Further clinical information was requested from the sponsor on each of these patients to address the possibility of a drug-induced hepatitis. The cases are described in more detail below.

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Table 26: Clinical description of patients with severe LFT derangements as identified in table 25

PT ID	UNDERLYING CONDITIONS	CONCOMITANT MEDICATIONS	STUDY TREATMENT	ADVERSE EVENTS	ADVERSE EVENT OUTCOME	DATE OF LABS	SGOT	SGPT	BILIRUBIN
140 / 10716	Myocardial infarction Ischemic heart disease Maxillary fracture Hypothyroidism Phlebectasis based on venous insufficiency Arterial hypertension cholecystolithiasis	Furosemide [redacted] Digoxin [redacted] Torecan [redacted]	400mg moxifloxacin (4/5/98 – 4/15/98)	Left ventricular (heart) Biliary colic Hypohydratation	Resolved for all	4/4/98 4/6/98 4/9/98 4/17/98 5/6/98	25 53 46 302 25	17 30 35 194 20	1.4 1.4 5.2 1.1 1.1
118 / 504	PID	NONE	400mg moxifloxacin (10/11/97 – 10/24/97)	Nausea Vomiting Vertigo Elevated SGOT Elevated SGPT Gammaglobulins increased	Resolved for all	10/11/97 10/15/97 10/27/97 10/30/97 11/15/97	35 39 117 92 67	40 34 152 140 78	0.2 0.2 0.5 0.5 0.7
119 / 118	NONE	[redacted] Doxycycline	400mg moxifloxacin (9/23/97-9/29/97)	Pancreatitis Diarrhea	Improved resolved	Pre-tx Day 3 – 5 End of tx 21 – 28 days post	108 684 35 20	42 150 51 14	0.6 0.7 1.2 1.6
121 / 483	Fractured left clavicle Fractured pelvis Adult respiratory distress syndrome Ruptured bladder Ruptured urethra Traumatic urethral stricture Repair of traumatic bladder rupture Urethral stricture	NONE	400mg moxifloxacin (7/28/97 – 8/10/97)	NONE	NONE	7/28/97 8/1/97 8/15/97	45 190 66	60 366 257	0.8 7.2 2.2

122 / 3013	Varicella	Aspirin Acyclovir	500mg cephalexin (12/27/96 - ?)	Hepatitis post varicella	Not Available	12/30/96 1/3/97	109 24	135 55	0.6 1.1
131 / 95	NONE	NONE	500mg cephalexin + metronidazole (12/12/97 – 12/19/97)	NONE		12/11/97 12/16/97	63 191	59 179	0.4 0.8
119 / 501	NONE	Triphasil Voltaren	Clarithromycin 500mg BID	NONE	NONE	Pre Dur End of tx Post	59 402 27 24	81 592 102 -	0.8 1.6 0.7 0.8

Patients 10716 and 483 were noted to have the most severe aberrations of liver function following the use of Moxifloxacin. In both cases, concurrent conditions offered additional explanations for the abnormalities noted. In the first case, cardiac failure and biliray colic appear to have affected the liver function tests. In the second case, the presence of extensive trauma suggest that a "shock liver" might have caused the abnormalities in liver function. Patient 504 did not have other conditions or medications to account for the elevation of transaminases which was probably caused by moxifloxacin. Patient 118 was noted to have an abnormal SGOT prior to treatment and the change in liver function was probably caused by pre-existing liver disease.

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Anemia:

A clinically significant fall in Hemoglobin appeared to be common in Moxifloxacin treated patients. A list was requested from the sponsor of all patients treated with Moxifloxacin or a comparator drug who had a hemoglobin <75% LLN. The difference between the pre-treatment hemoglobin and the minimum hemoglobin measured following the start of drug therapy was calculated for these patients. A treatment emergent a fall in hemoglobin >=1gm was seen in 29 patients, 19 treated with Moxifloxacin and 10 treated with comparator agents. Among the Moxifloxacin treated patients changes in hemoglobin did not appear to correlate with changes in platelet count or LDH as shown below.

