

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-085

PHARMACOLOGY REVIEW

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520
CONSULTATION FOR HFD-590**

NDA#: 21,085-000

Date CDER Received/Type of Submission: 12/10/98

Reviewer: Amy L. Ellis, Ph.D.

Date Assigned: 12/15/98

Number of Volumes: 356 (46 for pharm/tox)

Date Review Started: 1/18/99

Date 1ST Draft Completed: 11/29/99

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

Sponsor: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516
Phone: (203) 812-2000

Authorized Representative: Andrew S. Verderame
Associate Director, Regulatory Affairs
Phone: (203) 812-5172

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

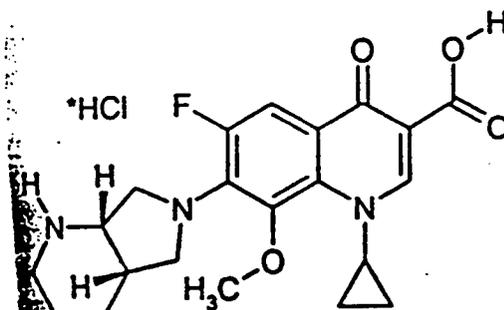
Code Name: BAY 12-8039

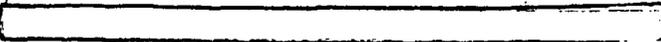
Generic Name: Moxifloxacin

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:



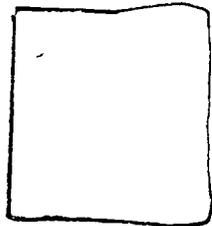
Relevant INDs/NDAs/DMFs: 

Indications: Acute sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia 

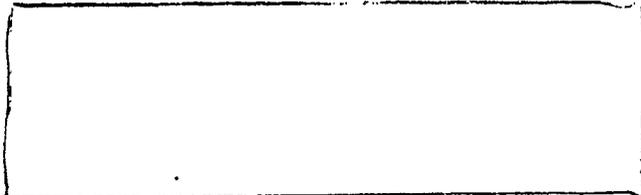
Clinical Formulation/Route of Administration:

Each 400 mg Oral Tablet contains:

- Moxifloxacin HCl
- Microcrystalline Cellulose
- Lactose Monohydrate
- Croscarmellose Sodium
- Magnesium Stearate



Tablet Coating:



Total Coated Tablet Weight 693.8-699.8 mg

Introduction and Drug History: Moxifloxacin is a member of the fluoroquinolone antimicrobial group and is an inhibitor of bacterial DNA gyrase. Like some of the other newer quinolones, it 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). The sponsor has submitted data suggesting that moxifloxacin has a much lower phototoxic potential than some of the other quinolones. However, it has the disadvantage of causing QTc prolongation in humans as well as experimental animals. Much of the nonclinical development of this drug has taken place in Wuppertal, Germany, location of Bayer AG, the parent company of the U.S. subsidiary.

Studies reviewed within this submission:

Safety Pharmacology Studies:

BAY 12-8039: CNS Safety Pharmacology After a Single Oral Administration (Bayer Report No. 51.997; Study FS 95002)

BAY 12-8039: Influence on Hemodynamics and ECG in Anesthetized Dogs After Intravenous Infusion Under Beta-Adrenergic Blockade with  (Bayer Report No. PH 27430)

BAY 12-8039: Influence on Hemodynamics and ECG in Anesthetized Dogs After Intravenous Infusion Under Normal and Reduced Serum-Potassium Levels (Bayer Report No. PH 27428)

Automatic QRS-Interval Measurement in Anesthetized Dogs by a Data-Acquisition and – Evaluation System: Detection Problems Under Certain ECG Configurations Exemplified by Evaluations from IV Studies with BAY 12-8039 and Additional Experimental Evidence (Bayer Report No. PH 27943)

BAY 12-8039: Influence on a Hemodynamics Cardiac Contractility and ECG in Anesthetized Dogs After Intraduodenal Administration (Bayer Report No. PH 24362)

BAY 12-8039: Influence on ECG and Hemodynamics in Anesthetized Dogs After Intravenous Infusion of 30 mg/kg within 15, 30, or 60 minutes (Bayer Report No. PH26684)

BAY 12-8039: Influence of Overdosage-Infusion on Hemodynamics and ECG in Anesthetized Dogs (Bayer Study No. PH 27429)

Sparfloxacin (BAY v 1749) versus Moxifloxacin (BAY 12-8039) Influence on Hemodynamics and ECG in Anesthetized Dogs After Intravenous Infusion (Bayer Report No. PH 27427)

A Respiratory and Cardiovascular Study of BAY 12-8039 in Monkeys (Bayer Report No. R 7104)

Effects of Moxifloxacin (BAY 12-8039) and Sparfloxacin on Cardiac Action Potentials and Potassium Currents (Bayer Report No. R 7223)

Effects of Moxifloxacin (BAY 12-8039) on Action Potentials (Bayer Report No. R 7265)

Potassium Channel Blocking Action of BAY 12-8039 (Moxifloxacin) and Sparfloxacin (Bayer Report No. R 7238)

Is There an Influence of BAY 12-8039 (Moxifloxacin) or Sparfloxacin on the Potassium Currents I_{Ks} Through $KvLQT1$? A Study of Stably Transfected Cells Expressing $KvLQT1$ and $minK$ (Bayer Report No. PH 27944)

Comparison of QT Prolongation and Arrhythmias in Rabbits Treated with BAY 12-8039 or Sparfloxacin (Bayer Report No. R 7264)

General Pharmacology of BAY 12-8039 in the Gastrointestinal Tract: Its Effects on Acetylcholine Induced Ileal Spasms, On the Stimulated Gastric Acid Secretion, and On Indomethacin-Induced Ulcers (Bayer Report No. PH 24316)

Safety Pharmacology of BAY 12-8039 in the Gastrointestinal Tract: Its Effects on the Intestinal Charcoal Transit, On the Gastric Tolerability, and On the Basal Gastric Acid Secretion in the Rat (Bayer Report No. PH 24317)

BAY 12-8039: Test for Renal Effects After Oral Administration in Rats (Bayer Report No. 24390)

BAY 12-8039: Effects on Blood Glucose and Serum Triglyceride Concentrations of Fasted and Fed Rats after Oral Administration (Bayer Report No. PH 24388)

BAY 12-8039: Blood Pharmacological Investigations (Bayer Report No. PH 24297)

BAY 12-8039: Effects of Oral Administration on Bronchoactivity in the Anesthetized Spontaneously-Breathing Guinea Pig (Bayer Report No. PH 24238)

General Toxicity Studies (with companion PK studies, as applicable):

Single Oral Dose Toxicity Study of BAY 12-8039 in Cynomolgus Monkeys (Bayer Report No. R 6907)

BAY 12-8039: Chronic Oral Toxicity Study in Rhesus Monkeys (26 Week Gavage Study) (Bayer Report No. PH 27460)

BAY 12-8039: Plasma Concentrations in Rhesus Monkeys After Oral Administration in a Chronic Toxicity Study (Bayer Report No. PH 27154)

BAY 12-8039: Study on Chronic Toxicity in Wistar Rats. Administration by Gavage Over 6 Months (Bayer Report No. PH 27401)

BAY 12-8039: Plasma Concentrations in Wistar Rats After Oral Administration in a Chronic Toxicity Study (Bayer Report No. PH 27201)

BAY 12-8039: Plasma Concentrations of Metabolite M-1 (BAY 31-8061) and M-2 in Wistar Rats After Oral Administration in a Chronic Toxicity Study (Bayer Report No. PH 27201A)

BAY 12-8039: Subacute Oral Toxicity Study in Beagle Dogs (4 Week Capsule Study) (Bayer Report No. PH 27061)

BAY 12-8039: Plasma Concentrations in Beagle Dogs After Oral Administration in a Subacute Toxicity Study (Bayer Report No. PH 26778)

Special Toxicity Studies (with companion PK studies, as applicable):

BAY 12-8039: Subacute Toxicity Study in Beagle Pups (4 Week Capsule Study) (Bayer Report No. PH 26506)

Determination of the Excitatory Potential of BAY 12-8039 *in vitro* in the Hippocampus Slice Model (Bayer Report No. PH 27002)

***In vitro* Effects of BAY 12-8039 (Irradiated and Non-Irradiated) on Cultured Astrocytes and Cortex Neurons of the Rat (Bayer Report No. 24940)**

A Cytotoxicity Study of BAY 12-8039 in Cultured Mammalian Cells (Bayer Report No. R 6982)

BAY 12-8039: Combined Single-Dosage and Seven-Day Oral Phototoxicity Study in Hairless Mice (Bayer Report No. MRC-00908)

A Repeated Dose Oculotoxicity Study of BAY 12-8039 Administered Orally to Beagle Dogs for 2 Weeks (Bayer Report No. R 7274)

Accelerated Bioassay in the Rat of BAY 12-8039 Quinolone (QL) in Target Organs of Human Carcinogenesis [REDACTED] (Bayer Report No. R 7239)

BAY 12-8039: Plasma Concentrations in Wistar Rats after Oral Administration in a Short Term Carcinogenicity Study (Bayer Report No. PH 27338)

Reproduction Toxicity Studies (with companion PK studies, as applicable):

BAY 12-8039: Plasma Concentrations in Pregnant Wistar Rats and Tissue Concentrations in Fetuses After Oral Administration in an Embryotoxicity Study (Bayer Report No. PH 25756)

Study of Pre- and Post-Natal Development in Rats After Oral Administration (Bayer Report No. PH 27379)

BAY 12-8039: Development Toxicity Study Following the Intravenous Administration in Rabbits (Bayer Report No. PH 27071)

BAY 12-8039: Additional Developmental Toxicity Study in Rabbits After Intravenous Administration (Bayer Report No. PH 26904)

BAY 12-8039: Plasma Concentrations in Pregnant Rabbits After Intravenous Administration in Two Embryotoxicity Studies (Bayer Report No. PH 27221)

BAY 12-8039 Oral (Gavage) Embryo-Fetal Developmental Study in the Cynomolgus Monkey (Segment II) (Bayer Report No. R 7023)

BAY 12-8039: Plasma Concentrations in Pregnant Cynomolgus Monkeys in an Embryo Toxicity Study (Report No. PH 26931; Study No. T 6055259)

BAY 12-8039: Plasma Concentrations in Cynomolgus Monkeys after Oral Administration in an Embryo-fetal Developmental Study- with Amendment (Report No. PH 27332; Study No. T 0054290)

Genotoxicity Studies:

BAY 12-8039: Mutagenicity Study for the Detection of Induced Forward Mutation in the CHO/HGPRT Assay *in vitro* (Bayer Report No. PH 26356)

BAY 12-8039: Mutagenicity Study for the Detection of Induced Forward Mutations in the V79-HGPRT Assay *in vitro* (Bayer Report No. PH 26367)

BAY 12-8039: Dominant Lethal Test on the Male Mouse (Bayer Report No. PH 25873)

Studies of Photostability and Lack of Photogenotoxicity of Moxifloxacin (Bayer Report No. R 7142)

Photomutagenicity Studies of Moxifloxacin in Comparison to Other Fluoroquinolones (Bayer Report No. R 7143)

Pharmacokinetic (ADME) Studies:

BAY 12-8039: Plasma Concentrations in Wistar Rats After Oral Administration in a 13-Week Toxicity Study (Bayer Report No. PH 25711)

BAY 12-8039: Plasma Concentrations in Rhesus Monkeys After Oral Administration in a Subchronic Toxicity Study (Bayer Report No. PH 25706)

BAY 12-8039: Plasma Concentrations in Rhesus Monkeys After Intravenous Infusion in a Subacute Toxicity Study (Bayer Report No. PH 25730; Study No. T 1060717)

[¹⁴C]BAY 12-8039: Secretion of Radioactivity into Milk of Lactating Rats after a Single Oral Administration (Bayer Report No. PH 27004)

Radiosynthesis of [¹⁴C]BAY 12-8039 (Bayer Report No. PH 24396)

Second Radiosynthesis of [¹⁴C]BAY 12-8039 (Bayer Report No. PH 25747)

Absorption and Excretion of Substance Associated Radioactivity in Female Rats (Bayer Report No. PH 27336)

[¹⁴C]BAY 12-8039: Investigation of the Enterohepatic Circulation in Male Rats (Bayer Report No. 27344)

BAY 12-8039: Pharmacokinetics of the Unchanged Compound in Wistar Rats after Single Intra-Colonic Administration (Bayer Report No. PH 26635)

[¹⁴C]BAY 12-8039: Biotransformation in Wistar Rat (Bayer Report No. PH 27324)

BAY 12-8039: Dose Dependence of Pharmacokinetics in Female Rhesus Monkeys After Single Intravenous Infusion (Bayer Report No. PH 26663)

[¹⁴C]BAY 12-8039: Distribution to Organs/Tissues of Male Wistar Rats After Single Oral Administration (Bayer Report No. PH 27223)

[¹⁴C]BAY 12-8039: Whole-Body Autoradiography in Female Rats After Intravenous Administration (Study No. I 3000922) (Bayer Report No. 26860)

[¹⁴C]BAY 12-8039: Whole-Body Autoradiography in Pregnant Rats After Single Intravenous and Oral Administration (Study Nos. I 5000807 and I 8000981) (Bayer Report No. PH 27305)

[¹⁴C]BAY 12-8039: Quantitative Organ Distribution and Placental Transfer of the Substance-Associated Radioactivity in Pregnant Wistar Rats After Single Oral Administration (Bayer Report No. PH 27189)

BAY 12-8039: Concentrations of Unchanged Compound in Skin Suction Blister Fluid, Plasma, and Lung Tissue of Male Wistar Rats After Single Intravenous and Oral Administration (Bayer Report No. PH 27342)

[¹⁴C]BAY 12-8039: Biotransformation in Rhesus Monkey (Bayer Report No. PH 27323)

