to present this data using other definitions of baseline, but the sponsor chose to limit themselves to one analysis.

On the placebo day QTc is relatively constant for the first 3 hours. Thereafter it increases and remains at that level throughout the reminder of the period of observation. With drug, the pattern is that of an earlier increase in QTc with maximum elevation around 6 hours after dosing. For the 400 mg dose, median ΔQTc is about 19 msec 6 hours after dosing. For the 1200 mg dose the median ΔQTc is 29 msec compared with a median increase of 11 msec 6 hours after placebo administration. Variability in the ΔQTc parameter does not appear to be substantially affected by moxifloxacin dose.

A. ΔQTc at C_{max} Using Different Definitions of Baseline

1. t=0 as baseline
The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown in Table 2 using the pre-dose (t=0) value on the corresponding day of treatment (i.e. t=0 as baseline).

Table 2
Mean (SD) ΔQTc at C_{max} Using t=0 as Baseline (N=61)

	ΔQTc Bazett's correction Mean	SD	ΔQTc Freidericia's correction 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 in Table 3 using the average of the pre-dose (t=0) values across all four treatment periods (i.e. average t=0 as baseline).

Table 3

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

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3. Corresponding time on placebo day as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown in Table 4 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).

Table 4
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 in Table 5 using an average of all values collected over the entire 12-hour interval following placebo administration (i.e. average on placebo day as baseline).

Table 5
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

B. Max ΔQTc Using Different Definitions of Baseline

In addition, to the ΔQTc at C_{max}, the maximal change in QTc from baseline (max ΔQTc) was analyzed. Table 6 summarizes the results using definitions #1,2, and 4 for baseline.

Reviewer's Comment: The sponsor did not calculate the max ΔQTc using the value obtained on placebo at the corresponding time of C_{max} for each of the moxifloxacin treatments (i.e. definition #3: corresponding time on placebo day as baseline).

Table 6
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				
Placebo	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

C. ANCOVA Results

Pairwise comparisons (moxifloxacin vs. placebo) showed the effects on QTc to be statistically significant for all doses. Tests for a linear trend of QTc prolongation with dose were highly statistically significant for each of the four presentations of ΔQTc.

With one exception (age in the 1200 mg vs. placebo comparison for Freidericia-corrected maximum QTc), age and gender were not significant when included in the model.

D. Concentration-effect

See Figure 2, attached at the end of this report. 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 ($p<0.001$).

Plots of concentration versus QTc were also prepared for each subject by the sponsor (data not shown) in order to examine the relationship for evidence of hysteresis. There was no consistent pattern of response either within or between subjects. No formal analytic approaches were employed by the sponsor. However, a crude analysis of the timing of maximal effect in relation to t_{max} was performed. As can be seen in Table 7 below, in general, C_{max} occurred before the maximal value of QTc.

Table 7
Relationship Between C_{max} and maximal QTc (Bazett)

	Number of observations (%)		
	400 mg n=61	800 mg n=61	1200 mg n=61
C_{max} before QT_{max}	44 (72%)	37 (61%)	25 (41%)
C_{max} at same time as QT_{max}	8 (13%)	5 (8%)	16 (26%)
C_{max} after QT_{max}	9 (15%)	19 (31%)	20 (33%)

E. Outlier QT values/changes

Criteria from the EMEA were used to identify values or changes in value of QT of interest and are abbreviated as follows:
Flag 1 = QTc ≥ 500 msec
Flag 2 = ΔQTc ≥ 60 msec
Flag 3 = ΔQTc ≥ 30 msec and QTc drug ≥ 450 msec for male or 470 msec for female
Flag 4 = ΔQTc ≥ 15% Baseline (t=0)
Flag 5 = any of above

Table 8 presents a summary of the outlier values/changes using all QTc data.

Table 8
Outlier values/changes in QTc
All QTc Data Using t=0 as Baseline (N=61)

	Number of subjects (%)				
	Flag 1	Flag 2	Flag 3	Flag 4	Flag 5
Placebo	0	0	0	0	0
Moxi 400 mg	0	2 (3%)	0	3 (5%)	3 (5%)
Moxi 800 mg	0	4 (7%)	3 (5%)	5 (8%)	7 (11%)
Moxi 1200 mg	0	9 (15%)	11 (18%)	10 (16%)	19 (31%)

F. ECG effects (T waves and U waves)

In one ECG, U-waves were observed 12 hours after application of 1200 mg of moxifloxacin. The most common abnormality reported was "non-specific ST segment and/or T wave changes" occurring in 12 subjects. The number of these reports increased with dose; n=4, 3, 15 and 22 for placebo, 400, 800 and 1200 mg respectively. The changes in one of these ECGs (6 hour timepoint, 400 mg moxifloxacin) were described as "clinically significant" whereas the others were judged by the investigator to be "clinically insignificant". Additionally, clinically significant ST segment depression was noted following the 1200 mg dose of moxifloxacin in two subjects (at 3 and 6 hours after dosing).

G. Safety - Analysis of adverse events

There were no deaths or serious adverse events in this study. Adverse event data are presented in summary by body system in Table 9 below.