Table 27: Treatment emergent changes in hemoglobin, LDH, platelet count creatinine and total bilirubin for patients treated with Moxifloxacin who had a Hb nadir <75% LLN and a treatment emergent fall in Hb>=1gm/dl

HB1-HB2	plat1-plat2	LDH2-LDH1	creat2-creat1	BR2-BR1
1	-23	0	0.1	-0.1
1.1	66	-24	-0.1	0.2
1.2	74	-206	0.5	-1.1
1.2	-26	6	0.8	-0.1
1.4	-194	-117	-0.1	-0.1
1.4	1	51	0.2	-0.4
1.4	40	-7	0.8	0
1.5	10	71	0.3	0.1
1.6	260	-221	0.1	0.4
1.7	0	-20	-0.2	0
1.9	166	-33	0.3	-0.1
1.9	54	14	0.3	0
2.2	-117	908	-0.9	-0.6
2.4	-108	36	0.3	0
2.8	-18	-105	-0.4	0
2.9	12	7	0.3	0.1
4	-30	480	-0.2	0
5.2	46	66	1.5	0.5
5.2	70	-45	0.43	-0.37

Transfusions were not recorded for any of the 19 patients. Medication was discontinued in one. Eleven were reported to resolve or improve, insufficient follow up was recorded in two and follow up information for this AE was unavailable for 5. One patient died and the relationship to treatment was described as remote (study 112 #72). Both patients with a treatment emergent fall in Hb of 5.2gm were nephrostomy patients. The anemia resolved in both and the relationship to drug was listed as "none" in one and "remote" in the other.

Hypoglycemia:

A list was provided of the 17 patients treated with moxifloxacin who developed minimal blood glucose concentrations below 50mg/dl. Two were recorded as receiving concurrent hypoglycemic drugs. Resolution of hypoglycemia was reported in 9, improvement in 1, insufficient follow up in one, and outcome of this adverse event was not reported in 8. Administration of parenteral glucose was not reported in any of these patients. Hypoglycemia <50mg/dl occurred in 12 comparator treated patients. Resolution was reported in 7, and the outcome of the event was not reported in 5. Two received hypoglycemic drugs, and one was treated with parenteral glucose. Hypoglycemic episodes neither appeared to be more severe nor to be associated with less favorable outcomes in patients treated with moxifloxacin compared to those treated with comparator agents.

Vital signs:

Systolic and diastolic blood pressures and heart rate were evaluated before during and after therapy. No significant differences were seen between the 4301 patients in worldwide controlled studies treated with Moxifloxacin, and 3415 controls.

The mean minimum and mean maximum changes in heart rate from baseline were -11.1 [redacted] and +1.2 [redacted] respectively for Moxifloxacin treated patients and -10.67 [redacted] and +0.88 [redacted] for comparator treated patients.

Changes in systolic and diastolic blood pressure were similar for patients treated with moxifloxacin and comparator drugs. (From appendix 1 b table 9 A2)

Drug interactions during phase III studies:
Theophylline:
Of 152 moxifloxacin treated patients with baseline serum theophylline levels <=20mcg/L, 4 (3%) developed elevations >=20mcg/L post treatment. One of these (D96-027, pat 384) experienced nausea and vomiting which the investigator attributed to extra doses of theophylline. Three control patients (4%) treated with clarithromycin developed theophylline levels >=20mcg/L after treatement. Toxic symptoms were not reported in these patients.

Among patients on theophylline who did not report low levels before treatment, 28/117 (24%) of patients treated with moxifloxacin and 15% of the clarithromycin treated controls developed post-treatment theophylline levels <10mcg/L. A single adverse event described as "Drug level increased" was reported in a patient on theophylline, on day 12 of a study using moxifloxacin 200mg QD. The event was of mild intensity, possibly related to study drug and resolved.

