CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-277

PHARMACOLOGY REVIEW

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520
Consultation for HFD-590

NDA#: 21,277-000

Date CDER Received/Type of Submission: 11/2/00; original NDA submission (also 2/9/01 response to request for information on Study Report R 7510)
Reviewer: Amy L. Ellis, Ph.D.
Date Assigned: 11/00
Number of Volumes: n/a; it is an electronic submission
Date Review Started: 12/6/00
Date 1ST Draft Completed: 7/6/01
Scientific Literature Reviewed: not necessary

KEY WORDS: Avelox, moxifloxacin, BAY 12-8039, fluoroquinolone, cardiotoxicity, QTc prolongation

Sponsor: Bayer Corporation
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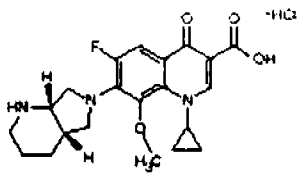
Manufacturer: Bayer AG
Business Group Pharma
Leverkusen, Germany

Review Contains Information to be Communicated to Sponsor: No

Submission Contains Any Integrated Tox Study Summaries in Lieu of Final Reports: No

Drug Information:

Class: Fluoroquinolone antimicrobial, DNA gyrase inhibitor
Code Name: BAY 12-8039
Generic Name: Moxifloxacin
Trade Name: Avelox
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:



Relevant INDs/NDAs/DMFs: NDA 21,085; [redacted]

Indication: The sponsor claims that this IV formulation is bioequivalent to the 400 mg moxifloxacin tablet that is already approved and seeks all indications that have been approved for the tablet (community acquired pneumonia, acute sinusitis, acute bacterial exacerbation of chronic bronchitis). They also request approval for penicillin-resistant *Streptococcus pneumoniae* for the sinusitis and community acquired pneumonia indications.

Clinical Formulation:

Quantity per 250 mL:

Moxifloxacin 0.400 g (0.436 g Moxifloxacin HCl)

[redacted]

pH= 4.2 (3.9-4.6)

Route of Administration: Intravenous

Introduction and Drug History: Moxifloxacin tablets were approved by CDER in December 1999. Due to concerns regarding QT interval prolongation, approval for skin and skin structure indications was not granted, and the sponsor agreed to several phase IV commitments to study and monitor the cardiac safety of moxifloxacin in patients. Like a number of the other newer fluoroquinolones (inhibitors of bacterial DNA gyrase), moxifloxacin can be administered once daily and has a broader spectrum of antimicrobial activity than many of the older drugs in this class (active against gram positive organisms as well as gram negative). It also appears to have a much lower phototoxic potential than some of the other drugs in this class.

Studies reviewed within this submission:

Safety Pharmacology Studies:

Comparison of QT prolongation and arrhythmias in rabbits treated with Bay 12-8039 or sparfloxacin (Bayer Report No. R 7510)

Effects of fluoroquinolones on hERG channels, stably expressed in HEK293 cells (Bayer Report No. R 7854)

Effect of moxifloxacin, ciprofloxacin and the comparator substances sparfloxacin, trovafloxacin, grepafloxacin, gatifloxacin, levofloxacin and ofloxacin on action potential parameters in dog isolated cardiac purkinje fibres (Bayer Report No. R 7856)

Special Toxicity Study:

BAY 12-8039: Effects of Moxifloxacin on Hippocampal Extracellular Recordings in Comparison to other Fluoroquinolones (Bayer Report No. PH 29842)

Studies not reviewed within this submission (and location of review):

Safety Pharmacology Study:

Effects of Moxifloxacin, Gatifloxacin, Grepafloxacin and Sparfloxacin on hERG channels, stably expressed in HEK293 Cells (Bayer Report No. R 7809)

Pharmacokinetic Studies:

[14C]Bay 12-8039: Plasma concentrations, distribution (whole-body autoradiography) and excretion of the substance-associated radioactivity in Wistar rats after single and repeated intravenous and oral administration (Bayer Report No. PH 27970)

[14C]Bay 12-8039: Distribution to organs/tissues of male Wistar rats after single intravenous administration (Bayer Report No. PH 28581)

Plasma concentrations in Wistar rats after intravenous administration in a 15 day mimicking study (Study No. T 8061939; Bayer Report No. PH 27502)