[¹⁴C]BAY 12-8039: Biotransformation in Microsomal Liver Fractions and Hepatocytes of Rat, Monkey, and Man (Bayer Report No. Bayer Report No. PH 27341)

BAY 12-8039: Chiral Inversion in Rats, Rhesus Monkey, and Man (Bayer Report No. PH 27325)

BAY 12-8039: Plasma and Skin Concentrations in Guinea Pig After Oral Single Dose Administration in Two Mimicking Phototoxicity Studies (Bayer Report No. 27440)

BAY 12-8039: Plasma Concentrations After Single Oral Administration of 1000 mg/kg BAY 12-8039 and 1000 mg/kg BAY 11-6371 to Male NMRI Mice (Bayer Report No. 27446)

BAY 12-8039: Plasma Concentrations in Wistar Rats After Oral Administration in a 16 Day Mimicking Study (Bayer Report No. PH 27470)

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

Safety Pharmacology Studies:

BAY 12-8039 (i.v.): Preliminary CNS General Pharmacology Profile in the Mouse (Bayer Report No. R-6722)

BAY 12-8039: Influence on Haemodynamics, Cardiac Contractility and ECG in Anaesthetized Dogs After Intravenous Administration (Bayer Report No. PH-25622)

BAY 12-8039: Influence on Haemodynamics, Cardiac Contractility and ECG in Anaesthetized Dogs After Intravenous Infusion (Bayer Report No. PH-25854)

Effect of BAY 12-8039 on Blood Pressure and Heart Rate in Conscious Rats (Study P7011672, Bayer Report No. PH-25629)

Effect of BAY 12-8039 on the Isolated Guinea Pig Ileum (Report No. PH 25853)

Effect of a Single Intravenous Administration of BAY 12-8039 on Diuresis of Rats (Study P4011642, Bayer Report No. PH-25657)

BAY 12-8039: Effects on Blood Glucose Concentrations of Fasted and Fed Rats after Intravenous Administration (Bayer Report No. PH 26105)

BAY 12-8039 i.v.: Blood-Pharmacological Investigations (Report No. PH 25888)

BAY 12-8039: Effects of Intravenous Administration on Bronchioactivity in the Anaesthetized Spontaneously-Breathing Guinea-Pig (Bayer Report No. PH-25600)

Toxicology Studies/Special Toxicity Studies (with companion PK studies, as applicable):

BAY 12-8039: Acute Toxicity in the Mouse and Rat After Oral and Intravenous Administration (Study Nos. T 5058219, T 9058222, T 0058223, T 1058224; Report No. PH 24156)

BAY 12-8039: Subacute Toxicity Study in Rats (Oral Administration for About 4 Weeks)
(Study No. T 2058126; Report No. PH 24416)

BAY 12-8039: Plasma Concentrations in Wistar Rats After Oral Administration in a Subacute Toxicity Study (Report No. PH-24430)

BAY 12-8039: Subacute Toxicology Study in Rats (Oral administration for about 4 weeks)
(Study No. T 5058372; Report No. PH 24285)

BAY 12-8039: Study on Subchronic Toxicity in Wistar Rats (13-Week Administration by Gavage with a Subsequent Recovery Period of About 4 Weeks) (Report No. PH 25813)

BAY 12-8039: Subacute Toxicity in Rats (Intravenous administration for about 4 weeks)
(Report No. PH-24651)

BAY 12-8039: Plasma Concentrations in Wistar Rats After Intravenous Administration in a 4 Week Study (PH-24836)

BAY 12-8039: Plasma Concentrations in Beagle Pups After Oral Administration in a Subacute Toxicity Study (Report No. PH 26076)

BAY 12-8039: Subacute Oral Toxicity in Rhesus Monkeys (Study No. T 2058072; Report No. PH 24386)

Review on Bone Marrow Findings Observed in Toxicology Studies with BAY 12-8039

BAY 12-8039: Plasma Concentrations in Rhesus Monkeys After Oral Administration in a Subacute Toxicity Study (Study No. PH 24428)

BAY 12-8039: Subacute Oral Toxicity Study in Rhesus Monkeys (4 week gavage study)
(Study No. T 1058305; Report No. PH 24419)

BAY 12-8039: Plasma Concentrations in Rhesus Monkeys After Oral Administration of 100 and 150 mg/kg in a Subacute Toxicity Study (Study No. PH 24429)

BAY 12-8039: Subchronic Oral Toxicity Study in Rhesus Monkeys (13 Week Gavage Study) (Bayer Report No. 25547; Study No. T5060045)

BAY 12-8039: Subacute Toxicity Study in Rhesus Monkeys (4 week intravenous administration) (Study No. T 0059024; Report No. PH 25354)

BAY 12-8039: Plasma Concentrations in Rhesus Monkeys After Intravenous Administration in a 4 Week Study (Study No. T 0059024, Report No. PH 24960)

BAY 12-8039: Subacute Toxicity Study in Rhesus Monkeys (4 week intravenous infusion) (Report No. 25970)

BAY 12-8039 in an In Vitro Model: A. Determination of Cytotoxicity on Cartilage Cells from Different Species, B. Determination of Phototoxicity on Mouse Fibroblasts 3T3 (Report No. PH 24281)

Phototoxicity Study of BAY 12-8039 in Balb/c Hairless Mice (Study No. JBC-96-MOPT-0372; Bayer Report No. 6798)

BAY 12-8039: Studies of the Photoreactive Potentials in Rats and Guinea Pigs (Report No. PH 24400)

BAY 12-8039: Study of the Photoreactive Potential in Guinea Pigs (Bayer Report No. PH 26067)

BAY 12-8039: Study of the Photoreactive Potential in Guinea Pigs (After 7 days Application) (Report No. PH 26140)

BAY 12-8039: Acute Toxicity of BAY 12-8039 in Combination with Nonsteroidal Antiphlogistics After Oral Administration in the Mouse (Study No. T 7058347, Report No. PH 24099)

BAY 12-8039: Local Tolerability Study in Dogs After Paravasal, Intravenous and Intraarterial Injections (Study No. T 0060608, Report No. PH-25510)

BAY 12-8039: Subacute Toxicity Study in the Rhesus Monkey- EEG-Measurements (Administration by Gavage for 4 Weeks) (Study No. T 2057352; Report No. R 6387)

BAY 12-8039: Subacute Oral Toxicity in Rhesus Monkeys for EEG-Measurements (4 Week Gavage Study) (Study No. T 2057352; Report No. PH 24384)

Reproduction Toxicity Studies:

BAY 12-8039: Study of Fertility and Early Embryonic Development in Rats After Oral Administration (Study No. T7055241; Bayer Report No. PH 25422)

Developmental Toxicity Study with BAY 12-8039 in the Rat (Report No. R-6690, RCC Project No. 617253, Bayer Project No. T 1 054 282)

BAY 12-8039: Oral (Gavage) Preliminary Embryo-Fetal Development Study in the Cynomolgus Monkey (Report No. R-6692, CHE Study No. 262-085, Bayer Study No. T 6 055 259)

Genotoxicity Studies:

BAY 12-8039 Salmonella/Microsome Test (Study No. T 0053967; Report No. PH 24726)

BAY 12-8039: Test on Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures *In Vitro* (Study No. T 0053985, Report No. PH 24703)

BAY 11-6371: Test of Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures *in Vitro* (Study Nos. T 3054022/T 0054047; Pharma Report No. 23945)

BAY 11-6371: Mutagenicity Study for the Detection of Induced Forward Mutations in the V79-HGPRT Assay *in Vitro* (Study No. T 5054024; Pharma Report No. 24426)

BAY 12-8039 In Vitro Mammalian Chromosome Aberration Test with Chinese Hamster V79 Cells (Study Nos. T 8053965 and T 805703; Report No. PH 25081)

BAY 12-8039: Micronucleus Test on the Mouse (Study No. T 5059308, Pharma Report No. 24451)

BAY 11-6371: Micronucleus Test on the Mouse (Study No. T 7058086; Report No. PH 23748)

Pharmacokinetic (ADME) Studies:

[14C]BAY 12-8039: Absorption, Plasma Concentrations and Excretion of the Substance-Associated Radioactivity in Wistar Rats after Single Administration (Pharma Reports No. 25291 and 25291a)

BAY 12-8039/[14C]BAY 12-8039: Pharmacokinetics of Unchanged Substance and Substance-Associated Radioactivity after Single Administration to Female Rhesus Monkeys (Pharma Report No. 24575)

BAY 12-8039: Pharmacokinetics of the Unchanged Compound in Wistar Rats after Single Intravenous and Oral Administration in Rats (Pharma Report No. 25642)

BAY 12-8039: Pharmacokinetics of the Unchanged Compound in Mice After Single Intravenous and Oral Administration (Report No. PH 25824)

BAY 12-8039: Pharmacokinetics of the Unchanged Compound in Female Dogs (Beagles) after Single Intravenous and Oral Administration (Pharma Report No. 25649)

BAY 12-8039: Pharmacokinetics of the Unchanged Compound in Female Göttingen Minipigs after Single Intravenous and Oral Administration (Pharma Report No. 25667)

[14C]BAY 12-8039: Basic Investigations on Binding to Plasma Proteins and Erythrocyte Plasma Partitioning In Vitro (Pharma Report No. 25644)

[14C]BAY 12-8039: Whole Body Autoradiography. Distribution of Substance-Associated Radioactivity in Male and Female Rats after a Single Oral or Intravenous Administration (Pharma Report No. 25293)

STUDY REVIEWS:

Safety Pharmacology Studies:

BAY 12-8039: CNS Safety Pharmacology After a Single Oral Administration (Bayer Report No. 51.997; Study FS 95002)

[REDACTED]
Report dated: 7/31/95 [REDACTED]

Vol. 10, pp. 35-71

Summary: Moxifloxacin (Batch No. 950314) was suspended in [REDACTED] and administered orally to groups of 5-10 male rats (HsdCpb:WU; 8-9 weeks old) or 10 male mice (HsdWin:NMRI; 4-5 weeks old). After single doses of 0, 10, 30, or 100 mg/kg were given to the rodents, each group was used for a different test, as follows:

Hot Plate (Nociception; Mice): Mice were placed on a metal hot plate (heated to 56.5°C) prior to administration, and 30, 45, 60 and 120 minutes after dosing. Time to pain reaction (licking paws or jumping) was recorded. No differences in the time to pain reaction were observed between the vehicle and moxifloxacin groups.

Traction, Balance Rod, Electroshock (Mice): To measure traction (30 minutes after dosing), mice had to grasp a horizontal wire (3 mm diameter) suspended 25 cm above the bench with their forepaws and hang suspended. They were considered to exhibit "reduced traction" if they failed to reach the wire with one of their hindpaws within 5 seconds after being placed on the wire. One mouse in the 100 mg/kg group had "reduced traction", and signs of sedation were observed in this group. Ten minutes later (40 minutes after dosing), mice were placed on a horizontal wooden rod (8 mm diameter) suspended 72 cm above the bench. They were considered to have impaired motor coordination if they fell 3 times within 3 minutes. None of the moxifloxacin-treated mice had impaired balance at any dose tested. Finally, after another 10 minutes (50 minutes after dosing), the mice were given electric shocks (voltage not specified) via the eyes (which were anesthetized). The test drug is considered to have an anticonvulsive effect if the mice do not show the tonic phase of tonic-clonic seizures after the shock is administered. All of the mice given electric shocks exhibited tonic seizures. One mouse in the control group died and 6 in the 100 mg/kg moxifloxacin group died after the electric shock-induced seizures.

[REDACTED] induced Convulsions (Mice): [REDACTED] was given intravenously to the mice 45 minutes after moxifloxacin dosing. The dose rate was 0.3 ml/min

and administration was stopped as soon as the mice exhibited a clonic seizure. The amount of [redacted] that it took to induce a seizure was compared among the groups of mice. The control mice received an average dose of 38.48 ± 0.88 mg/kg of [redacted] before seizures were induced and the 100 mg/kg mice received an average dose of 40.81 ± 1.94 mg/kg before seizures were induced. This was slightly, but statistically significantly higher than control. The average doses of [redacted] that induced seizures in the 10 and 30 mg/kg mice did not differ significantly from controls. The reviewer is not convinced that the statistically significant difference between the vehicle and 100 mg/kg mice truly represents a biologically significant anticonvulsive effect, although it should be noted that one of the control animals died following the seizures and none of the other mice did. A sedative effect was observed about 30 minutes after dosing in the mice given 100 mg/kg of moxifloxacin

Hexobarbital Sleeping Time (Mice): An intravenous dose of 75 mg/kg of hexobarbital was given to the mice 60 minutes after moxifloxacin was administered. The length of hexobarbital sleeping time was not altered by moxifloxacin treatment. The mice given 100 mg/kg of moxifloxacin appeared somewhat sedated 30 minutes after that drug was administered.

Catalepsy Test (Rats; n=10): The ability of rats to withdraw a forepaw from a block of cork, to remove a wooden stick from their mouths, to retract spread limbs was tested, along with righting reflex, corneal reflex, and vocalization upon touching. The tests were conducted 30, 60, 90, 120, 180, and 240 minutes after administration of moxifloxacin. The rats did not exhibit signs of catalepsy under the conditions of this test, despite a sedative effect at 100 mg/kg observed 30 minutes after dosing.

Modified Irwin Test (Observation for Clinical Signs; Rats; n=6): Rats were observed for behavioral and physiological changes every 15 minutes for 3 hours after moxifloxacin dosing, then 24 hours after administration. The only clinical symptom observed in any of the moxifloxacin-treated rats was sedation in 2/6 animals 30 and 45 minutes after dosing and 1/6 animals 60 minutes after dosing with 100 mg/kg. Sedation was no longer observed 75 minutes after the 100 mg/kg dose of moxifloxacin was given.