Table 9
Adverse Events by Body System
Number of subjects (%)

Body system	Placebo	Moxifloxacin 400 mg	Moxifloxacin 800 mg	Moxifloxacin 1200 mg
Any	12 (20)	11 (18)	28 (45)	33 (54)
Body as a whole	8 (13)	5 (8)	10 (16)	10 (16)
Cardiovascular	1 (2)	2 (3)	3 (5)	6 (10)
Digestive	3 (5)	4 (7)	12 (19)	16 (26)
Hematology and lymphatic	0 (0)	0 (0)	2 (3)	2 (3)
Musculoskeletal	0 (0)	0 (0)	1 (2)	0 (0)
Nervous	3 (5)	1 (2)	6 (10)	17 (28)
Respiratory	0 (0)	1 (2)	2 (3)	0 (0)
Skin and appendages	2 (3)	0 (0)	4 (6)	4 (7)
Special senses	1 (2)	0 (0)	1 (2)	3 (5)
Urogenital	0 (0)	0 (0)	1 (2)	0 (0)

Comments here are confined to all events whether or not judged due to drug. Around one fifth of patients reported an adverse event of some kind during the placebo and 400 mg periods of the study. There was no clear pattern of distribution in the COSTART-defined body systems affected for these two periods. With increasing dose (800 and 1200 mg moxifloxacin) the total number of subjects reporting an event increased (45% and 54% for the two periods, respectively). Adverse events in the nervous system, the digestive system and the cardiovascular system predominated and exhibited a relationship to dose. The adverse event "Dizziness" (in COSTART this is coded to the Nervous System) was reported by 3, 1, 6 and 15 subjects at doses of 0, 400, 800 and 1200 mg moxifloxacin respectively. Inspection of the 81 ECGs recorded during episodes of dizziness showed no evidence of rhythm disturbance.

Three subjects experienced vasovagal episodes (considered medically significant) all at the dose of 1200 mg. Two of the episodes were judged possibly related and one probably related to study drug by the investigator. All were associated with nausea and/or vomiting. In one case, a brief (10 second) syncopal period was documented. No ECG changes accompanied these events; hypotension was documented in 2 of the 3 episodes.

H. Evaluation laboratory parameters

In a number of instances elevated CPK levels were noted 7 days after administration of study drug (5 subjects. CPK levels returned to the normal range on retest. The sponsor felt that the lack of a relation to dose or reoccurrence on rechallenge makes it unlikely that these changes in CPK were related to drug.

CONCLUSIONS

- 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.

- Using data from the placebo treatment day, a diurnal increase in the QT interval was observed to occur during the first 6 hours after dosing (i.e. between 1 and 4 pm).

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

- Reporting of adverse events in this double blind study appeared to follow a dose-related pattern. An excess of nervous system and digestive system effects was evident following doses of 800 mg and 1200 mg moxifloxacin. Three subjects experienced vasovagal episodes, all at doses of 1200 mg.

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2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

VI. STUDY 100263: 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
Study Dates: 02 May 2000 - 13 July 2000
Investigators: Charles Ballow, MD; Kenneth Lasseter, MD
Study center(s):

OBJECTIVES

The primary purpose of this trial was to determine the effect of single oral doses of moxifloxacin, levofloxacin and erythromycin on the QT interval duration in healthy subjects. The following doses were evaluated: moxifloxacin 400 mg and 800 mg; levofloxacin 500 mg and 1000 mg, and erythromycin ethylsuccinate 1600 mg (equivalent to 1000 mg erythromycin base).

FORMULATIONS

- Avelox ® (moxifloxacin, BAY 12-8039), 400 mg tablets (encapsulated), Batch No. M000206 [Batch No. 527248C (tablets)]
- Levaquin ® (levofloxacin) 2 x 250 mg tablets (encapsulated); Batch No. M991206, [Batch No. 99P0713E (tablets)];
- E.E.S. (erythromycin ethylsuccinate), 4 x 400 mg filmtabs, Batch No. 29044CG21;
- Placebo capsules (microcrystalline cellulose), Batch No. M991202

SUBJECTS

Demographics	*# Subjects (%) or Mean (SD)*
All Ages	49 (100)
Young n (%)	17 (35)
Middle aged n (%)	15 (31)
Elderly n (%)	16 (33)
Sex = Male n (%)	24 (49)
Weight (kg), Mean (SD)	75 (10.6)
Race = Caucasian, n (%)	28 (57)
Race = Black, n (%)	3 (6)
Race = Hispanic, n (%)	17 (35)
Other, n (%)	1 (2)

STUDY DESIGN

This was a single-blind, randomized, six-period, crossover study in healthy subjects. 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. Subjects fasted overnight prior to study medication administration and continued to fast for 4 hours after dosing. A washout period of one week separated each dose.

Prior to randomization on Day -1, 12 lead ECGs were performed at 0, 1, 1.5, 2, 2.5, 3, 4, 6, and 12 hours. After randomization and following an overnight fast, 12 lead ECGs were performed and plasma samples obtained prior to dosing (t=0) and at 1, 1.5, 2, 2.5, 3, 4, 6, and 12 following oral doses of study drug in each of the 6 treatment arms.

Reviewer's Comment: Although QT data was collected from 9 timepoints on Day –1, the sponsor did not use this data in any of their four definitions of baseline, which were used to express the drug effect as a change from baseline. See Data Analysis section.

ANALYTIC METHODS

[redacted]

DATA ANALYSIS

The primary pharmacokinetic variables to be evaluated are the area under the concentration curve for moxifloxacin, levofloxacin, and erythromycin for the period 0 to 12 hours following dosing (AUC_{0-12}) and C_{max}.

A central laboratory, [redacted] provided central review of all post-screening electrocardiograms (ECG). A high-resolution scanner [redacted] was used for the analysis. In addition, a board-certified cardiologist reviewed the ECGs for the presence or absence of U-waves and T-wave abnormalities under blinded conditions.