Bay 12-8039: Plasma concentrations in pregnant Wistar rats and fetal tissues concentrations after intravenous administration in a developmental toxicity study (Study No. T 3060250; Bayer Report No. PH 27202)

Toxicology Studies:

Repeat Dose Toxicity Studies:

Subacute toxicity study in rhesus monkeys (4 week gavage study with 4 week recovery period) (Bayer Report No. PH 28666)

Subchronic oral toxicity study in dogs (Administration in gelatine capsules) (Bayer Report No. PH 29271)

Reproduction Toxicity Studies:

Study for fertility and early embryonic development in rats after intravenous administration (Bayer Report No. PH 27978)

Developmental toxicity study in rats after intravenous administration (Bayer Report No. PH 28433)

Special Toxicity Studies:

Study on liver enzyme induction in Wistar rats. Administration by gavage over 15 days (Bayer Report No. PH 27882)

Investigation of the cytotoxicity of different fluoroquinolones in primary hepatocyte cultures of rats, dogs, and humans (Bayer Report No. PH 29677)

Antigenicity study of Bay 12-8039 (Bayer Report No. R 7141)

STUDY REVIEWS:

Safety Pharmacology Studies:

Comparison of QT prolongation and arrhythmias in rabbits treated with Bay 12-8039 or sparfloxacin (Bayer Report No. R 7510)

D. Roden (Vanderbilt University, Nashville, TN, USA)

Report dated: 10/13/99, not GLP

Summary of Current Report R 7510: This report was issued by the sponsor to replace report R 7264 (reviewed previously under NDA 21,085 for moxifloxacin tablets- see summary below). The current report contains plasma levels for moxifloxacin and sparfloxacin that were not available when the initial report was written. Blood samples were drawn near the time of initial arrhythmia or during the last third of test compound infusion. Plasma levels of sparfloxacin or moxifloxacin did not directly correlate with observed arrhythmias in this study. The highest plasma level of sparfloxacin measured in this study was 17.5 µg/ml, in a rabbit that did not suffer an arrhythmia despite QTc prolongation. In contrast, a sparfloxacin plasma level of 8.4 µg/ml was measured in a rabbit that developed PVCs which progressed to ventricular tachycardia and ultimately to torsade de points. Three animals from the moxifloxacin group had plasma levels of around 19 µg/ml, but only one of these had PVCs. The other moxifloxacin-treated rabbits had plasma levels from 13-17 µg/ml; none had an arrhythmia. Additionally, the QT and QTc slopes over time for moxifloxacin and sparfloxacin were recalculated and corrected in the current report. End of infusion QTc interval increases for sparfloxacin and moxifloxacin were 138.2 ±

78.2 ms and 54.2 ± 55.8 ms, respectively, and were at their maxima for both drugs. In R 7510, the times of the arrhythmias were expressed based on the initiation of the methoxamine infusion and in R 7264 the times were based on the initiation of the infusion of the test compounds moxifloxacin or sparfloxacin; however, the incidence and types of arrhythmias did not differ between the 2 reports.

Summary of Study Report R7264: Male New Zealand White rabbits (6 per treatment group) were anesthetized with ketamine/xylazine. Animals underwent tracheotomy and were placed on a respirator (30-40 breaths per minute). Catheters were placed in the right femoral and right and left marginal ear veins to monitor cardiac parameters. EGC was monitored continuously. The animals received 10 μg/kg/min of methoxamine (an α-receptor agonist) via intravenous infusion for 10 minutes prior to the initiation of IV infusion of either sparfloxacin or moxifloxacin (2 mg/kg/min). Drugs (methoxamine plus either sparfloxacin or moxifloxacin) were continued for 60 minutes or until sustained arrhythmia occurred.

Sparfloxacin increased the QTc over the course of the infusion, with the greatest mean increase measured at the end of the infusion (138 ± 78 msec). Although moxifloxacin also tended to increase the QTc (56 ± 56 msec at the end of infusion), the increase was not statistically significantly higher than baseline (evidently due to variability). Premature ventricular contractions (PVCs) were seen in 1/6 moxifloxacin-treated rabbits 48 minutes after the start of infusion, but no other arrhythmias were observed in this group. In contrast, 4/6 rabbits treated with sparfloxacin developed PVCs (39 ± 14 minutes into the infusions), 3/6 demonstrated non-sustained ventricular tachycardia (45 ± 15 minutes into the infusions), and 1/6 had Torsade de Points (62 minutes after the start of infusion).