Body Temperature Measurement (Rats; n=6): The body temperature of rats was measured with a stomach probe 30, 60, 90, 120, 180, and 240 minutes after moxifloxacin administration. Moxifloxacin did not appear to affect body temperature.

Open-Field Test (Rats; n=10): Rats were placed in open field boxes 30, 60, and 120 minutes after moxifloxacin was given. The animals stayed in the boxes for 5 minutes each time and an automatic system was used to measure the distance traveled, resting time, and number of rearings. At 30 minutes after dosing, the 100 mg/kg rats spent more time resting and had a shorter total distance traveled than controls, but these differences were not statistically significant. Considering that some rats in this group appeared sedated at this time point, the differences may have biological significance, though they were not extremely large. Also at the 30 minute time point, the 100 mg/kg rats did have significantly fewer total rearings than the controls.

The results of this battery of tests indicate that single moxifloxacin doses of up to 100 mg/kg have few CNS effects. The absolute no effect level was 30 mg/kg because of sedation (and a few test results likely related to sedation, e.g., "reduced traction") seen in some mice and rats at 100 mg/kg.

BAY 12-8039: Influence on Hemodynamics and ECG in Anesthetized Dogs After Intravenous Infusion Under Beta-Adrenergic Blockade with d, [redacted] (Bayer Report No. PH 27430; Study No. P3011579)

R. Groß (Bayer AG, Wuppertal, Germany)

Report dated: 4/27/98 [redacted]

Vol. 10, pp. 158-198

Summary: Adult male or female beagle dogs (fasted overnight) were anesthetized with dehydrobenzperidol, fentanyl and nitrous oxide. Atropine and alcuronium chloride were used to dampen parasympathetic responses and induce skeletal muscle relaxation. Systolic and diastolic blood pressures were measured using a catheter tip manometer inserted into the abdominal aorta via the right femoral artery. ECG was used to measure heart rate and electrical activity. An automatic blood gas/electrolyte analyzer was used to measure arterial pH, partial pressures of O₂ and CO₂, sodium and potassium concentrations, and standard bicarbonate and base excess. Hematocrit was also determined with periodic blood samples.

Three groups of 3 dogs were used. The first 2 groups received 5 minute priming doses of [redacted] at 10 µg/kg/min (6 ml/hr) followed after a 20 minute interval with 60 minutes of continuous infusion with 12.5 µg/kg/min (7.5 ml/hr) of [redacted] BAY 12-8039 (Batch No. 05-127522-01; 1 mg/kg/min; 2 ml/kg/hr) or 5% glucose (control, 2 ml/kg/hr) was infused for 30 minutes beginning 10 minutes after the start of the continuous [redacted] infusion. The third group received a 30 µg/kg/min dose of [redacted] for 5 minutes, then a 37.5 µg/kg/min continuous infusion for 60 minutes, as above. These dogs also received 1 mg/kg/min of BAY 12-8039, as above.

Alone, even the higher dose of [redacted] had little effect on blood pressure. Addition of BAY 12-8039 caused a steady decrease in blood pressure (up to 18 mmHg systolic with low [redacted] 27 mmHg systolic with high [redacted] and 7-8 mmHg diastolic with either [redacted] dose). Heart rate was lowered by about 15 beats per minute with either [redacted] dose. Moxifloxacin infusion initially caused elevation of the heart rate back to the pretest value, though heart rate slowly fell again to 7 or 19 beats per minute below pretest value for the low and high doses of [redacted] respectively. In the glucose control group, continuous [redacted] infusion lowered heart rate to about 34 beats per minute below pretest value. In the presence of high dose [redacted] (which increased QTc interval about 30 msec alone), BAY 12-8039 further increased the QTc interval until it was increased 113 msec over pretest value. In the presence of the lower dose of [redacted] and BAY 12-8039, QTc interval was increased by 93 msec compared to pretest. After the infusion, the QTc intervals decreased slowly. No arrhythmias were observed in any animal during the study. The PQ intervals in each group increased or decreased moderately in inverse proportion to heart rate changes. The QRS interval was not changed in any of the dogs. No drug-related changes were observed in hematocrit, pO₂ or pCO₂, pH, sodium or potassium

concentrations or bicarbonate level. The average maximum plasma concentration of BAY 12-8039 in the low [] dogs was 54.3 µg/ml and in the high [] dogs was 48.8 µg/ml, with AUCs of 32.9 and 31.6 µg·hr/ml over the infusions.

The investigators believed that the QTc prolongation effects of moxifloxacin and [] were additive as opposed to synergistic, though the pharmacologist finds it difficult to see how they reached that conclusion since a group that received moxifloxacin but no [] was not included in this study.

BAY 12-8039: Influence on Hemodynamics and ECG in Anesthetized Dogs After Intravenous Infusion Under Normal and Reduced Serum-Potassium Levels (Bayer Report No. PH 27428; Study No. P5011580)

R. Groß (Bayer AG, Wuppertal, Germany)

Report dated: 4/27/98, []

Vol. 10, pp. 199-238

Summary: Furosemide (40 mg/day for 13 days and 80 mg/day for the final day) was used to deplete the serum potassium level in 3/6 adult beagle dogs used for this study. The furosemide treatment lowered the average serum potassium levels in the dogs from 3.6 ± 0.1 to 2.8 ± 0.1 mmol/l and the average serum sodium levels from 143 ± 1 to 139 ± 2 mmol/l. Each animal was infused intravenously with 1 mg/kg/minute (2 ml/kg/hr) of moxifloxacin over 30 minutes. In the potassium-depleted animals, this infusion occurred on the day following the last dose of furosemide. Dogs were anesthetized and cardiac and blood parameters were measured as in the previous study (P 3011579).

Hypokalemic dogs had higher hematocrits, pH, and bicarbonate levels than normokalemic dogs. Arterial pO₂ and pCO₂ were not affected by hypokalemia. The average concentration of moxifloxacin in the blood following the infusion was about 50 µg/ml with an AUC during the infusion of about 37.7 µg·hr/ml. Potassium depletion was not associated with a greater BAY 12-8039-induced QTc prolongation (about 20 msec) than seen in normokalemic animals dosed with the drug. No arrhythmias were observed during the study.

Automatic QRS-Interval Measurement in Anesthetized Dogs by a Data-Acquisition and -Evaluation System: Detection Problems Under Certain ECG Configurations Exemplified by Evaluations from IV Studies with BAY 12-8039 and Additional Experimental Evidence (Bayer Report No. PH 27943)

R. Groß, M. Hoffman (Bayer AG, Wuppertal, Germany)

Report dated: 9/25/98

Vol. 11, pp. 1-30

Summary: The authors of this report reviewed ECG tracings from a number of studies with moxifloxacin in adult beagle dogs (Reports PH 25854, PH 26684, PH 25622) and hypothesized that the automatic reader was not correctly measuring the QRS interval, leading to an overestimation, because the Q wave was not being recognized due to its small size. This was thought to be due to tachycardia induced by rapid infusion of moxifloxacin. Similar effects on Q wave size were induced experimentally by changing the position of anesthetized dogs while measuring their ECGs. An automatic evaluation of these ECG tracings was compared with a manual evaluation and the automatic reader was found to see a widening of the QRS when the Q wave was small, in contrast to the manual evaluation which found no widening of the QRS.

BAY 12-8039: Influence on a Hemodynamics Cardiac Contractility and ECG in Anesthetized Dogs After Intraduodenal Administration (Bayer Report No. PH 24362; Study No. P 3011498)

A. Knorr (Bayer AG, Wuppertal, Germany)

Report dated: 9/4/95, [REDACTED]

Vol. 11, pp. 31-84

Summary: BAY 12-8039 (Batch No. 950 314), suspended in 0.5% [REDACTED] was administered intraduodenally to adult beagle dogs at doses of 10, 31.5, and 100 mg/kg (dose volume was 1 ml/kg). The control group received vehicle only and each treatment group had 3 dogs (male or female). Dogs were anesthetized and cardiac and blood parameters were measured as in study P 3011579, above. Observation continued for 240 minutes after dosing.

None of the doses of moxifloxacin had an effect on left ventricular pressure, contractility index, central venous pressure, stroke volume or total peripheral resistance. Only the 100 mg/kg dose was associated with a small rise in blood pressure (systolic, diastolic, mean). Heart rate rose slightly after all doses, but the effect was not dose-related. The rate decreased to normal several minutes after administration of drug. Cardiac output also increased slightly after moxifloxacin dosing. No changes were observed in hematocrit, pO₂, or pCO₂ following administration of moxifloxacin. After 100 mg/kg was given, the blood pH, bicarbonate, and base excess levels fell during the first 90 minutes of observation. The plasma potassium concentration rose slightly after the 31.5 and 100 mg/kg doses, but the levels fell back toward normal beginning an hour after administration of drug. A slight prolongation was observed in the QT-interval after the 100 mg/kg dose of BAY 12-8039, but not the 2 lower doses. The report stated that it was still within the normal range for beagles. The average maximum plasma concentrations measured in the dogs were 4.26, 16.9, and 30.1 µg/ml for the 10, 31.5, and 100 mg/kg doses, respectively. Blood samples for pharmacokinetic analysis were taken 0.5, 1, 2, and 4 hours after administration of BAY 12-8039, and the C_{max} was seen at 0.5 hr for each dose.

BAY 12-8039: Influence on ECG and Hemodynamics in Anesthetized Dogs After Intravenous Infusion of 30 mg/kg within 15, 30, or 60 minutes (Bayer Report No. PH 26684; Study No. P 2011578)

A. Knorr (Bayer AG, Wuppertal, Germany)

Report dated: 10/30/97

Vol. 11, pp. 185-228

Summary: BAY 12-8039 (Batch No. 970422-311) was administered intravenously to adult beagle dogs at a dose of 30 mg/kg. The dogs were divided into groups of 3 animals (both genders) and each group received the same dose of moxifloxacin over a different infusion time, 15, 30, or 60 minutes (corresponding to infusion rates of 2, 1, and 0.5 mg/kg/min). The control group received 5% glucose over 15 minutes and the dose volume was 1 ml/kg for each group. Dogs were anesthetized and cardiac and blood parameters were measured as in study P 3011579, above. Observation continued for 60 minutes after dosing.

Blood pressure (systolic, diastolic, mean) rose slightly immediately following the 15 and 30 minute infusions, but this was soon followed by a small, but prolonged decrease (about 10 mmHg) in mean blood pressure. The 60 minute infusion was not associated with a change in systolic blood pressure, but caused a small reduction in diastolic blood pressure late in the infusion. Heart rate was increased in an infusion rate-dependant fashion. Hematocrit rose slightly after the slowest infusion, but pO₂ and pCO₂ were not affected. Arterial blood pH and base excess level fell slightly following any moxifloxacin infusion. There was a small increase in plasma sodium concentration after the 60 minute infusion and a transient drop in plasma potassium concentration after the 15 minute infusion. The QTc rose 20, 33, and 48 msec during the 60, 30, and 15 minute infusions, respectively. The mean maximum plasma concentrations for moxifloxacin immediately following these infusions were 24.3, 45.6, and 63.2 µg/ml. The AUC values were similar regardless of infusion rate.

BAY 12-8039: Influence of Overdosage-Infusion on Hemodynamics and ECG in Anesthetized Dogs (Bayer Report No. PH 27429; Study No. P 2011802)

R. Groß (Bayer AG, Wuppertal, Germany)

Report dated: 4/27/98

Vol. 11, pp. 229-289

Summary: Moxifloxacin (Batch No. 970828-312, 3% solution) was administered intravenously to 6 male and female adult beagle dogs as follows: 1 mg/kg/min for 60 minutes, then 2 mg/kg/min for 60 minutes, and finally 4 mg/kg/min for 90 minutes. One dog received placebo dose solution (exact content not specified in report) at the same infusion rates. Dogs were anesthetized and cardiac and blood parameters were measured as in study P 3011579, above, with the exception that only half of the moxifloxacin-treated dogs received atropine to reduce

parasympathetic response. The placebo animal did not receive atropine. Observation continued for 10-20 minutes after the moxifloxacin or placebo infusion was ended.

Blood pressure did not change in the animal given placebo. It rose up to 35 mmHg above baseline beginning during the 2 mg/kg/min moxifloxacin infusion (especially diastolic BP) in the dogs which did not receive atropine and declined to normal after the moxifloxacin infusions. In contrast, systolic and diastolic blood pressure fell by about 20 mmHg during the 2 mg/kg/min moxifloxacin in the dogs receiving atropine. Blood pressure recovered during the 4 mg/kg/min infusion, but fell below baseline again at the end of this infusion. Heart rate was not affected by placebo, and it initially rose during the first moxifloxacin infusion (smaller rise with atropine probably due to higher baseline) before decreasing slowly toward baseline during the rest of the study (regardless of atropine). Hematocrit increased during all infusions, including control, as did pCO₂. The pO₂ did not change. As blood pH fell during the highest rate of infusion, so did bicarbonate and base excess levels. The changes indicative of metabolic acidosis were greater in the moxifloxacin-treated animals than control. Moxifloxacin did not alter plasma concentrations of sodium or potassium. The QT and QTc intervals were increased in a dose-related manner by the moxifloxacin infusions. Increases ranged from about 225 to 500 msec above control. Prolongation was observed beginning with the 1 mg/kg/min infusion and T-wave changes (negative or biphasic) were seen in all dogs. The earliest arrhythmia (AV-nodal extrasystole) was seen in one dog (no atropine) during the 2 mg/kg/min infusion at the 104 minute mark. Changes in P-waves (negative, biphasic) were seen in two of the dogs (with atropine) during the 4 mg/kg/min infusion. The investigator believed that these most likely indicated premature atrial beats, but the report stated that sinus arrest concomitant with an atrial compensatory rhythm could not be excluded. In all but 2 dogs (one with atropine, one without), a variety of rhythm disorders were observed during the 4 mg/kg/min infusion. These included: AV-nodal ectopies, ventricular extrasystoles (doublets and triplets, up to ventricular tachycardia) and bigemini. Two dogs developed torsade de points which reversed spontaneously back to normal rhythm. The 2 dogs that did not develop arrhythmias had QTc intervals of about 690 msec (compared to control QTc of 247-323 msec). Of the 4 dogs that developed arrhythmias, all but one reverted to normal sinus rhythm within 10-20 minutes after stopping the moxifloxacin infusion. The mean plasma levels of moxifloxacin at the end of the 1, 2, and 4 mg/kg/min infusion periods were 50.6, 129, and 265 µg/ml, respectively. These are 11-58 times higher than the anticipated clinical C_{max} (4.5 µg/ml) at steady state with daily dosing of 400 mg/day.