The absolute value of QTc (either Bazett's or Freidericia's correction) was examined by dose and by time.

The relationship between QT interval duration and dose and plasma concentration of moxifloxacin was explored in various ways. Four different definitions of baseline values were used in order to express the drug effect as a change from baseline. Baseline was defined as:

5. the pre-dose (t=0) value on the corresponding day of treatment **(t=0 as baseline)**
6. an average of the pre-dose (t=0) values across all four treatment periods **(average t=0 as baseline)**
7. the value obtained on placebo at the corresponding time of C_{max} for each of the moxifloxacin treatments **(corresponding time on placebo day as baseline)**

8. an average of all values collected over the entire 12-hour interval following placebo administration **(average on placebo day as baseline)**

In order to characterize each subject's exposure to a given dose with a single value

- the effect at C_{max} was analyzed

- the maximal change in QTc from baseline was analyzed (independent of the maximum drug concentration)

All primary and the secondary variables were analyzed using an analysis of covariance (ANCOVA). An ANCOVA with terms for sequence, subjects within sequence, period, treatment and pre-dose baseline was performed. Pairwise comparisons of treatment groups were between moxifloxacin and placebo. Other treatment comparisons were between moxifloxacin and the two other drugs, levofloxacin and erythromycin. Comparison contrasts to test a linear trend in dose for each of the three drugs were performed.

An ANCOVA with terms for sequence, subjects within sequence, period, treatment, baseline, age, age*gender and treatment*age and a separate model including terms for sequence, subjects within sequence, period, treatment, baseline, age, gender, age*gender and treatment*gender were analyzed. The following tests for age and gender interactions were performed:

- Whether the comparison of moxifloxacin to placebo was independent of age or gender,
- Whether the comparison of moxifloxacin to levofloxacin or erythromycin was independent of age or gender.

The following presentations of the data were also prepared to examine the relationship between the QTc and the drug concentration:

- Plot of change in QTc at C_{max} from the corresponding time on the placebo day versus drug concentration at C_{max},
- Plot of all changes in QTc versus all concentrations.

No adjustments for multiple tests were to be performed.

Reviewer's Comment: The sponsor initially proposed in the protocol to examine the relationship between AUC_{0-12} for ΔQTc versus AUC_{0-12}. The sponsor noted that after further consideration of the analytic plans they felt that presentation of the effect data (the ECG changes) in relation to moxifloxacin AUC was unlikely to provide additional insight into the PK/PD relationship.

Supplementing the analysis of changes in mean values of QT, the number of subjects in which "outlier" QT values or changes in value occurred is presented. The threshold values used for the analyses are those proposed by the EMEA. An outlier was defined as an abnormal value or change at any time during the day.

RESULTS

Of the 49 subjects randomized to the study, 47 completed the study. One subject discontinued after taking erythromycin only (Period 1) due to an adverse event (vomiting). The other subject withdrew consent after completing all treatments, except moxifloxacin 800 mg. All other subjects completed the study as planned.

Reviewer's Comment: In addition to the two patients who discontinued from the study, no pharmacokinetic analysis was done on two patients (one during treatment with levofloxacin 500 mg and the other during treatment for levofloxacin 1000 mg).

Table 1 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).

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Table 1
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	4.0 -1.0
Moxi 800	47	46.9	11.1	47	6.1	1.5	47	2.4	1.1	6.0 - 1.0
Levo 500	47	41.5	10.8	47	6.7	1.9	47	1.5	0.6	4.0 - 1.0
Levo 1000	47	89.1	22.5	47	13.4	3.5	47	1.5	0.6	4.0 - 1.0
Erythro 1000	48	7.3	5.3	48	1.5	0.8	48	1.3	0.4	3.0 - 1.0

Plots of Change in Bazett QTc from t=0, median and distribution

See Figure 1, attached at end of this report. The distribution of QT data is provided by graphs showing the 5th, 25th, 75th, and 95th percentiles and the median values of ΔQTc using the pre-dose (t=0) value as baseline.

Reviewer's Comment: It is also possible to present this data using other definitions of baseline, but the sponsor chose to limit themselves to one analysis.

Following placebo treatment, the ΔQTc duration remained unchanged for the first 4 hours. Thereafter, there was a modest increase in, which was sustained for the duration of the study day.

A. ΔQTc at C_{max} Using Different Definitions of Baseline

1. t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown in Table 2 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}.

Table 2
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.

Reviewer's Comment: The mean ΔQTc for moxifloxacin 400 mg is lower than in the following three analyses. This effect seems to be due to the fact that the pre-dose (t=0) QTc for the moxifloxacin 400 mg treatment arm is higher (401 msec) than in the other treatment arms

2. Average t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown in Table 3 using the average of the pre-dose (t=0) values across all four treatment periods (i.e. average t=0 as baseline).

Table 3
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 in Table 4 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).

Table 4
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 in Table 5 using an average of all values collected over the entire 12-hour interval following placebo administration (i.e. average on placebo day as baseline).

Table 5
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

B. Max ΔQTc Using Different Definitions of Baseline

In addition, to the ΔQTc at C_{max}, the maximal change in QTc from baseline (max ΔQTc) was analyzed. Table 6 summarizes the results using definitions #1,2, and 4 for baseline.

Reviewer's Comment: The sponsor did not calculate the max ΔQTc using the value obtained on placebo at the corresponding time of C_{max} for each of the moxifloxacin treatments (i.e. definition #3: corresponding time on placebo day as baseline).