Effects of fluoroquinolones on hERG channels, stably expressed in HEK293 cells (Bayer Report No. R 7854; Study No. T2064976)

S.H. Heinemann (Friederich Schiller University Jena, Jena, Germany)

Report dated 8/28/2000, Not GLP

Methods: Human embryonic kidney cells (HEK293) stably transfected with the hERG (human ether-a-go-go related gene) were used for this assay. The hERG encodes the rapid component of the human cardiac delayed rectifier potassium current (IKr). Whole cell patch clamp techniques were used for the assay. A borosilicate glass pipette (tip resistance of 1.5-3 MΩ) containing 135 mM KCl, 2 mM $MgCl_2$, 10 mM EGTA, and 10 mM HEPES (pH 7.4) was attached to an individual cell being studied. During the assay, hERG cells were bathed in a solution of 140 mM NaCl, 10 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, and 10 mM HEPES (pH 7.4). For the altered potassium concentration experiments with 100 μM moxifloxacin, the extracellular fluid contained 4 mM KCl and 146 mM NaCl or 40 mM KCl and 110 mM NaCl. The hERG currents were elicited using 1 second pulses at 10 second intervals up to +40 mV, followed by a 300 ms hyperpolarization to −120 mV. The holding potential was −80 mV. Tail currents (inward currents) were measured at −120 mV and plotted as a function of time. The percent inhibition of the peak tail current was used to assess a compound's effect on the hERG channel.

The quinolones tested in the assay were moxifloxacin, gatifloxacin, grepafloxacin, sparfloxacin, levofloxacin, ofloxacin, and ciprofloxacin. Each concentration of drug was tested on 5 different preparations of cells and at least 3 different concentrations of each drug was tested, between 5 and 500 μM. All of the compounds were dissolved in the cell bath solution. Sparfloxacin was tested only up to 50 μM due to its potency and the 500 μM gatifloxacin data were not used because the compound was not completely soluble at that concentration. Effectively, gatifloxacin was only tested up to 100 μM. The hERG-specific blocker E-4031 was used as a positive control, but its data were not presented.

Results: Sparfloxacin, grepafloxacin, moxifloxacin, and gatifloxacin inhibited the hERG current in a dose-dependant manner. Sparfloxacin was the most potent fluoroquinolone out of those tested in this experiment. Next was grepafloxacin, followed by moxifloxacin, then gatifloxacin. The investigator considered moxifloxacin and gatifloxacin to be equivalent. The data were plotted as logarithmic concentration/response curves and both IC30 and IC 50 values were estimated. The remaining compounds, levofloxacin, ofloxacin, and ciprofloxacin were much weaker blockers of hERG. They reduced the hERG current by only 10-30% at 500 μM, the highest concentration tested.

Effects of Fluoroquinolones on hERG Current in HEK293 Cells (mean ± SEM)

	IC50 (μM)	IC30 (μM)
Sparfloxacin	25 ± 2	10 ± 1
Grepafloxacin	82 ± 6	39 ± 4
Moxifloxacin	200 ± 16	86 ± 7
Gatifloxacin	242 ± 22	104 ± 9

Reducing the concentration of KCl in the extracellular fluid from 10 mM to 4 mM increased the hERG current reduction caused by 100 μM moxifloxacin from about 30% to over 50%. Increasing the KCl level to 40 mM from 10 mM did not cause a significant change in response to 100 μM moxifloxacin. Reducing the potassium concentration of the extracellular fluid inactivates the hERG potassium channels, drastically reducing outward current. To further investigate the role of potassium channel activation state, an experiment was performed with a HEK293 cell line containing a mutant hERG gene (S620T). The mutant gene codes for potassium channels that are resistant to inactivation. The cells with the mutant gene have a greater outward current during depolarization than those with wild-type channels. The mutant was less efficiently blocked by 500 μM moxifloxacin than cells containing the wild-type hERG channels. This suggests that moxifloxacin-induced hERG channel blockade is dependant upon the state of activation/inactivation.