Sparfloxacin (BAY v 1749) versus Moxifloxacin (BAY 12-8039) Influence on Hemodynamics and ECG in Anesthetized Dogs After Intravenous Infusion (Bayer Report No. PH 27427; Study No. P 2011839)

R. Groß (Bayer AG, Wuppertal, Germany)

Report dated: 4/27/98

Vol. 11, pp. 290-335

Summary: Sparfloxacin was administered intravenously to 3 adult beagle dogs (male and female) at a dose level of 30 mg/kg over 30 minutes. The study was conducted as per report PH

26684, and the data generated with the 30 mg/kg dose of moxifloxacin over 30 minutes in that experiment were compared with the current sparfloxacin data.

In contrast to moxifloxacin which tended to increase blood pressure slightly, sparfloxacin was associated with small decreases (11-13 mmHg) in systolic and diastolic blood pressures at the end of infusion. Sparfloxacin was not associated with an increased heart rate during infusion (though the rate did climb by 5-15 beats per minute after infusion was over), unlike moxifloxacin which was associated with a transient increase at the beginning of infusion. Changes in blood parameters over the course of dosing were similar with sparfloxacin and moxifloxacin. During the sparfloxacin infusion, the QTc increased steadily up to 58 msec. When moxifloxacin was infused, the QTc increased transiently up to 23-28 msec, but fell to baseline prior to the end of infusion. In the 3 sparfloxacin dogs, changes in the P- and T-waves were observed (polarity reversal, biphasic, morphology). Neither drug changed the QRS-interval. Sparfloxacin shortened the PQ-interval slightly (6 msec), but moxifloxacin did not. The mean maximum plasma concentration of sparfloxacin (measured at the end of infusion) was 32.1 µg/ml, which is similar to that measured at the end of the moxifloxacin infusion, 33.6 µg/ml. The AUC (0-1.5 hr) for sparfloxacin, however, was lower than that for moxifloxacin 23.9 vs. 45.6 µg·hr/ml.

A Respiratory and Cardiovascular Study of BAY 12-8039 in Monkeys (Bayer Report No. R 7104; Study No. SBL 95-87)

Report dated: 3/20/98

Vol. 11, pp. 336-371

Summary: Male adult (4-5 years old) cynomolgus monkeys were fasted overnight and anesthetized with sodium pentobarbital. BAY 12-8039 (Lot No. 519481) was administered to the animals intraduodenally via a catheter as a suspension in 0.5% carboxy methylcellulose in a dose volume of 1 ml/kg. The dose groups were vehicle (control) 10, 31.5, and 100 mg/kg and each group contained 3 monkeys. A tracheal cannula attached to a respiration sensor was used to monitor respiration and a cannula connected to a pressure transducer was placed in the right femoral artery to measure blood pressure. To monitor blood flow, an electromagnetic blood flow meter probe was attached to the left femoral artery. ECG was recorded using several limb leads. Monitoring was continued for 240 minutes after administration of the test substances.

No dose of BAY 12-8039 was associated with a change in respiratory rate. The 10 mg/kg dose of BAY 12-8039 did not affect blood pressure, heart rate, femoral blood flow, or electrocardiogram. The 31.5 mg/kg dose caused only a small (about 7%) decrease in systolic and diastolic blood pressure 15-30 minutes after administration. The 100 mg/kg dose of moxifloxacin was associated with a larger (up to 15%) decrease in systolic and diastolic blood pressure beginning 15 minutes after administration and returning to normal around 90 minutes after dosing. This high dose was also associated with a decrease in heart rate beginning 15 minutes after administration of moxifloxacin and returning to baseline about 120 minutes after dosing. Femoral blood flow was reduced significantly 30-60 minutes after administration of

moxifloxacin. The QTc interval was not altered by any dose of moxifloxacin used in this experiment.

Effects of Moxifloxacin (BAY 12-8039) and Sparfloxacin on Cardiac Action Potentials and Potassium Currents (Bayer Report No. R 7223)

Report dated: 6/25/98

Vol. 11, 384-401

Summary: The right ventricular papillary muscles from guinea pigs hearts were isolated and bathed with a modified [redacted] solution at 36.5°C. Action potentials from the muscle were monitored using intracellular microelectrodes filled with [redacted]. Action potentials were elicited using 2 platinum wires with 1 msec pulses of 4-8 mA current at a frequency of 1 Hz. Preparations were allowed to equilibrate for 90 minutes prior to testing with moxifloxacin and sparfloxacin.

Current measurements were undertaken in single ventricular myocytes isolated from guinea pig hearts via enzymatic digestion. Cells were suspended in [redacted] solution and whole cell voltage clamp techniques [redacted]

[redacted] were used to measure currents. In some studies, the inward calcium current was blocked using 1 μ M nisoldipine and the inward sodium current was inactivated by holding the cells at -40 mV.

The threshold concentrations of sparfloxacin and moxifloxacin that caused action potential prolongation were 3 and 50 μ M, respectively. In the presence of 50 μ M BAY 12-8039 or 50 μ M sparfloxacin, the action potential of the guinea pig papillary muscle was prolonged by 25.4 ± 1.6 msec and 68.3 ± 10.7 msec, respectively. The action potential recordings for both drugs indicated that the final repolarization was delayed, but the rate of rapid repolarization was not affected. This suggested to the investigators that the delayed rectifier (outward) potassium current was affected by the drugs, but not the inward rectifier potassium current.

Results from the isolated myocyte experiments suggested that moxifloxacin interferes with the slow potassium delayed rectifier current, but did not appear to block the rapid component of this potassium current.

Effects of Moxifloxacin (BAY 12-8039) on Action Potentials (Bayer Report No. R 7265)

Report dated: 3/9/98

Vol. 11, pp. 402-411

Summary: The right ventricular papillary muscles from guinea pigs hearts were isolated and bathed with a modified [redacted] solution at 36.5°C. Action potentials from the muscle were monitored using intracellular microelectrodes filled with [redacted]. Action potentials were elicited using 2 platinum wires with 1 msec pulses of 4-8 mA current at a frequency of 1 Hz. Preparations were allowed to equilibrate for 90 minutes prior to testing.

The maximum upstroke velocity of the action potential was reduced significantly (9-11%) by 50 µM moxifloxacin after 30-45 minutes of drug exposure. The amplitude of the action potential and resting membrane potential were not affected.

Potassium Channel Blocking Action of BAY 12-8039 (Moxifloxacin) and Sparfloxacin (Bayer Report No. R 7238)

[redacted]

Report dated: 8/21/98

Vol. 11, pp. 412-422

Summary: Cultured AT-1 cells (mouse atrial tumor cells) were incubated with moxifloxacin and sparfloxacin. Under appropriate voltage clamp conditions, the only time-dependent outward current in these cells is the rapid component of the delayed rectifier potassium current. The IC_{50} for the reduction of this current was 0.75 ± 0.31 µM for moxifloxacin and 0.23 ± 0.07 µM for sparfloxacin- about a 3-fold difference in potency.

Is There an Influence of BAY 12-8039 (Moxifloxacin) or Sparfloxacin on the Potassium Currents I_{Kr} Through KvLQT1? A Study of Stably Transfected Cells Expressing KvLQT1 and minK (Bayer Report No. PH 27994)

T. Krahn (Bayer AG, Elberfeld, Germany)

Report dated: 9/25/98

Vol. 11, pp. 423-434

Summary: CHO DUKX cells stably transfected with the genes for the proteins KvLQT1 and minK were used for these experiments. Together, these transfected proteins form functional potassium channels for the slow component of the delayed rectifier current and this cell line allows specific study of this current. Rubidium flux out through the potassium channels was measured to determine whether these channels were blocked. The cells were loaded with rubidium prior to incubation with test chemicals. Mefenamic acid and/or potassium D-gluconate was used to activate the channels and sparfloxacin and moxifloxacin were included in the system to see whether they could block the activation. A known inhibitor of the channels, 17-β-estradiol was used as a positive control. The intracellular and extracellular concentrations of rubidium were measured in the presence and absence of test chemicals to determine rubidium flux.

At concentrations up to 30 μM (the highest tested), neither sparfloxacin nor moxifloxacin blocked the activation of rubidium flux from the transfected CHO DUKX cells. This suggests that they are not blockers of the slow component of the delayed rectifier potassium current under the conditions of this experiment. The results from this experiment confirm the results of previous studies suggesting that these drugs can inhibit the rapid component of the delayed rectifier current.

Comparison of QT Prolongation and Arrhythmias in Rabbits Treated with BAY 12-8039 or Sparfloxacin (Bayer Report No. R 7264)

[REDACTED]

Report dated: 10/1/98

Vol. 11, pp. 435-447

Summary: 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. ECG was monitored continuously. The animals received 10 $\mu\text{g}/\text{kg}/\text{min}$ of [REDACTED] via intravenous infusion for 10 minutes prior to the initiation of IV infusion of either sparfloxacin or moxifloxacin (2 $\text{mg}/\text{kg}/\text{min}$). Drugs ([REDACTED] 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).

General Pharmacology of BAY 12-8039 in the Gastrointestinal Tract: Its Effects on Acetylcholine Induced Ileal Spasms, On the Stimulated Gastric Acid-Secretion, and On Indomethacin-Induced Ulcers (Bayer Report No. PH 24316)

A. Grassi (Bayer, Milan, Italy)

Report dated: 9/15/95 [REDACTED]

Vol. 12, pp. 1-16

Summary: BAY 12-8039 (Batch No. 950314) was dissolved in water for use with the isolated organ preparation and suspended in 0.5% [] for intraduodenal or oral administration.

The effect of moxifloxacin on acetylcholine-induced ileal spasms was examined using 4 preparations of isolated guinea pig ileum from both genders. A basal tension of 1 g was applied to the tissue, the preparations were allowed to equilibrate for at least 30 minutes, and isotonic contractions were measured using a force transducer and recorded on a polygraph. Moxifloxacin (tested at concentrations of 10^{-8} , 10^{-7} , or 10^{-6} M) or vehicle was added to the preparations 2 minutes prior to induction of contractions using 2.3×10^{-7} M acetylcholine chloride. After 30 seconds, the test substances were washed out of the organ bath. At the concentrations tested, moxifloxacin did not have any effect on the spasms induced by acetylcholine in the isolated guinea pig ileum.

Female rats (8 per dose group) fasted for 18 hours were anesthetized and the jugular vein, esophagus, and stomach cannulated. The stomach was perfused with physiological saline and samples of the effluent perfusate were collected every 15 minutes so that their acid content could be measured. After gastric acid samples were collected for 30 minutes, histamine was infused via the jugular vein (6 mg/kg/ml/hr for 2.5 hours) to stimulate gastric acid secretion. Sixty minutes after the histamine infusion was begun, moxifloxacin or vehicle was administered intraduodenally at doses of 0, 10, 30, and 100 mg/kg and gastric acid secretion was measured for 1.5 hours. Moxifloxacin treatment did not have any effect on gastric acid secretion induced by histamine in the rats.

Male rats (15 per dose group) fasted for 18 hours received 15 mg/kg of indomethacin intraperitoneally (to induce ulcers) at the same time as vehicle or moxifloxacin doses of 10, 30, or 100 mg/kg were given orally. Five hours later, animals were sacrificed and the stomachs examined for gastric lesions. Moxifloxacin did not affect the severity of the gastric lesions induced in the rats by indomethacin.

Safety Pharmacology of BAY 12-8039 in the Gastrointestinal Tract: Its Effects on the Intestinal [] Transit, On the Gastric Tolerability, and On the Basal Gastric Acid Secretion in the Rat (Bayer Report No. PH 24317)

A. Grassi (Bayer, Milan, Italy)

Report dated: 9/15/95, []

Vol. 12, pp. 34-47

Summary: BAY 12-8039 (Batch No. 950314) was suspended in 0.5% [] for intraduodenal or oral administration at doses of 0 (vehicle), 10, 30, and 100 mg/kg.

Male rats (5/group) were fasted for 16 hours, then given moxifloxacin or vehicle via oral gavage 30 minutes prior to oral administration of 3 ml of a 12.5% [] in 0.5% []. The rats were sacrificed 30 minutes after dosing with [] and the length of transit of [] passage through the small intestine was determined. Moxifloxacin did not influence the intestinal transit of charcoal.

Groups of 15 male rats were fasted for 18 hours before receiving moxifloxacin or vehicle via oral gavage. The animals were sacrificed 5 hours later and their stomachs were inspected for lesions. Gastric lesions were not observed in the rats.

Female rats (8/group) were fasted for 18 hours prior to anesthesia. The esophagus and stomach of each animal was cannulated and the stomachs perfused with 0.5 ml/min of physiological saline. After 30 minutes of perfusion, samples of effluent saline were collected every 15 minutes for 60 minutes. Next, animals received moxifloxacin or vehicle via intraduodenal administration. Effluent saline was collected every 15 minutes for the next 2 hours. The amount of acid in each saline sample was measured. Moxifloxacin administration did not alter the basal secretion of gastric acid.