Table 6
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

C. ANCOVA Results

The effect of moxifloxacin on ΔQTc is significantly greater that of placebo. The 400 mg dose of moxifloxacin produces a significantly greater effect than both doses of levofloxacin. The 800 mg dose of moxifloxacin produces a significantly greater effect on QTc than either dose of levofloxacin. The effect of moxifloxacin (either 400 or 800 mg) is greater than the effect of erythromycin. Additional contrasts between levofloxacin vs. placebo and erythromycin vs. placebo show a statistically significant, though numerically smaller, prolongation of QTc for these other agents at each dose studied.

With one exception (the responses of males and females to the 800 mg dose of moxifloxacin and erythromycin), age and gender were not significant when included in the model.

D. Concentration-effect

See Figure 2, attached at the end of this report. 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.

Reviewer's Comment: The sponsor omitted a single aberrant point from the graph of the moxifloxacin data obtained with the moxifloxacin 800 mg dose (C_{max} = 5128.49; ΔQTc = -58).

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): ΔQTc (from t=0) = -2.35 + (0.003498)C_{max} (p=0.005)

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

Plots of concentration versus QTc were also prepared for each subject by the sponsor (data not shown) in order to examine the relationship for evidence of hysteresis. There was no consistent pattern of response either within or between subjects. No formal analytic approaches were employed by the sponsor. However, a crude analysis of the timing of maximal effect in relation to T_{max} was performed. As can be seen in Table 7 below, In comparison with moxifloxacin, C_{max} for levofloxacin and erythromycin tends to occur before the maximal observed ΔQTc; this is particularly the case for erythromycin.

Table 7
Relationship Between C_{max} and maximal QTc (Bazett)

	Proportion of observations (%)				
	Moxi 400 mg n=48	Moxi 800 mg n=47	Levo 500 mg n=47	Levo 1000 mg n=47	Erythro 1000 mg n=48
C_{max} before QT_{max}	63	55	83	72	88
C_{max} at same time as QT_{max}	15	19	6	1	3
C_{max} after QT_{max}	23	26	11	15	6

Reviewer's Comment: The time of the max QTc (QT_{max}) was determined in relation to the time of C_{max} (T_{max}). As shown in the table below, the mean QT_{max} occurs later than the mean T_{max}, but is highly variable.

Drug	*T_{max} (hours)*		*QT_{max} (hours)*	
	N	*Mean (SD)*	*N*	*Mean (SD)*
Moxifloxacin 400 mg	*48*	*2.0 (0.8)*	*48*	*5.2 (3.6)*
Moxifloxacin 800 mg	*47*	*2.4 (1.1)*	*47*	*4.3 (3.2)*
Levo 500 mg	*47*	*1.5 (0.6)*	*47*	*5.5 (3.9)*
Levo 1000 mg	*47*	*1.5 (0.6)*	*47*	*5.3 (3.9)*
Erythromycin 1000 mg	*48*	*1.3 (0.4)*	*48*	*5.9 (4.0)*
Placebo	–	–	*48*	*6.1 (3.8)*

E. Outlier QT values/changes

Criteria from the EMEA were used to identify values or changes in value of QT of interest and are abbreviated as follows:
Flag 1 = QTc $\geq$ 500 msec
Flag 2 = ΔQTc $\geq$ 60 msec
Flag 3 = ΔQTc $\geq$ 30 msec and QTc drug $\geq$ 450 msec for male or 470 msec for female
Flag 4 = ΔQTc $\geq$ 15% Baseline (t=0)
Flag 5 = any of above

Table 8 presents a summary of the outlier values/changes using all QTc data.

Table 8
Outlier values/changes in QTc
All QTc Data Using t=0 as Baseline

	Number of subjects (%)				
	Flag 1	Flag 2	Flag 3	Flag 4	Flag 5
Placebo n=48	0	0	0	0	0
Moxi 400 mg n=48	0	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Moxi 800 mg n=47	0	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Levo 500 mg n=48	0	1 (2%)	0	1 (2%)	1 (2%)
Levo 1000 mg n=48	0	0	1 (2%)	0	1 (2%)
Erythro 1000 mg n=48	0	0	0	0	0

F. ECG effects (T waves and U waves)

The most common abnormality reported was non-specific ST segment and T wave changes and was a finding in each of the treatment groups in the study (including placebo). Nine subjects had reports of this nature during placebo, for moxifloxacin (both doses), levofloxacin (both doses) and erythromycin the number of subjects affected was 11, 7 and 5, respectively. Other findings included U waves and T wave inversion. As with the nonspecific T wave abnormalities, these were reported as "clinically insignificant". A preponderance of the T wave findings was in subjects on moxifloxacin. However, of the four subjects with these findings on moxifloxacin, two had similar findings with other study drugs. Other ECG abnormalities identified included: atrial bigeminy, atrial trigeminy, premature atrial complexes, premature ventricular contractions (18 ECGs) and atrial ectopic rhythm. No relation to a particular drug or dose (within moxifloxacin and levofloxacin) could be discerned by the sponsor.

G. Safety - Analysis of adverse events

There were no deaths or serious adverse events in this study. One subject as withdrawn from the study prior to the final period in which she was due to receive moxifloxacin 800 mg. In a previous period of the study, levofloxacin 1000 mg had caused a "pounding" cardiac sensation, nausea and itchy palms. The investigator (who was aware that the subject was due to receive 800 mg moxifloxacin in the final period of the study) initiated the withdrawal of the subject from the study as a precaution against the recurrence of these symptoms.