The IC50/IC30 data for sparfloxacin, grepafloxacin, moxifloxacin and gatifloxacin from this experiment are almost identical to another hERG study conducted by this investigator (R 7809). The rank order of potency for inhibition of the hERG current was sparfloxacin > grepafloxacin > moxifloxacin ≥ or ≈ gatifloxacin >> levofloxacin, ofloxacin, and ciprofloxacin. Moxifloxacin inhibition of the hERG current was more potent under conditions favoring the inactivation of hERG potassium channels.

Effect of moxifloxacin, ciprofloxacin and the comparator substances sparfloxacin, trovafloxacin, grepafloxacin, gatifloxacin, levofloxacin and ofloxacin on action potential parameters in dog isolated cardiac purkinje fibres (Bayer Report No. R 7856; Study No. T4065021)

S. Fraser (Quintiles Scotland Ltd., Edinburgh, Scotland, UK)

Report dated 9/29/2000, UK, OECD, US, and Japanese GLP

Methods: Purkinje fibers were harvested from beagle dogs after sacrifice with pentobarbital. In all, 65 adequate fiber preparations (6 per drug and 17 for vehicle controls) were obtained from 56 male and female dogs (approximately 6-30 months old). The Purkinje fibers were maintained at 35-36°C and continuously perfused with oxygenated physiological salt solution (125 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 1.0 mM $MgCl_2 \cdot 6H_2O$, 1.2 mM $NaH_2PO_4 \cdot 2H_2O$, 25 mM $NaHCO_3$, 5.5 mM D-glucose). Each preparation was allowed to equilibrate briefly before electrodes were inserted. The electrical activity of the Purkinje fibers was monitored continuously using glass

Each fiber preparation was stimulated with sufficient voltage to evoke an action potential, then that voltage was increased 50-100% to achieve a suprathreshold stimulation voltage. The action potential elicited from each fiber preparation was evaluated and the preparations that met the acceptance criteria ($APD_{90} \geq 190$ms but ≤ 450ms, MRD ≥ 300 V/s, UA ≥ 100 mV) were equilibrated for at least 1 hour until a stable waveform was recorded. Baseline measurements (

l. The drugs tested were moxifloxacin (Lot No. 309796T), ciprofloxacin, sparfloxacin, trovafloxacin, grepafloxacin, gatifloxacin, levofloxacin, and ofloxacin. Sparfloxacin, trovafloxacin, and gatifloxacin were prepared as 25 mM stock solutions in DMSO and the remaining drugs were prepared as 10 mM stock solutions in sterile water. Each drug was tested on 6 different Purkinje fiber preparations at ascending concentrations of 3, 10, 30, and 100 µM. The corresponding concentrations of DMSO present at each drug level were 0.012%, 0.04%, 0.12% and 0.4%, respectively. DMSO was added to the perfusion solutions for the drugs dissolved in the sterile water vehicle to keep conditions consistent at each drug concentration level. DMSO was used as the vehicle control since the small amounts of sterile water added to the physiological saline solution were not considered capable of having any effect. Physiological saline solution containing each concentration of the test compounds perfused the Purkinje fiber preparations for 30 minutes at 1 Hz and then at 0.5 Hz as action potentials were measured. At the highest concentration of each drug, measurements were also made at 3 Hz and 0.2 Hz. The positive control substance E-4031 (100nM) was used on fiber preparations from test drugs that did not cause changes in the activity of the Purkinje fibers (excepting ciprofloxacin) to confirm the sensitivity of the individual preparations.