MO comment: Theophylline levels were more inclined to fall on treatment than to rise. A non-significant trend supporting this was seen in the phase II drug interaction studies described later.

Warfarin toxicity was not specifically investigated in clinical trials. However 333/2705 (12%) of the moxifloxacin exposed patients with normal pre-study PTs developed elevations of PT after treatment. 54 (2%) had values >=16 seconds. One of these had an adverse event recorded as haemmorhage. Four of the 54 patients with PTs >16 seconds were receiving warfarin.

MO comment: Patients with significant prolongations of PT were more likely not to be receiving warfarin.

Hypoglycemic agents: A total of 281 subjects participating in phase II and III trials were treated with hypoglycemic agents. 13 had glucose levels <=70mg/dl during or at the end of therapy. None of these was associated with clinical symptoms.

Other drugs: Probenecid, digoxin and ranitidine were given respectively to 2, 65 and 25 patients treated with moxifloxacin. A review of adverse events among these patients did not suggest drug interactions.

The effects of gender race and age:
Females reported more adverse events than males (1317/2579 (51%) and 971/2347 (41%) respectively). Numerically most frequent, nausea occurred in12 % of females and 4% of males (10% and 3% respectively in controls). Caucasians had higher adverse event rates than Blacks and Asians though no specific adverse event was particularly associated with one racial group.
Age:

Adverse events were generally slightly more common in the elderly than in young patients. both in Moxifloxacin and control treated patients. The difference was most marked in patients reporting dizziness as shown below:

Table 28: Age related differences in adverse event reports

	Moxifloxacin			Contol		
	18-64	65-74	>74	18-64	65-74	>74
Any event	1498/3306 45%	282/603 47%	197/388 51%	522/1187 44%	223/467 48%	130/272 48%
Dizziness	111/3306 3%	34/603 6%	20/388 5%	55/1187 2%	16/467 3%	6/272 2%

MO comment: Elderly patient appeared more prone to dizziness on Moxifloxacin than on control medications.

Pregnancy:
Animal toxicity studies in rats, rabbits and cynomolgus monkeys using doses of Moxifloxacin greater than 12.5 times the human dose, showed decreases in fetal weight, and fetal malformations in rabbits.

Among 8341 patients enrolled in Phase II and III studies, 9 pregnancies occurred during study medication treatment and 9 after completion of treatment. Eleven of the 18 pregnancies were receiving Moxifloxacin. Drug was discontinued prematurely in 5 patients. Two patients delivered normal healthy babies. Pregnancy outcome was not known in the remaining 16.

MO comment: The number of pregnant patients was too small to evaluate safety of Moxifloxacin. Since no adverse events were noted in these few patients, and animal toxicity was apparent with very high doses, normal human doses should be considered only if a justifiable treatment benefit is anticipated.

Clinical data on the safety of Moxifloxacin in nursing mothers and pediatric patients was not available. The youngest patients studied were four 17 year olds. One had dizziness and one reported salpingitis. Both these adverse events were described as mild.

Dose relation.
Overall adverse event rates were 45% in patients treated with 200mg Moxifloxacin QD compared with 47% in those treated with 400mg QD. Nausea was reported in 4% of the low dose patients and 9% of the high dose patients. Premature discontinuations due to nausea occurred in 3/556 (.5%) of patients on low dose treatment and 39/4370 (0.9%) of patients on high dose treatment.
Drug related adverse events occurred in 28% of patients treated with 200mg daily and 32% of patients treated with 400mg daily. Nausea accounted for 3% and 8% in each respective group. Premature discontinuations were equivalent between dosing groups.

MO comment: Evaluation of adverse effects was complicated by inferior efficacy and comparatively small numbers in the lower dose group. Nausea was the most consistent dose related adverse event.