During the final period of the study (moxifloxacin 400 mg) one subject developed T-wave inversion suggestive of ischemia. The subject was asymptomatic and blood draws for cardiac enzymes were negative on two occasions. The subject was kept overnight with telemetry monitoring of the ECG. Subsequent thallium imaging was negative. On review, the investigator felt that these changes were most likely not due to drug, since non-specific changes were seen at about the same time of day during other treatment periods.

All adverse event data are presented in summary by body system in Table 9 below.

Table 9
Adverse Events by Body System

	Placebo (n=48)	Moxi 400 mg (n=48)	Moxi 800 mg (n=47)	Levo 500 mg (n=48)	Levo 1000 mg (n=48)	Erythro 1000 mg (n=49)
Body System	%	%	%	%	%	%
Any body system	6	10	38	17	19	18
Body as a whole	2	8	9	4	4	8
Cardiovascular	0	2	2	0	2	0
Digestive	2	2	26	6	10	6
Hematology and lymphatic	0	0	4	6	2	0
Nervous	0	0	17	0	6	0
Respiratory	0	0	2	0	0	0
Skin and appendages	0	0	0	0	6	2
Special senses	2	0	4	2	0	0
Urogenital	0	4	2	2	2	2

Digestive and nervous system events were most notable. Nausea and dizziness were frequent following moxifloxacin 800 mg. The AE rate at the therapeutic dose of moxifloxacin (400 mg) was, however, not substantially different from the placebo rate. The reports of dizziness were further examined. Eight subjects experienced dizziness, seven after 800 mg moxifloxacin and three following 1000 mg levofloxacin. The reports were generally around the time of C_{max}. ECGs obtained, per protocol, showed all patients in sinus rhythm. A number of "non-specific ST and/or T wave abnormalities" seen in one subject appeared at other time on other study days including the placebo treatment day (without symptoms of dizziness). The sponsor felt that the ECG findings were unrelated to symptoms in this particular patient.

H. Evaluation laboratory parameters

On a total of three occasions, transiently elevated CPK was noted in two subjects. Moxifloxacin 800 mg was the study drug preceding two of the observations, erythromycin was the drug in the other case (one subject had elevated CPK following both erythromycin and moxifloxacin 800 mg). CPK fell to the normal range or fell rapidly towards the normal range without other sequelae. Liver enzymes were elevated in two additional subjects (following erythromycin). The sponsor indicated that the relationship of these findings to the single doses of study drug is uncertain.

CONCLUSIONS

- 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.

- Using data from the placebo treatment day, a small diurnal increase in the QT interval was observed to occur about 6 hours after dosing which was sustained until the end of the period of observation (12 h).

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

- Adverse events, particularly in the digestive, nervous and cardiovascular system, were most common following moxifloxacin 800 mg. Of the five drug treatments, the moxifloxacin 800 mg was least well tolerated, however, at the lower dose of 400 mg, moxifloxacin was as well tolerated as levofloxacin and erythromycin. There were no consistent findings on laboratory evaluations and vital signs measurement.

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VII. STUDY 100264: 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
Study Dates: 01 May 2000 - 10 July 2000
Investigators: Stuart Harris, MD; Randall Stoltz, MD.
Study center(s):

OBJECTIVES

The primary purpose of this trial was to determine the effect of therapeutic doses of moxifloxacin and sparfloxacin on the QT interval duration on Day 1 and Day 10 of a ten-day period of dosing.

Other objectives were to provide an assessment of the pharmacokinetics of a 10-day course of dosing with moxifloxacin including an analysis of a sulfate and a glucuronide conjugate designated "M1" and "M2" respectively.

FORMULATIONS

- Avelox ® (moxifloxacin) 400 mg tablets, Batch No. 527248C
- Zagam ® (sparfloxacin) 200 mg tablets, Batch No. 22008
- Placebo capsules (microcrystalline cellulose), Batch No. M991202

SUBJECTS

Demographic Data	*# Subjects (%) or Mean (SD)*
All Ages	48 (100)
Young n (%)	17 (35)
Middle aged n (%)	15 (31)
Elderly n (%)	16 (33)
Sex = Male (%)	24 (50)
Weight (kg), Mean (SD)	75.4 (14.0)
Race = Caucasian, n (%)	25 (52)

STUDY DESIGN

This was a randomized, 2-period crossover study in healthy adult male and female subjects. 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. Subjects fasted overnight prior to study medication administration and continued to fast for 4 hours after dosing. A 9-day washout interval separated the two periods.

This was an open-label study. Subjects were not told which drug was administered, and study personnel responsible for monitoring adverse events were blinded to the identity of the study drug. The reading of the ECG traces was conducted under blinded conditions.

The protocol planned for the enrolment of 48 healthy subjects with age and gender distribution shown:

18-39 years 8 male, 8 female
40-60 years 8 male, 8 female
> 60 years 8 male, 8 female

On Day -1 of each study period, placebo capsules were administered and a complete ECG profile was obtained. Plasma samples were obtained for pharmacokinetic analysis and 12-lead ECGs were recorded on Day 1 and Day 10 of each period prior to dosing and at 1, 1.5, 2, 2.5, 3, 4, 6, 12, 16, and 24 hours following oral doses of study drug on Days –1, 1 and 10 of both study periods.

ANALYTIC METHODS

[redacted]

DATA ANALYSIS

The primary pharmacokinetic variables to be evaluated are the area under the concentration curve for moxifloxacin, moxifloxacin metabolites M1 and M2, and sparfloxacin for the period 0 to 24 hours following dosing (AUC_{0-24}) and C_{max}.