Results: None of the fluoroquinolones tested had an effect on RMP, UA, or MRD. Ciprofloxacin, trovafloxacin, levofloxacin, ofloxacin, and DMSO vehicle did not significantly change APD, but moxifloxacin, sparfloxacin, grepafloxacin, and gatifloxacin were all associated

with dose-related increases in APD_{60} and APD_{90} at both 1.0 and 0.5 Hz. Biologically significant increases in APD_{60} and/or APD_{90} compared to baseline (most increases were also statistically significant, $p \leq 0.05$, as well) were observed at ≥ 10 μM for grepafloxacin and sparfloxacin, ≥ 30 μM for moxifloxacin, and ≥ 100 μM for gatifloxacin. The investigators thought that the change in APD due to sparfloxacin may have been underestimated because a much smaller effect was observed in one Purkinje fiber preparation compared to the others. None of the drugs affected MRD at 3 Hz and no incidents of early after-depolarizations were observed at 0.2 Hz. When the positive control E-4031 (100 nM) was added to the Purkinje preparations that had completed testing with vehicle, trovafloxacin, levofloxacin, or ofloxacin significant changes in APD were observed, demonstrating the sensitivity of those preparations.

Mean Fluoroquinolone-Induced Changes in APD of Isolated Canine Purkinje Fibers at 100 μM

	Moxifloxacin	Sparfloxacin	Grepafloxacin	Gatifloxacin
1 Hz				
APD_{60}				
Absolute Increase	66 ms	78 ms	78 ms	35 ms
% Increase	32%	39%	40%	15%
APD_{90}				
Absolute Increase	79 ms	99 ms	105 ms	50 ms
% Increase	31%	38%	44%	18%
0.5 Hz				
APD_{60}				
Absolute Increase	95 ms	113 ms	116 ms	56 ms
% Increase	41%	52%	55%	21%
APD_{90}				
Absolute Increase	117 ms	138 ms	150 ms	77 ms
% Increase	41%	46%	58%	24%

The fluoroquinolones ciprofloxacin, trovafloxacin, levofloxacin, and ofloxacin were not associated with changes in the action potential of isolated canine Purkinje fibers at concentrations up to 100 μM under the conditions of this study. The rank order of potency for increased APD caused by the remaining fluoroquinolones tested was sparfloxacin ≈ grepafloxacin > moxifloxacin > gatifloxacin.

Special Toxicity Study:

BAY 12-8039: Effects of Moxifloxacin on Hippocampal Extracellular Recordings in Comparison to other Fluoroquinolones (Bayer Report No. PH 29842)

G. Schmuck (Bayer AG, Wuppertal, Germany)

Report dated 4/26/00, non-GLP screening study

Summary: Slices of hippocampus (450 µm) were obtained from young adult female rats and bathed in artificial cerebrospinal fluid ([redacted], 2 ml/min, 34°C. Electrical stimulation of the CA_2 area consisted of 10 pulses of 200 µsec duration, 3-8 V, at 10 second intervals. Glass electrodes in the CA_1 pyramidal area were used to record the extracellular field potential. Stimulation and recording under control conditions was performed for 30 minutes, then in the presence of 2 µM of a test compound for 30 minutes, followed by another 30 minutes under control conditions once more. The drugs tested were moxifloxacin, ciprofloxacin, grepafloxacin, gemifloxacin, gatifloxacin, and trovafloxacin. These were dissolved in DMSO. The concentration of that solvent in the [redacted] was 1%. Each drug was tested in 6 separate hippocampal slices from 2 different rats. The amplitude of the extracellular field potential under control conditions and in the presence of drug was compared to determine each compound's excitatory potential on the brain tissue.

DMSO alone increased the amplitude of the extracellular field potential by 42%. Increases for each drug (with the DMSO increase subtracted from each) in order of potency were:

Moxifloxacin	57 ± 12%
Ciprofloxacin	62 ± 7%
Gatifloxacin	98 ± 30%
Trovafloxacin	176 ± 31%
Gemifloxacin	185 ± 31%
Grepafloxacin	195 ± 12%

LABELING RECOMMENDATIONS:

The addition of the data from the fertility and developmental toxicity studies conducted in rats using IV moxifloxacin is acceptable (see page 18 of proposed label, ***Carcinogenesis, Mutagenesis, Impairment of Fertility*** and ***Pregnancy*** sections). The reviewer recommends adding dose comparisons so that the sponsor's proposed additions read as follows:

"Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 12 times the maximum recommended human dose based on body surface area (mg/m^2) or at intravenous doses as high as 45 mg/kg/day, approximately equal to the maximum recommended human dose based on body surface area (mg/m^2)."

"Intravenous administration of 80 mg/kg/day (approximately 2 times the maximum recommended human dose based on body surface area (mg/m^2)) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta."