BAY 12-8039: Test for Renal Effects After Oral Administration in Rats (Bayer Report No. 24390)

C. Hirth-Dietrich (Bayer, Wuppertal, Germany)

Report dated: 9/1/95 [REDACTED]

Vol. 12, pp. 48-56

Summary: -BAY 12-8039 (Batch No. 950314) was suspended in 0.5% [REDACTED] and administered at doses of 0 (vehicle) 10, 30, or 100 mg/kg (10 ml/kg dose volume) via oral gavage to fasted male rats (HsdCpb:WU; 10 per group). After dosing, the rats were placed in metabolism cages for 6 hours and the urine collected. Average urine volumes and the amounts of sodium and potassium excreted by the rats were similar among the groups.

BAY 12-8039: Effects on Blood Glucose and Serum Triglyceride Concentrations of Fasted and Fed Rats after Oral Administration (Bayer Report No. PH 24388)

H. Bischoff (Bayer, Wuppertal, Germany)

Report dated: 9/20/95, [REDACTED]

Vol. 12, pp. 72-84

Summary: BAY 12-8039 (Batch No. 950314) was suspended in 0.5% [REDACTED] and administered at doses of 0 (vehicle) 10, 30, or 100 mg/kg (10 ml/kg dose volume) via oral gavage to groups of fasted (18 hours) and fed [REDACTED] male rats (HsdCpb:WU; 6 per group).

Blood samples were drawn (retroorbital sinus puncture) from the groups of fasted and fed rats 30, 60, 120, and 240 minutes after administration of moxifloxacin or vehicle and the levels of glucose and triglycerides were measured. In the fed rats, neither blood glucose nor serum triglyceride level was changed significantly after moxifloxacin administration. In the fasted rats, serum glucose levels were not affected by moxifloxacin and serum triglyceride levels were not affected by the 10 or 30 mg/kg moxifloxacin doses. At 100 mg/kg of moxifloxacin, the serum

triglyceride level was reduced by about 37% at the 30 minute time point and by about 27% at the other time points.

When a glucose tolerance test was performed on fasted rats (2 g/kg glucose given with moxifloxacin or vehicle), the 10 and 30 mg/kg doses of moxifloxacin did not appear to have a significant effect. After the 100 mg/kg dose, the blood glucose levels in the rats were slightly (but not significantly) less than control 30 and 60 minutes after dosing; 120 minutes after dosing, the mean blood glucose levels in these rats were slightly and significantly elevated (control, 3.71 ± 0.31 mmol/l; 100 mg/kg, 4.33 ± 0.38 mmol/l). The effect is small and the reviewer is not convinced of its biological significance.

BAY 12-8039: Blood Pharmacological Investigations (Bayer Report No. PH 24297)

E. Perzborn (Bayer, Wuppertal, Germany)

Report dated: 8/31/95, [REDACTED]

Vol. 12, pp. 96-112

Summary: BAY 12-8039 (Batch No. 950314) was suspended in 0.5% [REDACTED] and administered at doses of 0 (vehicle) 10, 30, or 100 mg/kg (10 ml/kg dose volume) via oral gavage to groups of fasted (18 hours) male rats (HsdCpb:WU; 5 per group). A blood sample was drawn from each animal 1 hour after administration so that the following hematologic parameters could be measured: counts of red and white blood cells and platelets, hemoglobin, hematocrit, collagen induced platelet aggregation, thrombin time, and thromboplastin time. No significant differences in any of the parameters was observed between the control rats and those treated with moxifloxacin.

BAY 12-8039: Effects of Oral Administration on Bronchoactivity in the Anesthetized Spontaneously-Breathing Guinea Pig (Bayer Report No. PH 24238; Study No. P9011494)

U.P. Patel, H.P. Francis (Bayer, Stoke Court, UK)

Report dated: 7/6/95 [REDACTED]

Vol. 12, pp. 132-228

Summary: Male [REDACTED] guinea pigs (58-73 days old, 8 assigned to each treatment group so that data from 5-6 per group would be available) were anesthetized and the trachea, esophagus, common carotid artery, and an external jugular vein were cannulated. Transpulmonary pressure was measured via the esophageal cannula and the tracheal cannula was connected to a pneumotachograph to measure respiratory flow. Mean blood pressure and heart rate were measured using a transducer connected to the carotid cannula. After cannulas were placed, the guinea pigs were allowed to equilibrate for 20-46 minutes before BAY 12-8039 (Batch No. 950314) suspended in 0.5% [REDACTED] was given at a dose of 0 (vehicle), 10, 30, or 100 mg/kg into the stomach via the esophageal cannula (5 ml/kg dose volume). The animals were

monitored for 90 minutes following administration of moxifloxacin or vehicle, then histamine was given intravenously at ascending doses from 1-8 µg/kg. Two to three animals in each dose group were excluded for reasons such as low, erratic respiratory rate, low or variable pressure signal, or erratic respiration.

The animals treated with vehicle experienced a small decrease in pulmonary resistance immediately after dosing. In contrast, there was little change in the pulmonary resistance from baseline in the animals that received moxifloxacin. Dynamic lung compliance did not differ between any of the treatment groups. Respiratory rate did not change much from baseline for the vehicle treated guinea pigs and only small increases in the group mean were observed in the moxifloxacin treated animals.

IV administration of histamine caused a dose related increase in pulmonary resistance coupled with a decrease in dynamic lung compliance. Although there was not a statistically significant difference between the vehicle and moxifloxacin groups, there was a dose-related trend towards more severe histamine responses in the moxifloxacin treated guinea pigs.

General Toxicity Studies:

Single Oral Dose Toxicity Study of BAY 12-8039 in Cynomolgus Monkeys (Bayer Report No. R 6907; Study No. SBL 95-43)

[REDACTED]

Report dated: 12/11/95, [REDACTED]

Vol. 13, pp. 203-242

Summary: Single oral doses of BAY 12-8039 (Lot No. 519481, suspended in 0.5% [REDACTED]) were administered to groups of 2 male fasted cynomolgus monkeys (4-5 years old) at 250, 750, or 1500 mg/kg (dose volume of 10 ml/kg). Animals were observed for 13 days following administration of moxifloxacin.

At 250 mg/kg, decreased spontaneous activity, tremor, and somnolence were observed 4-6 hours after administration. Soft stool was observed from days 1-6. In the second animal at this dose level, only soft stool was seen (on day 2).

The same clinical signs were observed in both monkeys at 750 mg/kg, but vomiting was also seen in these monkeys about 5-6 hours after administration of drug. Tonic convulsion was observed in one of the 750 mg/kg monkeys about 6 hours following the moxifloxacin dose and twitching was observed at about the same time in the other. Soft stool was seen until day 3 in one monkey and until day 6 in the other.

One monkey given 1500 mg/kg of moxifloxacin died during the night after administration of drug. This animal exhibited not only the clinical signs discussed above, but also palpebral ptosis, dyskinesia, mydriasis, sedation, and, finally, coma (6 hours after dosing). The second animal in this group exhibited the same clinical signs, except for coma and death. Dyskinesia and decreased spontaneous activity persisted until about day 6 and soft stool or diarrhea until day 7.

Necropsy of the monkey that died revealed hemorrhage of the thymus and the jejunum and ileum contained bloody contents (including clots). Abnormalities were not observed when gross necropsy was conducted on the other animals 14 days after administration of moxifloxacin. Histopathological examination of the tissues showed hemorrhage and congestion of the lamina propria of the jejunum, ileum, and thymus of the 1500 mg/kg monkey that died. Microscopic changes were not observed in tissues from the remaining animals.

BAY 12-8039: Chronic Oral Toxicity Study in Rhesus Monkeys (26 Week Gavage Study)
(Bayer Report No. PH 27460; Study No. T 1061121)

J. Ruf, V. Geiß (Bayer, Wuppertal, Germany)

Report dated: 8/5/98, [REDACTED]

Vol. 26, pp. 1-545

Animals: Adult male and female Rhesus monkeys (4-14 years old, 4.03-7.95 kg), 4/sex per dose group [REDACTED]

Diet: [REDACTED] was offered daily (140 g) about 1-2 hours after the daily dose of drug was given and fresh fruit (apple pieces or peeled banana) was also offered daily. Tap water was available *ad libitum*.

Drug Dose and Route of Administration: Moxifloxacin (Batch No. 960704A) was suspended in 0.5% [REDACTED] and given orally by gavage at a dose volume of 5 ml/kg. Dose groups included 0 (vehicle control), 15, 45, and 135 mg/kg. The drug was given once daily for 26 weeks and the doses were set based upon the results of a 13 week oral toxicity study previously conducted in this species of monkey.

Length and Conduct of Study: The monkeys received moxifloxacin or vehicle for 26 weeks and were sacrificed and necropsied during week 27. Food intake was determined daily and body weights were measured weekly. Ophthalmoscopic examinations occurred prior to the initiation of dosing and during weeks 6, 13, and 26 of administration. Blood pressure was measured before the start of dosing and during weeks 6, 13, 20 and 26. Blood samples were taken for hematologic and clinical chemistry evaluation before the start of dosing and during weeks 2, 6, 13, 20, and 26. Urine was collected for urinalysis according to the same time schedule. Collection occurred overnight (during a 16 hour period) and food and drinking water were not available during this time. At necropsy, tissue samples from Achilles tendons and both shoulder, knee, cubital, and hip joints (bone and cartilage) were taken for microscopic analysis along with the tissues listed on the histopathology check list.

Blood samples for toxicokinetics were taken on day 1 of the study and during weeks 4 and 25 prior to administration of drug and 2, 4, 7, and 24 hours after dosing. Results of the toxicokinetic analysis were reported separately (below).

Results: A male in the 135 mg/kg group was found dead during the second week of the study and was replaced. The second animal was found dead about a week later. Necropsy revealed that these animals died as the result of dosing accidents. The second dead male in the 135 mg/kg group was also replaced. One female from the 135 mg/kg group was sacrificed during week 14 in moribund condition. The necropsy did not reveal a specific cause of moribundity, but the investigators believed the poor condition of the animal to be related to moxifloxacin.

Salivation was observed in most of the moxifloxacin-treated animals in the study, as was occasional vomiting of mucus. The investigators believed that these symptoms might have been related to the bitterness of the drug. Vomiting of food by the monkeys in the 135 mg/kg group was likely to have been drug-related, as were the clinical signs spasm, rapid breathing and tendency of the monkeys to assume a lateral position.

Food intake was frequently reduced in the monkeys from the 135 mg/kg dose group and the body weights of the males in this group were reduced slightly compared to control at the end of the study.

Ophthalmic examination did not reveal changes in any of the animals. During week 26, the 135 mg/kg males had slightly decreased diastolic blood pressure and pulse rates were lower than controls in both genders of this dose group. Hematologic evaluation did not reveal striking differences among the dose groups. One male in the 135 mg/kg dose group had a slightly reduced erythrocyte count and total hemoglobin in weeks 13 and 26 and a slight reduction in hemoglobin in week 26- these parameters tended to be slightly lowered in the other animals from this group, too.

Some changes in serum chemistry parameters were observed in individual animals over the course of the study. Small increase in AST were seen in one 135 mg/kg male during week 6 and in one female from the same group during weeks 3 and 20. Small increases in ALT were seen in one male at 45 mg/kg during week 20 and in one 135 mg/kg female during week 2. Glutamate dehydrogenase was increased in two males at 45 mg/kg during week 20 and weeks 20 and 21, respectively. It was also increased in 2 females from the 135 mg/kg group during weeks 2 and 3, respectively. Total bilirubin was increased in 2 males from the 135 mg/kg group; one during week 6 and the other during weeks 26 and 27. The investigators thought that these elevations were probably drug-related, but this reviewer finds that to be an extremely conservative interpretation of the data because most of the increases observed were small and sporadic and did not persist until the end of the study despite continued dosing with moxifloxacin. Additionally, the AST and ALT increases did not occur in the same monkeys. The animal with increased bilirubin at the end of the study did not have an accompanying increase in AST or ALT at the same time (this animal had a small AST increase during week 6 only). One male in the 135 mg/kg group had an elevated urea level during weeks 20 and 27 that was believed to have been secondary to the monkey's emaciated condition.

Urinalysis revealed an increased incidence of monkeys with protein detected in their urine at 135 mg/kg compared to controls. One female from this group also had an increase in urinary ketone bodies in a urine specimen collected during week 26. No drug-related renal changes were observed during microscopic evaluation of kidney tissue, however.

An increase in absolute and relative mean liver weights compared to control was observed in the female monkeys from the 135 mg/kg dose group, but one animal accounts for this increase.

Drug-related macroscopic findings were not observed at necropsy with the exception of low body fat in several animals from the 135 mg/kg group. Several animals in all dose groups including controls had evidence of lung infections with *Pneumonyssus* mites. Most monkeys (except for those in the high dose group) had *Balantidium* infection in their GI mucosa. Glycogen inclusions (identified via staining procedures) were observed in the centriacinar hepatocytes of 2 animals each from the 15 and 45 mg/kg dose groups and in 4 animals from the 135 mg/kg dose group. In 3 of the 4 monkeys at 135 mg/kg, the size and number of these inclusions was much greater than in the other monkeys. The pathology report states that these type of inclusions have been observed in control animals to the same degree as was seen in the 15 and 45 mg/kg monkeys, but that the degree of these inclusions in the 135 mg/kg monkeys was greater than commonly observed and may be drug-related. Degenerative changes in liver tissue (inflammation or hepatocyte necrosis) were not observed. Some degeneration of the articular cartilage was seen in various joints in monkeys from all dose groups including controls. These changes (superficial erosion, rough surface, cartilage regeneration, fibrous tissue replacement of cartilage at distal humerus) did not grossly or microscopically resemble the characteristic quinolone arthropathy and did not appear drug-related. Generalized serous atrophy of the bone marrow (yellow portion) was seen in 3 monkeys from the high dose group and may be related to reduced nutritional status and poor condition. This finding has been observed in other moxifloxacin studies in monkeys. Isolated areas of serous bone marrow atrophy were seen in some monkeys from the other moxifloxacin treatment groups. A hypocellular focus was observed in the bone marrow from a single bone in one 135 mg/kg female. This observation was not reported for any other bones from this animal or any of the bones from other drug-treated monkeys.