A central laboratory, [redacted] provided central review of all post-screening electrocardiograms (ECG). A high-resolution scanner [redacted] was used for the analysis. In addition, a board-certified cardiologist reviewed the ECGs for the presence or absence of U-waves and T-wave abnormalities under blinded conditions.

The absolute value of QTc (either Bazett's or Freidericia's correction) was examined by dose and by time.

The relationship between QT interval duration and dose and plasma concentration of moxifloxacin and sparfloxacin was explored in various ways. Four different definitions of baseline values were used in order to express the drug effect as a change from baseline. Baseline was defined as:

9. the pre-dose (t=0) value on the corresponding day of treatment **(t=0 as baseline)**

10. an average of the pre-dose (t=0) values on Day –1 and Day 1 **(average t=0 using Day –1 and Day 1 from both study periods) as baseline**

11. the value obtained on placebo (Day –1) at the corresponding time of C_{max} for each treatment **(corresponding time on Day -1 as baseline)**

12. an average of all values collected over the entire 12-hour interval following placebo administration on Day –1 of the respective period **(average on Day -1 as baseline)**

In order to characterize each subject's exposure to a given dose with a single value

- the effect at C_{max} was analyzed

- the maximal change in QTc from baseline was analyzed (independent of the maximum drug concentration)

Analysis of variance (ANOVA) was performed with terms for sequence, subjects within sequence, period, treatment and pre-dose baseline. Pairwise comparison of treatment groups was also performed. Primary comparisons were between moxifloxacin and placebo. Comparison contrasts to test for a linear trend by dose was performed.

Tests were performed to establish whether the comparison of moxifloxacin with placebo was independent of age or gender.

Supplementing the analysis of changes in mean values of QT, the number of subjects in which "outlier" QT values or changes in value occurred is presented. The threshold values used for the analyses are those proposed by the EMEA. An outlier was defined as an abnormal value or change at any time during the day.

RESULTS

Forty-eight subjects were valid for safety analysis. Two subjects were withdrawn for adverse events. One patient was withdrawn during sparfloxacin treatment for premature ventricular contractions (PVCs) after having completed the moxifloxacin arm. Another subject was withdrawn from the study during the washout period after moxifloxacin treatment and before sparfloxacin treatment for an intercurrent illness (sinusitis) considered unrelated to drug. The third patient withdrew consent in Period 1 during treatment with sparfloxacin. In summary, 45 subjects completed the entire study and provided data from Day 1 and Day 10 data during both periods. One subject received moxifloxacin only and another received sparfloxacin only. Of the 47 subjects who received sparfloxacin, two provided Day 1 data only. The assay data from one subject showed moxifloxacin concentrations below the limit of quantitation for Day 1, but ECG data and safety data were available for this time point.

Tables 1-4 below present the mean (SD) pharmacokinetic data for moxifloxacin, metabolite M1, metabolite M2, and sparfloxacin, respectively.

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

	AUC_{0-24} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)			$C_{pre\text{-}dose}$ (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

Table 2
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)			$C_{pre\text{-}dose}$ (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

Table 3
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)			$C_{pre\text{-}dose}$ (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

Table 4
Mean (SD) Pharmacokinetic Parameters for Sparfloxacin on Days 1 through 10

	AUC_{0-24} (mg*h/L)			C_{max} (mg/L)			T_{max} (h)			$C_{pre\text{-}dose}$ (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

Tables 5-7 summarize the influence of age and gender on moxifloxacin, M1 and M2 pharmacokinetics.

Table 5
Ratio of Geometric LS Mean for Moxifloxacin Pharmacokinetic Parameters
Age and Gender

	AUC_{0-24}		$AUC_{0-24,norm}$		C_{max}		$C_{max,norm}$	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
Elderly vs. Young	1.09	1.10	1.10	1.12	1.03	1.08	1.04	1.10
Females vs. Males	1.13	1.01	0.98	0.88	1.29	1.16	1.11	1.00

Females had significantly higher moxifloxacin AUC and C_{max} than males on Day 1. For AUC this difference was not statistically significant once the data were normalized. For C_{max} the gender difference persisted after normalization, however the difference was small.

Females also had a significantly higher C_{max} than males on Day 10, but was not significant when the data were normalized

There was no significant difference in AUC or C_{max} between elderly and young subjects, either on Day 1 or Day 10.

Table 6
Ratio of Geometric LS Mean for Metabolite M1 Pharmacokinetic Parameters
Age and Gender

	AUC_{0-24}		$AUC_{0-24,norm}$		C_{max}		$C_{max,norm}$	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
Elderly vs. Young	1.33	1.14	1.37	1.17	1.29	1.21	1.50	1.50
Females vs. Males	1.09	0.89	0.95	0.79	1.07	0.87	1.00	0.67

Elderly subjects had a significantly higher AUC and C_{max} of metabolite M1 than young subjects, which was more pronounced on Day 1 than Day 10.

Table 7
Ratio of Geometric LS Mean for Metabolite M2 Pharmacokinetic Parameters
Age and Gender

	AUC_{0-24}		$AUC_{0-24,norm}$		C_{max}		$C_{max,norm}$	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
Elderly vs. Young	1.23	1.15	1.23	1.17	1.05	1.13	1.09	1.17
Females vs. Males	1.18	0.95	1.03	0.83	1.10	0.93	1.00	0.79

There appeared to be no consistent pattern to suggest an age or gender effect on the M2 metabolite.