In the ***Animal Pharmacology*** section, the pharmacologist recommends modifying the first sentence in the paragraph that discusses ocular toxicity and adding doses for the 6 month rat and monkey studies referred to in the paragraph so that the sentences read:

"No ocular toxicity was observed in a 13 week oral repeat dose study in dogs with a moxifloxacin dose of 60 mg/kg. Ocular toxicity was not observed in 6 month repeat dose studies in rats and monkeys (daily oral doses up to 500 mg/kg and 135 mg/kg, respectively)."

The other changes requested by the sponsor in the ***Carcinogenesis, Mutagenesis, Impairment of Fertility*** and ***Pregnancy*** sections and in the ***Animal Pharmacology*** section (pages 18, 22, and 23) are acceptable.

OVERALL SUMMARY AND EVALUATION:

NDA 21,085 for Avelox (moxifloxacin) tablets was approved in 1999 for a variety of antimicrobial indications. Further details on the nonclinical toxicity of this compound can be found in the pharmacologist's review of that NDA.

The final summary paragraph taken from the pharmacologist's review of NDA 21,085 is applicable to the current NDA for intravenous moxifloxacin and reads as follows: *"Several of the toxic effects observed in animals following moxifloxacin administration are similar to those which have been seen with other quinolones. These include the induction of arthropathy in juvenile dogs, convulsions and other CNS disturbances, and fetotoxicity in the offspring of several species exposed to this drug in utero. When moxifloxacin was administered to monkeys at high doses, microscopic liver injury was observed in some animals. In rats, a high dose of moxifloxacin given for a long period of time was also associated with hepatocellular necrosis. Liver changes were not seen in these species when more moderate doses were administered, even for a 6 month dosing period. The potential for moxifloxacin to prolong the QTc was clearly demonstrated in anesthetized dogs. This effect has also been observed in humans. In the dogs, the approved drug, sparfloxacin, appeared to be a more potent prolonger of the QTc than moxifloxacin."*

There are no apparent differences in the general patterns of nonclinical toxicity for intravenously administered vs. orally administered moxifloxacin. However, higher Cmax values are observed following IV administration of this drug and these could be associated with a greater likelihood of QT prolongation or CNS disturbances compared to oral moxifloxacin (e.g., tablets) when the drug is used clinically. The clinical data are being carefully evaluated by the medical and biopharmaceutics reviewers to determine this risk for humans.

RECOMMENDATIONS: The nonclinical pharmacology and toxicology data for intravenous Avelox (moxifloxacin) contain no information that would preclude approval of this product in the opinion of the pharmacologist.

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Please initial below to indicate that you have seen the paper copy of this review and agree that it should be put into DFS as a final, archival document:

HFD-520/REOsterberg
HFD-520/LGavrilovich

cc:
HFD-590/PharmTL/Hastings
HFD-590/CSO/Jensen
HFD-590/MO/Meyerhoff

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/s/

Amy Ellis
7/12/01 02:21:18 PM
PHARMACOLOGIST

The nonclinical pharmacology and toxicology data for intravenous Avelox [moxifloxacin] contain no information that would preclude approval of this product in the opinion of the pharmacologist.

Bob- You signed the paper copy of this review on 7/11/01.

Robert Osterberg
7/17/01 03:30:42 PM
PHARMACOLOGIST

Lillian Gavrilovich
7/24/01 05:22:39 PM
MEDICAL OFFICER

Kenneth Hastings
8/2/01 07:52:29 AM
PHARMACOLOGIST

5. Reviewer's comments on Study 200036:

1) Subgroup analyses:

Since many subgroups showed statistically significant effects in Study 100039, similar subgroup analyses were performed for Study 200036 by the reviewer. Since several variables collected in Study 100039 were not collected in Study 200036, only the effects on severity stratum, smoking history, and gender were assessed. Based on logistic regression analyses on per protocol population, only severity stratum showed a statistically significant subgroup effect at 0.10 level. The subgroup analyses are summarized in Table 10.

Table 10: Subgroup analyses in valid for efficacy population for Study 200036.