The NOAEL for oral moxifloxacin in this 6 month monkey study was 45 mg/kg. A dose of 135 mg/kg was associated with reduced food intake, reduced body weight in males, mortality (one female sacrificed in moribund condition) and clinical signs of toxicity in some animals such as spasm, rapid breathing and tendency of the monkeys to assume a lateral position. Inclusions described as "glycogen lakes" were observed in the centriacinar hepatocytes of some monkeys in the 135 mg/kg group. Smaller, but similar inclusions were observed in a few monkeys at 15 and 45 mg/kg as well, but they were comparable to what the pathologist has observed in control monkeys from other studies.

BAY 12-8039: Plasma Concentrations in Rhesus Monkeys After Oral Administration in a Chronic Toxicity Study (Bayer Report No. PH 27154; Study No. T 1061121)

C. Kohlsdorfer, J. Ruf (Bayer, Wuppertal, Germany)

Report dated: 2/4/98

Vol. 27, pp. 1-43

Summary: This is the toxicokinetics report for the 26 week monkey study (directly above). There appeared to be some accumulation at the high dose based on the AUC data. Half life for moxifloxacin calculated on day 1 was about 4.5 hours for the 15 and 45 mg/kg doses and 7.7

hours for the 135 mg/kg dose. There did not appear to be any differences in plasma level based on gender, so the data from males and females was combined.

Mean Toxicokinetic Parameters in Rhesus Monkeys After Moxifloxacin Dosing

	15 mg/kg	45 mg/kg	135 mg/kg
Day 1			
AUC ₀₋₂₄ (µg·hr/ml)	14.3	51.5	104
C _{max} (µg/ml)	2.22	5.75	9.06
T _{max} (hr)	2.00	3.62	3.8
Day 22			
AUC (µg·hr/ml)	15.7	60.8	171
C _{max} (µg/ml)	2.41	6.24	15.3
T _{max} (hr)	2.00	4.00	3.93
Day 169			
AUC (µg·hr/ml)	17.3	63.3	206
C _{max} (µg/ml)	2.42	5.5	15.3
T _{max} (hr)	2.55	4.6	7.00

BAY 12-8039: Study on Chronic Toxicity in Wistar Rats. Administration by Gavage Over 6 Months (Bayer Report No. PH 27401; Study No. T 6061298)

K.H. Leser, M. Rinke (Bayer, Wuppertal, Germany)

Report dated: 4/16/98 [redacted]

Vol. 18 p.1 - Vol. 19 p. 241

Animals: Male (153-186 g) and female (105-148 g) Wistar rats, 6-7 weeks old at the start of the study, 20/sex per group

Diet: [redacted] pellets and water were available *ad libitum* (except diet was removed during urine collection).

Drug Dose and Route of Administration: Moxifloxacin (Batch No. 522381D) was suspended in 0.5% [redacted] and administered orally via gavage at doses of 0 (vehicle), 20, 100, or 500 mg/kg (dose volume 5 ml/kg) for 28 weeks. The doses were based upon the results of a 13 week study in the same species.

Length and Conduct of Study: Rats received moxifloxacin or vehicle for 28 weeks and were sacrificed and necropsied at the end of the treatment period. Food consumption and body weights were measured weekly. Ophthalmoscopic examinations occurred prior to the initiation of dosing and at the end of dosing. Blood samples were taken for hematologic and clinical chemistry evaluation during weeks 14 and 27. Urine was collected for urinalysis according to the same time schedule. At necropsy, tissue samples from Achilles tendons and both shoulder, knee,

cubital, and hip joints (bone and cartilage) were taken for microscopic analysis along with the tissues listed on the histopathology check list.

Blood samples for toxicokinetics (5 rats/sex per time point) were taken on days 1, 31, and 184 of the study. For the 20 mg/kg group, blood was drawn 10 minutes and 6 hours after administration of drug; the other dose groups were sampled 1.5 and 24 hours after dosing. Results of the toxicokinetic analysis were reported separately (below).

Results: There appeared to be no drug-related mortality in the study. Except for one female at 500 mg/kg where a cause of death was not determined from the necropsy findings, the other rats that died during the study (one female each from the vehicle and 20 mg/kg groups, one male and one female at 100 mg/kg, and one male and two females at 500 mg/kg) did so due to dosing or blood collection accidents.

Few drug-related clinical signs were observed during the study. Several animals at 500 mg/kg experienced increased salivation at the time of drug administration. Increased water intake (generally at the beginning of the study) was seen in about half of the 100 mg/kg males and almost all of the 500 mg/kg rats of both genders. Increased fecal excretion was seen in all 500 mg/kg rats.

Body weight gain was reduced in the 500 mg/kg rats compared to control. At the end of the study, the males in the 500 mg/kg group weighed about 7% less than controls and the females weighed about 11% less. Food consumption, however, was not reduced in any of the moxifloxacin-treated rats, including the 500 mg/kg rats.

Ophthalmological examination (ophthalmoscopy and slit lamp) did not reveal any changes related to moxifloxacin. Treatment related differences in hematologic parameters were not observed.

In the male rats, a slight increase in mean AST was observed during week 14 at 100 and 500 mg/kg. At week 27, a slight increase in both mean AST and ALT was seen in the 100 mg/kg males, but a much greater increase was seen in these serum liver enzymes in the 500 mg/kg males. Comparable increases were not observed in the females at these dose levels. Additionally, a modest elevation in alkaline phosphatase was seen in males at 100 mg/kg during weeks 14 and 27, with greater increases at 500 mg/kg. In females, there was a modest increase only at 500 mg/kg during week 27. Finally, increased mean lactate dehydrogenase levels were seen in the 500 mg/kg males during week 27, as was a slight increase in total bilirubin.

Urinalysis did not reveal any drug-related adverse effects. The rats in the 500 mg/kg group tended to excrete less, but more concentrated urine than the other rats (statistically significant only for the females during week 27). This is likely a consequence of the increased fecal excretion and occasional diarrhea in this group- intestinal loss of water is greater, so the kidneys don't need to excrete as much water.

Homogenized liver samples from the rats were analyzed for N-demethylase (NDM), O-demethylase (ODM), and cytochrome P-450. The amounts of NDM and ODM in liver tissue from male rats in the 100 and 500 mg/kg dose groups was significantly, but modestly reduced compared to control (NDM: control, 116 mU/g; 100 mg/kg, 91.1 mU/g; 500 mg/kg, 85.7 mU/g; ODM: control, 8.7 mU/g; 100 mg/kg, 5.8 mU/g; 500 mg/kg, 5.8 mU/g). In females, the amount of cytochrome P450 was slightly increased in drug-treated rats compared to controls and in males the amount of cytochrome P450 was slightly decreased compared to controls. However, the

differences were relatively small and the reviewer is not convinced that they have biological significance.

Gross necropsy did not reveal any drug-related findings. Mean relative organ weights did not differ between groups in a biologically significant manner. Reduced mean absolute weights of some organs in 500 mg/kg females were clearly related to the reduced mean body weight in this dose group. Microscopic examination revealed increased numbers of degenerated hepatocytes (smaller than normal with dark eosinophilic cytoplasm and small dense nuclei) or diffuse single cell necrosis in 6/20 females (graded minimal) and 11/20 males (graded minimal to moderate) in the 500 mg/kg dose group. Slightly increased numbers of multinucleated hepatocytes were also observed in the 500 mg/kg group (5/20 males, 3/20 females). All males in this dose group also had a reduced amount of periportal fat (probably related to the decreased body weight gain in this group), compared with 6/20 control males. Although thyroid changes were not observed in female rats at doses up to 500 mg/kg, 6/20 males in this high dose group had small follicles in the thyroid that contained little colloid. Hypertrophy of follicular epithelium was observed at a greater incidence in 500 mg/kg male rats than controls (14/20 vs. 4/20), as was colloidal alteration (12/20 vs. 5/20). The thyroid changes in the male 500 mg/kg rats were graded minimal to slight.

The NOEL in this 6-month oral moxifloxacin study was 20 mg/kg for male rats and 100 mg/kg for females. Male rats at 100 mg/kg demonstrated slight increased serum liver enzymes (ALT and AST) at the end of the study, although there were no microscopic liver changes observed in this group. Males at 500 mg/kg had greater increases in both of these serum enzymes. A number of males and females in this dose group exhibited degeneration of hepatocytes or diffuse single cell necrosis in their liver tissue with the changes tending to be more pronounced in the males. Several male and female 500 mg/kg rats had multinucleated hepatocytes. Minimal to slight microscopic thyroid changes were observed in some 500 mg/kg male rats, but not females. Body weight gain was reduced in the rats from the 500 mg/kg dose group compared to controls.

BAY 12-8039: Plasma Concentrations in Wistar Rats After Oral Administration in a Chronic Toxicity Study (Bayer Report No. PH 27201; Study No. T 6061298)

C. Kohlsdorfer, K.H. Leser (Bayer, Wuppertal, Germany)

Report dated: 2/12/98

Vol. 20, pp. 1-34

Summary: ~~This is~~ the toxicokinetics report for the 6 month rat study (directly above). Blood samples were drawn on days 1, 31, and 184 ten minutes and 6 hours after administration of drug for the 20 mg/kg group and 1.5 and 24 hours after dosing for the 100 and 500 mg/kg groups. Plasma concentrations were lower for female rats than males.

**Mean Moxifloxacin Plasma Concentrations ($\mu\text{g/ml}$) in
Male and Female Rats After Oral Administration**

	Day 1		Day 31		Day 184	
	Male	Female	Male	Female	Male	Female
20 mg/kg						
10 minutes	0.624	0.252	0.987	0.331	1.48	0.490
6 hours	0.102	BLQ	0.213	0.011	0.288	0.011
100 mg/kg						
1.5 hours	2.14	0.495	2.49	0.301	3.18	0.822
24 hours	0.025	*	0.143	**	0.074	***
500 mg/kg						
1.5 hours	11.0	2.80	7.48	1.67	10.3	4.01
24 hours	0.325	****	0.909	0.007	1.34	0.069

BLQ, below limit of quantification

*2/5 BLQ, others 0.005-0.022 $\mu\text{g/ml}$

**3/5 BLQ, others 0.030 and 0.006 $\mu\text{g/ml}$

***2/5 BLQ, others 0.009-0.037 $\mu\text{g/ml}$

****3/5 BLQ, others 0.014 and 0.033 $\mu\text{g/ml}$

BAY 12-8039: Plasma Concentrations of Metabolite M-1 (BAY 31-8061) and M-2 in Wistar Rats After Oral Administration in a Chronic Toxicity Study (Bayer Report No. PH 27201A)

C. Kohlsdorfer, K.H. Leser (Bayer, Wuppertal, Germany)

Report dated: 9/28/98

Vol. 48, pp. 173-231

Summary: This is an amendment to the toxicokinetics report for the 6 month rat study (directly above). M1 is the sulfate conjugate of moxifloxacin and M2 is its glucuronide.

**Mean M1 and M2 Plasma Concentrations ($\mu\text{g/ml}$) in
Male and Female Rats After Oral Administration**

	Day 1		Day 31		Day 184	
	M1	M2	M1	M2	M1	M2
Males						
20 mg/kg						
10 minutes	0.169	0.821	nc	1.28	0.255	1.97
6 hours	<0.025	0.138	nc	0.163	Nc	0.121
100 mg/kg						
1.5 hours	0.414	1.82	0.060	1.46	0.628	2.05
24 hours	<0.025	0.034	<0.025	0.039	Nc	0.052
500 mg/kg						
1.5 hours	0.307	8.46	0.311	4.47	1.56	5.38

24 hours	Nc	0.339	nc	0.463	0.597	1.18
Females	M1	M2	M1	M2	M1	M2
20 mg/kg						
10 minutes	0.236	1.07	0.350	1.32	1.14	1.27
6 hours	<0.025	0.066	<0.025	0.056	Nc	0.050
100 mg/kg						
1.5 hours	0.227	1.10	0.124	0.531	0.606	1.05
24 hours	<0.025	0.031	<0.025	0.027	Nc	0.037
500 mg/kg						
1.5 hours	0.976	4.22	0.634	2.55	3.84	4.90
24 hours	<0.025	nc	<0.025	nc	0.085	0.152

Higher levels of M1 were observed in females compared to males, while males often had higher levels of M2 in their plasma. Larger amounts of M1 were seen at the end of the study than after the first dose. Levels of M2 were greater than M1 and the amount of M2 did not change over the course of the study.

BAY 12-8039: Subacute Oral Toxicity Study in Beagle Dogs (4 Week Capsule Study) (Bayer Report No. PH 27061; Study No. T 9061264)

J. Ruf, V. Geiß (Bayer, Wuppertal, Germany)

Report dated: 1/23/98, [REDACTED]

Vol. 21, pp. 1-344

Animals: Male and female beagle dogs, 19-23 weeks old, 5.9-9.1 kg, 4/sex per treatment group

Diet: [REDACTED] pellets (300 g/day) were offered 2 hours after the daily drug administration. Tap water was available at all times.

Drug Dose and Route of Administration: Moxifloxacin (Batch No. 960704A) in gelatin capsules was administered orally once per day at doses of 0 (empty capsules), 10, 30, or 90 mg/kg for 28-29 days.