Plots of Change in Bazett QTc from t=0, median and distribution

See Figure 1, attached at end of this report. The distribution of QT data is provided by graphs showing the 5th, 25th, 75th, and 95th percentiles and the median values of ΔQTc using the pre-dose (t=0) value as baseline.

Reviewer's Comment: It is also possible to present this data using other definitions of baseline, but the sponsor chose to limit themselves to one analysis.

Following placebo treatment, the QTc duration remained unchanged for the first 4 hours. Thereafter there was a modest increase in ΔQTc, which was sustained for the duration of the study day.

A. ΔQTc at C_{max} Using Different Definitions of Baseline

1. t=0 as baseline

The ΔQTc at the time of maximal moxifloxacin concentration (C_{max}) is shown in Table 8 using the pre-dose (t=0) value on the corresponding day of treatment (i.e. t=0 as baseline).

Table 8
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 in Table 9 using the average of the pre-dose (t=0) values on Day –1 and Day 1 (i.e. average t=0 as baseline).

Table 9
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 in Table 10 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).

Table 10
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 in Table 11 using an average of all values collected following placebo administration on Day –1 (i.e. average of Day –1 as baseline).

Table 11
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

B. Max ΔQTc Using Different Definitions of Baseline

In addition, to the ΔQTc at C_{max}, the maximal change in QTc from baseline (max ΔQTc) was analyzed. Table 12 summarizes the results using definitions #1,2, and 4 for baseline.

Reviewer's Comment: The sponsor did not calculate the max ΔQTc using the value obtained on Day -1 at the corresponding time of C_{max} (i.e. definition #3: corresponding time on Day -1 as baseline).

Table 12
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

C. ANCOVA Results

The difference in ΔQTc (Bazett's) between Day 1 and Day 10 for moxifloxacin was statistically significant for both C_{max} and max QTc.

The difference in ΔQTc between moxifloxacin and sparfloxacin on Days 1 and 10 was statistically significant for both C_{max} and max QTc using both Bazett's and Freidericia's formulas. The only exception was the max ΔQTc (Freidericia's) on Day 10, which was not significant.

D. Concentration-effect (Figure 2, attached at the end of this report):

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 Table 13 below.

Table 13
Regression Equations (Bazett)
QTc = Intercept + Slope*C_{max}

	Intercept	Slope	p-value[#]
Spar Day 1			0.54
Moxi Day 1			0.18
Spar Day 10			0.046
Moxi Day 10			0.12

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

Plots of concentration versus QTc were also prepared for each subject by the sponsor (data not shown) in order to examine the relationship for evidence of hysteresis. There was no consistent pattern of response either within or between subjects. No formal analytic approaches were employed by the sponsor. However, a crude analysis of the timing of maximal effect in relation to T_{max} was performed. As can be seen in Table 14 below, for both moxifloxacin and sparfloxacin, C_{max} tends to occur before the maximal QTc on Day 1 and to a lesser degree on Day 10.

Table 14
Relationship Between C_{max} and maximal QTc (Bazett)

	Number of observations (%)			
	Moxi Day 1	Moxi Day 10	Spar Day 1	Spar Day 10
C_{max} before QT_{max}	38 (84%)	30 (68%)	27 (84%)	19 (42%)
C_{max} at same time as QT_{max}	4 (9%)	5 (11%)	3 (9%)	6 (13%)
C_{max} after QT_{max}	3 (7%)	9 (20%)	14 (7%)	20 (44%)

Reviewer's Comment: The time of the max QTc (QT_{max}) was determined in relation to the time of C_{max} (T_{max}). As shown in the table below, the mean QT_{max} occurs later than the mean T_{max}, but is highly variable.

Drug	*T_{max} (hours)*		*QT_{max} (hours)*	
	N	*Mean (SD)*	*N*	*Mean (SD)*
Moxifloxacin Day 1	*46*	*1.9 (0.8)*	*47*	*5.2 (3.3)*
Moxifloxacin Day 10	*47*	*2.0 (0.8)*	*47*	*4.8 (3.2)*
Sparfloxacin Day 1	*47*	*4.7 (2.5)*	*47*	*5.9 (3.3)*
Sparfloxacin Day 10	*45*	*3.2 (1.4)*	*45*	*5.7 (3.5)*

E. Outlier QT values/changes

Criteria from the EMEA were used to identify values or changes in value of QT of interest and are abbreviated as follows:
Flag 1 = QTc ≥ 500 msec
Flag 2 = ΔQTc ≥ 60 msec
Flag 3 = ΔQTc ≥ 30 msec and QTc drug ≥ 450 msec for male **or** 470 msec for female
Flag 4 = ΔQTc ≥ 15% Baseline (t=0)
Flag 5 = any of above

Table 15 presents a summary of the outlier values/changes using all QTc data.

Table 15
Outlier values/changes in QTc
All QTc Data Using t=0 as Baseline

	Number of subjects (%)				
	Flag 1	Flag 2	Flag 3	Flag 4	Flag 5
Moxi Day 1 (n=47)	0	0	1(2%)	1(2%)	2(4%)
Moxi Day 10 (n=47)	0	2(4%)	2(4%)	4(9%)	6(11%)
Spar Day 1(n=47)	0	4(9%)	1(2%)	5(11%)	6(13%)
Spar Day 10 (n=45)	1(2%)	6(13%)	1(2%)	8(18%)	8(18%)

F. ECG effects (T waves and U waves)

T and U wave changes were reported in 12 subjects. These changes were all described by the reviewer as "clinically insignificant" and consisted predominantly of ST segment depression and non-specific T wave abnormalities. Inverted T waves and/or U waves were seen in a number of recordings in one subject. Nine subjects had abnormalities in the pre-dose period (for two of these subjects, the only abnormalities occurred at this time). Eight and seven subjects had abnormalities of the T wave in the moxifloxacin and sparfloxacin periods respectively.