		Moxifloxacin	*Control*	*p-value*
Gender	*Male*	*142/166 (85.5%)*	*133/180 (73.9%)*	*0.292*
	Female	*74/92 (80.4%)*	*74/100 (74.0%)*	
CAP severity stratum	*Mild/mod. CAP*	*111/129 (86.0%)*	*111/143 (77.6%)*	*0.086*
	Severe CAP	*105/129 (81.4%)*	*97/137(70.8%)*	
History of smoking	*No*	*95/110 (86.4%)*	*83/110 (75.5%)*	*0.211*
	Yes	*121/148 (81.8%)*	*124/170 (72.9%)*	

The lack of differences in the subgroups might be due to population differences between the two studies. Particularly, the difference in response rates between the CAP severity strata (about 6%) was smaller than the difference observed in Study 100039 (about 12%). Notice that the percentage of severe patients in this study was higher than the percentage enrolled in Study 100036 (51.6% in Study 200036 and 31.2% in Study 100039). As it was mentioned before, since not all the patients had culture or serology performed at enrollment, there is greater difficulty in assessing the level of severity of CAP based on the bacteriology assessment in the severe stratum of this study in comparison to Study 100039.

Since the study was conducted in several countries from Europe, the Mid-east and South Africa, subgroup analysis by country was also performed by this reviewer. The result of this subgroup analysis showed that the response rates are reasonably consistent among countries.

2) Response at TOC and 21-28 days post therapy:

Another interesting observation was that the response rates dropped about 10% at the visit 21-28 days post therapy from the TOC visit. Such drops cause concerns about the accuracy of the assessment at the TOC visit.

V. Summary and Conclusion:

The fundamental difference between the two studies was that Study 100039 was double blinded, while Study 200036 was open label. Open label studies are inherently more susceptible to bias and, therefore, is given less weight than the double-blind study, Study 100039, in the overall assessment of the efficacy of moxifloxacin I.V. In addition, the two studies were conducted in different regions with different populations and using different controls.

Overall, the results of the two studies were quite different, with moxifloxacin numerically inferior to the control in Study 100039 and moxifloxacin superior to the control in Study 200036. However, the overall response rates in the moxifloxacin treatment arms in both studies were similar if the visit at 21-28 post therapy was used to determine the overall response in Study 200036. This does not mean the comparisons between the two treatment groups were free of bias in Study 200036. The differences in response rates in control arms between the two studies might be due to the different drugs used as controls, or it could possibly be due to the difference in study design, i.e., double blinded versus open label.

For severe CAP, the interpretations of the results observed in the two studies were complicated by some uncertain factors. For Study 100039, the response rates between the moxifloxacin and control groups were similar in the valid for safety and valid for efficacy population and numerically lower in the moxifloxacin group than the control in the microbiologically valid population. However, the different response rates in the two control phases in the control arm raise the issue of the validity in combining the two control phases as it is not clear if the difference was due to the two controls or other variations. The results based on analyses without combining the two control phases make it difficult to accept the seemingly similar response rates in the valid for efficacy and valid for safety populations. When only the levofloxacin phase, which contains the majority of the study patients, is used to compare the two treatment groups, the moxifloxacin severe stratum has much lower response rate than the control. In fact, none of the sensitivity analyses in the severe CAP stratum support the conclusion based on the valid for safety and valid for efficacy populations. For Study 200036, the response rates in the severe stratum in moxifloxacin group were numerically better than the control in all three patient populations. However, due to the fact of open label study design, major protocol deviations (only a subgroup of patients performed bacteriological findings), and the wide difference of response rates between the TOC visit and the follow-up visit, the results from Study 200036 cannot stand alone.

In conclusion, the two studies suggested that the moxifloxacin I.V./PO sequential treatment was non-inferior to the controls in treating patients with the mild/moderate CAP. However, the evidence for treating patients with severe CAP stratum was inconclusive statistically for the comparison between the moxifloxacin I.V./PO sequential treatment and the controls. The decision on the moxifloxacin treatment for patients with severe CAP should be a judgment based on the overall risk benefit assessment.

Qian Li, Sc.D
Mathematical Statistician

Concur:

Karen Higgins, Sc.D
Team Leader

CC:
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HFD-725/Division File
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HFD-725/Dr. Higgins
HFD-725/Dr. Li

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/s/

Qian Li
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