Length and Conduct of Study: Drug was given daily for 28 or 29 days and animals were sacrificed on day 29 or 30 (one day after final administration). Food intake was estimated daily. Body weights were measured weekly. Reflexes (pupillary, corneal, patellar, extensor, postural, and flexor) were tested prior to dosing and during week 4. Ophthalmic examination and measurement of body temperature. Hemotologic and clinical chemistry evaluations and urinalysis (6 hour collection period in individual metabolism cages after gavage administration of 250 ml water) were performed prior to the initiation of the study and during weeks 2 and 4 of dosing. EKG and blood pressure measurements were performed prior to the initiation of dosing, and immediately before and 2 hours after moxifloxacin dosing during weeks 1 and 4 of the study. On the first day of dosing and during week 4, plasma for toxicokinetic analysis was drawn from

the dogs prior to administration of moxifloxacin, then 2, 4, 7, and 24 hours after dosing. The results of the toxicokinetics portion of this study have been reported separately. At necropsy, tissue samples from both shoulder, knee, cubital, and hip joints were taken for microscopic analysis along with the tissues listed on the histopathology check list.

Results: One female in the 90 mg/kg dose group was sacrificed early (during week 2 of the study) due to poor general condition thought to be related to moxifloxacin administration. This animal exhibited reduced food consumption and reduced body weight prior to sacrifice.

In the 10 and 30 mg/kg dose groups, no reductions (compared to controls) in food consumption or body weight were observed. In the surviving dogs from the 90 mg/kg group, occasional reductions in daily food consumption were noted, but mean body weights did not significantly differ from control. However, a male in this group was felt by the investigator to have "meager" nutritional status by the end of the study.

Salivation and vomiting were observed in some dogs at 90 mg/kg. Dose-dependant bending of the forepaws was seen in one dog at 10 mg/kg and in greater numbers at 30 and 90 mg/kg. There were no moxifloxacin-related changes in reflex measurements at 10 or 30 mg/kg, but the extensor-postural-flexor reflex could not be measured in one male and one female animal (besides the female that was sacrificed early) during week 4 of the study due to the severity of the bent forepaws in these dogs.

No drug-related changes in body temperature, heart rate, or blood pressure were observed in the dogs. During week 1, there was a tendency toward prolongation of the QT interval in 90 mg/kg males. This type of QT effect was seen in the 90 mg/kg females during week 4. Although the prolongations were slight, the investigators believed them to be drug-related in light of other information available on moxifloxacin cardiac effects. The EKG measurements were performed 2 hours after dosing at what the sponsor assumed would be around C_{max}, but C_{max} may not necessarily have occurred 2 hours after dosing in all or any of the animals. Concurrent plasma moxifloxacin measurements were not taken at the time of EKG.

Ophthalmic examination did not reveal drug-related changes in the 10 and 30 mg/kg dogs. In all surviving dogs from the 90 mg/kg group, vacuolization of the subcapsular cortex in the lens was observed.

No moxifloxacin-related changes in mean hematologic parameters were observed in any of the treatment groups. In one female dog from the 90 mg/kg group, ALT and glutamate dehydrogenase levels were elevated during week 2 of treatment; however, the levels of both of these enzymes were at normal levels when measured at the end of week 4. No other changes in clinical chemistry parameters were observed in the dogs. One female in the 90 mg/kg group had a slight elevation of cytochrome P450 in its liver tissue. The levels of N-demethylase, O-demethylase, and cytochrome P450 were similar in liver tissue from the other dogs, regardless of dose group.

Urinalysis did not reveal significant drug-related changes. Some females in the 90 mg/kg group had a small amount of protein in their urine samples, but this is of questionable significance in the absence of other changes, including microscopic changes in the kidney.

Absolute and relative spleen weights were increased in females from the 90 mg/kg group and absolute and relative thyroid weights were increased in females given 30 and 90 mg/kg of moxifloxacin. No drug-related histopathologic changes in these organs were observed, however. Gross changes in the surface (roughening and/or blisters) of articular cartilage could be observed

at one or more locations in all of the 90 mg/kg dogs and increased synovial fluid was also observed in some of the joints. Microscopic examination of the joint tissue revealed the characteristic quinolone-induced degeneration of articular cartilage. Moxifloxacin-induced chondropathy was also observed microscopically in the right scapula of 1/4 female dogs from the 30 mg/kg group. A greater incidence and severity of matrix and chondrocyte degeneration at the epiphyseal plate of several bones was observed in 90 mg/kg dogs compared to animals from the other groups (slight degeneration at an epiphyseal plate was seen in a few dogs from each treatment group, including controls). Slight thymus atrophy was seen in 2 females from the 90 mg/kg dose group. One of these animals was the female in emaciated condition that had to be sacrificed during week 2 and the thymus atrophy could be related to the poor condition of the dog. As this finding has been observed in control animals, it may not be specific to moxifloxacin treatment.

The NOAEL in this 4-week oral moxifloxacin study in beagle dogs was 10 mg/kg. One female animal in the 90 mg/kg group had to be sacrificed early due to emaciation. Clinical signs of toxicity observed at 90 mg/kg included salivation and occasional vomiting. All of the dogs in this dose group and one in the 30 mg/kg group demonstrated moxifloxacin-induced joint lesions. EKG evaluation suggested slight QT prolongation in the dogs 2 hours after a moxifloxacin dose of 90 mg/kg. Examination of the eyes revealed vacuolization of the subcapsular cortex in the lens in all surviving dogs from the 90 mg/kg group.

BAY 12-8039: Plasma Concentrations in Beagle Dogs After Oral Administration in a Subacute Toxicity Study (Bayer Report No. PH 26778)

C. Kohlsdorfer, J. Ruf (Bayer, Wuppertal, Germany)

Report dated: 10/30/99

Vol. 22, pp. 1-36

Summary: This is the toxicokinetics report for the 4 week beagle study (directly above). Blood samples were drawn on days 1 and 24 prior to dosing as well as 2, 4, 7, and 24 hours after administration. Plasma concentrations were similar in male and female animals, so the data were combined. The half life for moxifloxacin (calculated for day 1 only) was 6-8 hours in the dogs.

Mean Toxicokinetic Parameters in Beagle Dogs After Moxifloxacin Dosing

	10 mg/kg	30 mg/kg	90 mg/kg
Day 1			
AUC ₀₋₂₄ (µg·hr/ml)	18.9	72.4	146
C _{max} (µg/ml)	2.11	7.03	12.5
T _{max} (hr)	2.97	3.31	2.55
Day 24			
AUC ₀₋₂₄ (µg·hr/ml)	24.0	84.4	196
C _{max} (µg/ml)	2.19	8.12	16.4
T _{max} (hr)	2.38	3.36	4.52

Special Toxicity Studies:

BAY 12-8039: Subacute Toxicity Study in Beagle Pups (4 Week Capsule Study) (Bayer Report No. PH 26506; Study No. T 4060675)

J. Ruf, V. Geiß (Bayer, Wuppertal, Germany)

Report dated: 1/18/97, [redacted]

Vol. 22, pp. 37-299

Animals: Male and female beagle pups, 2/sex/group, 11-13 weeks old and 3.9-5.9 kg at the initiation of dosing, group housed in one room

Diet: [redacted] pellets were available *ad libitum* 2 hours after the daily drug administration. Water was available at all times.

Drug Dose and Route of Administration: Moxifloxacin (Batch No. 950710A) in gelatin capsules was administered orally once per day at doses of 0 (empty capsules), 10, 30, or 90 mg/kg for 28 days.

Length and Conduct of Study: Drug was given daily for 28 days and animals were sacrificed on day 29. Body weights were measured weekly. Food consumption was not determined. Reflexes (pupillary, corneal, patellar, extensor, postural, and flexor) were tested prior to dosing and during week 4. Ophthalmic examination, measurement of body temperature, urinalysis (6 hour collection period in individual metabolism cages), hemotologic, and clinical chemistry evaluations were also performed at these times. On the first day of dosing and during week 4, plasma for toxicokinetic analysis was drawn from the dogs prior to administration of moxifloxacin, then 2, 4, 7, and 24 hours after dosing. The results of the toxicokinetics portion of this study have been reported separately. At necropsy, tissue samples from both shoulder, knee, cubital, and hip joints were taken for microscopic analysis along with the tissues listed on the histopathology check list.

Results: One female in the 90 mg/kg dose group was sacrificed during week 3 of the study due to its poor condition. This animal lost weight from week 2 to week 3 of the study after an initial weight gain.

Clinical signs of toxicity were not observed in the 10 or 30 mg/kg groups, but vomiting, salivation, and joint problems (starting during week 2) were seen in the 90 mg/kg dogs. The dogs in the 90 mg/kg group weighed less than the other dogs during the last 2 weeks of the study. Body weight gain was reduced in these dogs compared to controls and to the other dose groups. At gross necropsy, both female 90 mg/kg dogs and one female 30 mg/kg dog had reduced body fat compared to the other animals.

Reflex testing did not reveal any abnormalities. Body temperatures were within the normal range for beagles. Ophthalmoscopy did not reveal drug-related ocular changes.

Hematologic parameters in peripheral blood did not appear to differ between the treatment groups, despite the histopathological finding of bone marrow suppression in some high dose dogs. Few differences were observed between the dogs with regard to serum chemistry. The 90 mg/kg female dog that was sacrificed early had slight decreases in serum protein and albumin and also had a decreased T4 level. The other female in this group also had slightly reduced serum albumin. The small reductions in protein and albumin may be related to the decreased nutritional state of these dogs. One of the males in the 90 mg/kg group had a slightly higher level of cytochrome P450 than controls. Urinalysis did not reveal any drug related changes in the dogs except that the 90 mg/kg female dog that was sacrificed early had elevated urinary protein in a sample collected during week 2 of treatment (the last specimen available for this dog). It should be noted that the volume for this specimen was relatively low.

Absolute organ weights tended to be lower in the 90 mg/kg group (especially the females) than control. Gross pathology revealed blisters in the articular cartilage of all 90 mg/kg dogs and one male in the 30 mg/kg group had blisters at a hip joint. Histopathology revealed the characteristic chondropathy associated with quinolone-induced lesions. Microscopy also revealed multifocal cartilage alterations (matrix degeneration and chondrocyte degeneration) in the epiphyseal plates of the 90 mg/kg dogs. A control male had a dark red area in the cartilage of the right scapula. Microscopic examination showed a shallow pit in the cartilage that did not resemble the quinolone-induced lesions in the other dogs. Focal degeneration of apophyseal cartilage was observed in the cartilage of the scapula and hip in dogs from all dose groups, including controls. The pathologist believed this to be related to the remodeling of bone and cartilage that occurs as the animals grow. Bone marrow hypocellularity associated with sinusoidal hyperemia was observed in several locations in the 90 mg/kg female that was sacrificed early as well as in 1-2 locations (e.g., sternum, scapula, tibia) in the second female and also a male from this dose group. Bilateral cortical degeneration of the lenses was seen in one 90 mg/kg female dog, but the pathologist indicated that the finding was consistent with delayed or disturbed fiber maturation that can be an inherited disorder. The pathologist did not believe that this finding was drug-related and no lenticular changes were observed in the other dogs from this dose group. The 90 mg/kg female dog that was sacrifice early also had esophageal erosions and splenic, thymic, and lymphatic atrophy that was theorized to have been secondary to the poor physical and nutritional condition of the animal.

The NOAEL for 4 weeks of daily oral moxifloxacin doses to juvenile beagles was 10 mg/kg. Dose-related increases in the incidence and severity of quinolone-induced arthropathy were seen at 30 and 90 mg/kg. Clinical signs of moxifloxacin toxicity such as vomiting and salivation were observed at 90 mg/kg and body weight gain was reduced in this group compared to controls. Bone marrow toxicity was also observed at 90 mg/kg and one female at this dose level had to be sacrificed early due to poor condition.

Determination of the Excitatory Potential of BAY 12-8039 *in vitro* in the Hippocampus Slice Model (Bayer Report No. PH 27002)

G. Schmuck (Bayer, Wuppertal, Germany)

Report dated: 1/8/98,

Vol. 29, pp. 32-47

Summary: Brains were removed from young adult female rats and 450 μm slices were cut from the middle of the hippocampus. The slices were incubated in artificial cerebrospinal fluid at room temperature for 1-2 hours before *in vitro* testing began. Experiments were performed at 34°C and electrical stimulation was used to stimulate the tissue. Recordings of the activity of the pyramidal cell layer were measured using glass electrodes. After 30 minutes of electrical stimulation (10 pulses with a pulse width of 200 μsec , a pulse interval of 10 sec, and electric tension of 3-8 V) the baseline activity was recorded. Next, test compound (moxifloxacin, ciprofloxacin, or trovafloxacin) was added to a concentration of 0.5-4 μM , electrical stimulation continued, and the activity of the pyramidal cells were observed for another 30 minutes. This was followed by washout of the drugs and another 30 minute stimulation/observation period in drug-free artificial cerebrospinal fluid.

Trovafloxacin was much more excitatory to the pyramidal cells than either moxifloxacin or ciprofloxacin. Trovafloxacin increased the amplitude of the spikes demonstrating pyramidal cell activity by 270% above baseline at a concentration of 2 μM . The test system could not tolerate 4 μM trovafloxacin. At 4 μM , moxifloxacin and ciprofloxacin increased the amplitude of the pyramidal spikes by 180% and 191% above baseline, respectively.

In this rat hippocampal slice model, moxifloxacin demonstrated an excitatory potential similar to ciprofloxacin and much less than trovafloxacin.

***In vitro* Effects of BAY 12-8039 (Irradiated and Non-Irradiated) on Cultured Astrocytes and Cortex Neurons of the Rat (Bayer Report No. 24940)**

G. Schmuck (Bayer, Wuppertal, Germany)

Report dated: 3/27/96, [REDACTED]

Vol. 29, pp. 48-76

Summary: Primary neuronal cell cultures were prepared from the cerebral cortices of rat fetuses. Astrocytes were isolated from rat fetal brains and put into culture. Both types of cultures were incubated for 3, 5, or 7 days with moxifloxacin (non-irradiated drug and irradiated drug) at concentrations of 0.01, 0.1, 0.5, 1 and 10 $\mu\text{g/ml}$. Cell viability of the cultures was determined using a [REDACTED] solution followed by fluorescence detection and also by measuring conversion of yellow MTT dye to purple by mitochondrial dehydrogenase in viable cells. Acetylcholinesterase levels in the cultures were also measured, as were the amounts of choline acetyltransferase activity. [REDACTED] methods were used to identify cytoskeleton components (e.g., neurofilaments) and measure the levels of a variety of neurotransmitters and their metabolizing enzymes (e.g., dopamine, glutamic acid, GABA, serotonin) in the cultured neuronal cells.