G. Safety - Analysis of adverse events

There were no deaths or serious adverse events in this study. A single subject was withdrawn from the sparfloxacin arm of the study for a significant medical reason; the occurrence of premature ventricular complexes (PVCs) seen on the ECG. At the time of withdrawal from the study, the subject had completed period 1 (moxifloxacin) and was on the second day of the 10-day course of sparfloxacin. The investigator had noted PVCs during the moxifloxacin period of dosing, however the frequency of their occurrence and the timing of their occurrence (at the time when the highest drug concentrations were anticipated) caused a sufficient safety concern for the investigator to withdraw the patient from the study. An additional subject was withdrawn from the study during the washout period after Period 1 and before Period 2 for intercurrent illness (sinusitis) considered unrelated to drug.

All adverse event data are presented in summary by body system in Table 16 below.

Table 16
Adverse Events by Body System

	Number of subjects (%)	
Body system	Moxi 400 mg (n=47)	Spar 200 mg (n=47)
Any	29 (62%)	29 (62%)
Body as a whole	16 (34%)	12 (26%)
Cardiovascular	2 (4%)	3 (6%)
Digestive	15 (32%)	10 (21%)
Metabolic & Nutritional	0 (0%)	1 (2%)
Musculoskeletal	3 (6%)	1 (2%)
Nervous	7 (15%)	3 (6%)
Respiratory	3 (6%)	1 (2%)
Skin and appendages	6 (13%)	15 (32%)

Twenty-nine (29) of the 47 subjects experienced an adverse event during the period of moxifloxacin dosing; the same number reported an adverse event in the sparfloxacin dosing period. Minor differences in the pattern of adverse events for each treatment period (by COSTART body system) were noted. Reporting rate differences for the two periods were greater than 5% for the Digestive System (moxi > spar), the Nervous System (moxi > spar) and Skin and Appendages (spar > moxi). Of particular significance was the observation that "dizziness" (in COSTART this is coded to the Nervous System) was experienced by five subjects (2 elderly males, 1 elderly female, 1 young male, 1 young female). Three subjects were receiving moxifloxacin and 2 sparfloxacin during the episodes of dizziness. One elderly female subject reported dizziness twice while on moxifloxacin, on the first and tenth day of administration. She had 5 ECGs recorded during the events, with findings of "normal sinus rhythm", "within normal limits" on all ECGs. The two other subjects with 6 episodes of dizziness experienced 3 of the events at times compatible with the expected peak levels of moxifloxacin, and 3 events remote from times at which high drug concentrations would be anticipated. One subject experienced dizziness, "intermittent dizziness", and "dizziness while supine" during moxifloxacin administration. No ECG tracings were made at the time of these complaints. This subject experienced PVCs early during the period of sparfloxacin dosing. The investigator withdrew the subject from the study on Day 3 for safety reasons. One elderly male subject had 4 ECGs recorded during a dizziness episode during the sparfloxacin period. Reports from these ECGs (read under double-blind conditions) showed, "normal sinus rhythm".

H. Evaluation laboratory parameters

Elevations of CPK, LDH, SGOT and SGPT were noted in a single subject on Day 10 of sparfloxacin dosing. With the exception of CPK, which remained marginally above the normal limit for the laboratory, all had returned to the normal range 8 days following the last dose. A transient increase of CPK alone was noted in another subject (on sparfloxacin) during Period 1; again this resolved spontaneously by day 8 of moxifloxacin treatment (the following week).

Two subjects were diagnosed with renal calculi shortly after the conclusion of the trial. Microscopic hematuria was found on screening in one subject, the finding was considered insufficient to exclude the subject from the study. Subsequently a renal calculus was diagnosed by ultrasound. Fifteen days after the last exposure to study drug the subject was admitted to hospital for the investigation and subsequent removal of a renal stone – this was reported to be a calcium phosphate stone. The sponsor considered the occurrence of renal calculi to be coincidental and not related to either study drug.

CONCLUSIONS

- Mean moxifloxacin $AUC_{0\text{-}24}$ on Day 10 was 40% greater than the Day 1 value, and the mean Cmax 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.
- Adverse events were rather frequently recorded in this 10-day trial. Rates for moxifloxacin and sparfloxacin were comparable although there were minor differences in the pattern of reporting with GI and nervous system complaints being more common with moxifloxacin and skin complaints being more frequent with sparfloxacin.

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VIII. POOLED PHARMACOKINETIC ANALYSIS

STUDIES 100263, 100264, and 100265 By Age and Gender
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.

Methods
Age was categorized as:

- Young (18-39 years)
- Middle Aged (40-60 years)
- Elderly (>60 years)

The natural logarithms of AUC_{0-12} and C_{max} were analyzed using a two-way ANOVA with terms for age, gender, and age*gender. Pairwise comparisons of groups were performed using two-sided 90% confidence intervals for the ratio of geometric LS means. In addition, p-vlaues for two-ailed tests of equality of group comparisons were also calcuated. Pairwise comparisons were made between each of the age and gender groups, singly and combined. The comparison test p-values were examined in search of paterns that would suggest gender or age differences in pharmacokinetics. Where p-values suggested statistical significance for the data, the effect was re-examined after adjustment for body weigth (normalized data).

Results
Age

- The AUC_{0-12} of 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).

Conclusion
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.