Irradiation of moxifloxacin (unspecified type and amount) did not appear to affect the results of these assays. As determined by the MTT assay, moxifloxacin caused reduced viability of the cultured astrocytes beginning on day 3 of incubation at 1 $\mu\text{g/ml}$ (81.3% of control). The other viability assay did not demonstrate any moxifloxacin-induced effects on either astrocytes or

neuronal cell cultures. The levels of acetylcholinesterase or choline acetyltransferase in the cells was not affected by moxifloxacin, nor were any of the neurotransmitters, metabolizing enzymes or cytoskeleton elements measured by [redacted]

In the absence of any positive controls, historical or comparative data for these assays, the pharmacologist does not find the results to be particularly meaningful with regard to the neurotoxic potential of moxifloxacin.

A Cytotoxicity Study of BAY 12-8039 in Cultured Mammalian Cells (Bayer Report No. R 6982; Study No. SBL 95-44)

[redacted]

Report dated: 1/12/96

Vol. 29, pp. 94-120

Summary: The cytotoxicity of BAY 12-8039 to several lines of cultured mammalian cells (CHL/TU, HeLa, and L929) was determined. The methods of determining cytotoxicity were crystal violet staining, neutral red uptake, and measurements of LDH leakage. The concentrations of BAY 12-8039 used in the studies were 7.8, 15.6, 31.3, 62.5, 125, 250, and 500 µg/ml.

The IC₅₀ concentration for moxifloxacin-induced growth inhibition in the [redacted]

[redacted] Moxifloxacin did not induce the leakage of LDH from any of the cell lines.

The point of this study is not clear to the pharmacology reviewer.

BAY 12-8039: Combined Single-Dosage and Seven-Day Oral Phototoxicity Study in Hairless Mice [redacted] (Bayer Report No. MRC-00908; Study No. 1702-001)

[redacted]

Report dated: 10/15/98, [redacted]

Vol. 30, p. 1- Vol. 32, p. 391

Animals: Male and female albino hairless mice (CrI:SKH1-hrBR), approximately 8 weeks of age at the initiation of the study, 12 per treatment group for phototoxicity testing, 4 satellite mice per time point in each drug treatment group for analysis of moxifloxacin or lomefloxacin in blood and skin. Mice were individually housed and fluorescent [redacted] lamps [redacted] [redacted] were used in animal rooms to limit their exposure to UVR.

Diet: [redacted] and tap water (purified via reverse osmosis with

chlorine added as a bacteriostat) were supplied *ad libitum*, except that food was not available for 4 hours prior to administration of drugs.

Drug Dose and Route of Administration, UVR Exposure and Length/Conduct of Study:

Moxifloxacin (Lot No. 501578) and lomefloxacin were suspended in 0.5% carboxymethyl cellulose for oral administration at a dose volume of 50 ml/kg. Mice in the single dose phototoxicity study received one dose of vehicle, moxifloxacin (30, 100, or 300 mg/kg), or lomefloxacin (30 or 200 mg/kg) followed by UVR exposure (400 RBU of simulated sunlight, equivalent to about 1 minimal erythemal dose- total exposure lasted about 1 hour) starting 20 ± 5 minutes after administration. Mice in the 7 day phototoxicity study received 7 consecutive daily oral doses of vehicle, moxifloxacin (10, 30, or 100 mg/kg), or lomefloxacin (30 or 200 mg/kg) followed by UVR exposure (300 RBU of simulated sunlight- total exposure lasted about 45 min) starting 20 ± 5 minutes after administration. The 200 mg/kg lomefloxacin + UV exposure had to be stopped after 3 days instead of 7 due to severe skin reactions. Mice were observed for up to 14 days after the initiation of exposure to drugs and UVR and their skin responses evaluated daily. Skin thickness was measured at 3 sites per mouse prior to drug/UVR exposure, then on days 3, 5, 7, and 14. Mice were sacrificed on day 14 of the study, and skin samples were harvested for histopathological analysis (shipped in 10% buffered formalin to [redacted])

The radiation source was a [redacted] was used to attenuate UVB radiation. A solar light detector was used to monitor the amount of UVR.

Skin reactions were graded as follows:

- Erythema: 1 = barely perceptible light redness
 2 = distinct redness
 3 = "beet red" color
- Edema: 1 = mild, raised < 1 mm
 2 = moderate, raised 1-2 mm
 3 = marked, raised > 2 mm
- Flaking: 1 = barely perceptible *scales*
 2 = distinct *scales*
 3 = pronounced flaking with *denuded* sites

scale defined as "small, thin dry exfoliation shed from the upper layer of skin"
denude defined as "to remove the protective layer"

Mice (4/sex/group/time point) were sacrificed 5, 30, 60, and 90 minutes after the final dose of drug was given and blood (plasma) and skin samples were collected for analysis of drugs using a validated [redacted] In the case of the 200 mg/kg lomefloxacin repeat dose mice, skin and plasma samples were harvested on day 14.

Toxicokinetic groups were as follows:

1. 30 mg/kg moxifloxacin + UVR, single dose
2. 300 mg/kg moxifloxacin + UVR, single dose
3. 300 mg/kg moxifloxacin, no UVR, single dose
4. 30 mg/kg lomefloxacin + UVR, single dose
5. 200 mg/kg lomefloxacin + UVR, single dose
6. 10 mg/kg moxifloxacin + UVR, 7 doses
7. 100 mg/kg moxifloxacin + UVR, 7 doses
8. 100 mg/kg moxifloxacin, no UVR, 7 doses
9. 30 mg/kg lomefloxacin + UVR, 7 doses
10. 200 mg/kg lomefloxacin + UVR, 3 doses

Results: In the single dose study, one female mouse in the 30 mg/kg moxifloxacin group was moribund sacrificed on day 13. In the 7 day study, one male in the 10 mg/kg moxifloxacin group was found dead on day 5, one female in the 30 mg/kg lomefloxacin group was found dead on day 5, and one male and one female in the 200 mg/kg lomefloxacin group were found dead on day 10. The investigators did not believe that any of these deaths were related to drugs because they did not occur in a dose-related fashion in the moxifloxacin-treated mice and these doses of lomefloxacin are often used in this laboratory without mortality. Additionally, clinical signs of drug toxicity were not observed in this study. Changes in group mean body weights compared to controls were not observed in the drug-treated mice.

Single doses of 30, 100, or 300 mg/kg moxifloxacin with simulated sunlight exposure were not associated with phototoxic skin responses. Some skin changes including erythema, edema, or flaking (all grade 1 responses) and slight thickening were seen in a few mice from all dose groups including controls starting about 2 days after dosing and UVR and are the consequence of the exposure to simulated sunlight. A skin ulcer was seen on day 9 on one female 100 mg/kg moxifloxacin mouse, but not on day 10 and it did not appear to indicate a phototoxic response. Skin thickening was more pronounced in the mice given single doses of 200 mg/kg lomefloxacin. Dose-dependant increases in erythema, edema, and flaking were seen in the lomefloxacin-treated mice, ranging from grade 1-3 in severity (mostly the higher grades). Ulceration and scabs were also observed in some of animals.

Seven days of dosing with 10, 30, or 100 mg/kg of moxifloxacin with daily exposure to simulated sunlight was not associated with phototoxic skin responses. Again, there were some skin changes that were seen in mice from all dose groups including controls that are the consequence of simulated sunlight exposure. These included erythema (grade 1 observed in a few mice, grade 2 seen in one control mouse), edema (mostly grade 1, some grade 2), and flaking (grade 1). Skin thickening was not greater in the moxifloxacin-treated mice than controls, but it was significantly greater in both groups of lomefloxacin-treated mice. The 200 mg/kg lomefloxacin dose with UVR could only be continued for 3 days instead of the planned 7 days due to the severity of the phototoxic skin reactions. Dose-dependant increases in erythema, edema, and flaking were seen in these mice, ranging from grade 1-3 in severity (erythema and edema frequently progressing to the higher grades). Ulceration and scabs were also observed in several of these lomefloxacin-treated mice (especially at the higher dose) and a skin tumor was seen in one female mouse from the 30 mg/kg lomefloxacin group on days 13 and 14.

Microscopic examination of skin samples revealed no difference between moxifloxacin-treated animals and vehicle controls. Skin changes that were observed in all of these groups

included epidermal thickening associated with minimal to mild hyperplasia and hyperkeratosis, sebaceous gland hyperplasia, and occasional focal areas of inflammatory cell infiltration in the dermis. These changes are the consequence of UVR exposure. In contrast, skin samples from lomefloxacin-treated mice showed marked thickening of the epidermis secondary to hyperplasia and hyperkeratosis (greater severity than seen with the vehicle or moxifloxacin-treated mice), increased dermal inflammation, and invagination and dilation of the hair follicle remnants with keratin accumulation. In some lomefloxacin-treated mice, the skin changes were so severe that sebaceous glands could not be identified.

Both moxifloxacin and lomefloxacin could be found in the skin during the irradiation period and skin levels were usually higher than plasma levels. The lomefloxacin data indicate that this drug remained in the skin for over a week after the completion of dosing. The range of drug levels in the skin and plasma of the mice are presented in the following table:

**Concentrations of Moxifloxacin or Lomefloxacin in Skin ($\mu\text{g/g}$)
or Plasma ($\mu\text{g/ml}$) of Hairless Mice from 5-90 Minutes After Oral Administration**

Treatment Group	Skin				Plasma			
	Conc. Range		Tmax (min)		Conc. Range		Tmax (min)	
	M	F	M	F	M	F	M	F
Moxifloxacin Single Dose								
30 mg/kg			5	5			5	5
300 mg/kg			90	30			5	30
300 mg/kg (no UVR)			30	90			5	5
Moxifloxacin 7 Days								
10 mg/kg			5	5			5	5
100 mg/kg			30	5			30	5
100 mg/kg (no UVR)			5	30			5	5
Lomefloxacin Single Dose								
30 mg/kg			5	5			5	5
200 mg/kg			5	5			5	5
Lomefloxacin 3-7 Days								
30 mg/kg			5	5			5	5
200 mg/kg*			---	---			---	---

*Skin and plasma harvested on day 14 of the study, not after last dose was given
BLQ, below limit of quantification

Moxifloxacin was not phototoxic when given to hairless mice at a single dose up to 300 mg/kg or 7 days of dosing up to 100 mg/kg accompanied by simulated sunlight exposure. The

positive control, lomefloxacin, induced characteristic phototoxic responses under these conditions.

A Repeated Dose Oculotoxicity Study of BAY 12-8039 Administered Orally to Beagle Dogs for 2 Weeks (Bayer Report No. R 7274; Study No. SBL 96-11)

Report dated: 10/8/98,

Vol. 36, pp. 1-55

Summary: Groups of 4 adult male beagle dogs (12-18 months old, 8.2-13.4 kg) received oral doses (powder in gelatin capsules) of moxifloxacin (Batch No. 502601) at doses of 30, 60, or 90 mg/kg or nalidixic acid at 100 mg/kg once daily for 2 weeks. Two of the 90 mg/kg animals were kept for an additional 8 week drug-free period to assess the reversibility of toxicity. Ophthalmic examinations including electroretinography (ERG) were performed in all dogs twice before the initiation of dosing, on days 2, 5, 8, and 11 during the period of administration (before the daily dose was given), and on the day after the end of the dosing period. These examinations were performed in the recovery group dogs at the end of weeks 1, 2, 4, 6, and 8 of the recovery period.

No mortality was observed during the study, but vomiting and salivation were observed in all 90 mg/kg moxifloxacin dogs and vomiting was seen in all 60 mg/kg moxifloxacin dogs. Vomiting and salivation were also seen in the nalidixic acid dogs and additional signs observed in some of these animals included soft stool, bloody stool, decreased spontaneous activity, loss of appetite, and prone position. Decreases in body weight were observed in 2 high dose moxifloxacin dogs and in 3 nalidixic acid dogs.

Slow pupillary light reflex was seen in one dog each from the 60 and 90 mg/kg moxifloxacin groups and in 2 dogs from the nalidixic acid group. This persisted into the recovery period in one of the 90 mg/kg dogs. One of the nalidixic acid dogs also had a red conjunctiva. Slit lamp and funduscopic examinations did not reveal abnormalities at any time during the study. Electroretinography showed changes (e.g., reductions in a- and/or b-wave latency or amplitude) in one dog from the 60 mg/kg group beginning on day 5 of dosing and two dogs from the 90 mg/kg group beginning on day 2 of dosing. Changes were also observed in the nalidixic acid dogs, but they were less severe. The ERG changes appeared to recover somewhat during the drug-free 8 week period, but they did not return to normal levels.

Histopathologic examination of the eyes revealed slight to marked atrophy of the outer nuclear, outer plexiform, and rod and cone layers in the retina of one animal of the 90 mg/kg group that was sacrificed immediately after the dosing period. This was one of the dogs that had marked ERG changes. Similar changes, graded slight to moderate were also observed in one of the 90 mg/kg dogs assigned to the recovery group. This was also an animal that had exhibited marked ERG changes and had slow pupillary light reflex persisting into the recovery period. None of the other animals demonstrated histopathologic abnormalities of the eyes or optic nerves.

The NOAEL for ophthalmic changes (including ERG) in this 2 week oral moxifloxacin dog study was 30 mg/kg. Histopathological changes in the retina were observed in the 90 mg/kg