Clinical concerns particular to the use of quinolones:
Hypersensitivity:
Eleven patients were reported to have allergic reactions out of 4926 patients treated with Moxifloxacin 10 had facial edema and 3 discontinued drug, 78 had a rash and 24 discontinued drug, 32 had a maculopapular rash and one discontinued, 6 had urticaria and 3 discontinued the drug.
No cases of anaphylaxis were reported.

Phototoxicity: Double blind placebo controlled studies failed to demonstrate phototoxicity from UV A or B light. Preclinical studiesshowed that Moxifloxacin was not photodegreaded, and not phototoxic to mouse 3T3 fibroblasts. Animal studies in guinea pigs, rats and hairless mice showed no phototoxicity.

Among 4926 Moxifloxacin treated patients in clinical trials, 4 reported phototoxicity as an adverse event. Two of these were considered drug related and are described below.

(study 125 D96-023, # 19001) A 56 year old white woman on Moxifloxacin 400mg QD for acute sinusitis developed "mild" photosensitivity on exposure to sunlight one day after starting therapy. The event was judged 'possibly" drug related and resolved without having to stop therapy.
(study 125 D96-023 #14016) A 27 year old white woman who was on the beach 3 days after the last dose of moxifloxacin 400mg QD, developed typical sunburn. The event was mild, considered probably treatment related and resolved spontaneously in 2 days.

MO comment: Given the infrequency of this adverse event, Moxifloxacin is not thought to present a particular risk for photosenstivity

Cardiac Safety: See specific review of electrocardiographic data

CNS disturbances:
Dizziness was reported by 195 patients (4%) among Moxifloxacin treated patients in phase II and III studies, resulting in discontinuation of medication in 32/4926 compared with 9/3415 comparator treated patients. Seizures occurred in 3/4926 patients treated with moxifloxacin. Two had a history of prior seizure disorders.
"Sleep disorders" occurred in 3/4926 patients. Medication was prematurely discontinued in one. Insomnia was reported in 64 (1.3%) patients treated with moxifloxacin.
MO comment: The long term effects of Moxifloxicin on CNS function were not evaluated.

Arthropathy: Oral Moxifloxacin caused lameness with permanent cartilage lesions in immature dogs. Oral doses in animals twice those in humans given for 28 days resulted inarthropathy. This was not reproduced in monkey or rats. The clinical database examined short dosage periods in an adult population.
MO comment: The theoretical risk to pediatric patients remains a concern.

Tendinopathy:
Two patients treated with moxifloxacin developed tendinopathy or pain in the Achilles tendon
(study 0119 # 119) A patient developed mild tendinopathy considered probably related to study drug, that persisted for 2 weeks and resulted in premature drug discontinuation. The condition resolved.
(study 0124 #813) A patient developed mild Achilles tendon pain, probably related to study drug. The event resolved without discontinuing treatment.
MO While these events were rare, the possibility that more prolonged dosage may constitute a greater risk has not been excluded.

Enteric disorders:
Diarrhea occurred in 359/4926 (7%) of patients treated with Moxifloxacin, colitis in 4 and pseudomembranous colitis in 1. A single patient in the comparator group treated with clarithromycin also developed pseudomembranous colitis.

Crystalurea was not observed in chronic safety studies in rats and monkeys. Crystaluria was reported in 6 patients. All were considered remotely drug-related. Only one of these patients received Moxifloxacin 400mg QD and the event, considered mild in intensity, resolved spontaneously.

Review of general safety in phase I and II studies.

Table 29: Clinical pharmacology studies providing supportive safety data

Type of study	Number of studies	Number of subjects
Dose ranging	8	121
Food effect	3	32
Bioequivalence	3	42
Absorption	2	22
Drug interactions	9	116
Special populations	3	86
Tissue distribution	4	88
Special studies- Dosage form	5	183
Photosensitivity	1	32
Total	38	722

Study 0158 with 18 subjects was incomplete and is not included in the safety pool.
A total of 613 subjects provided safety information. (Some volunteers participated in more than one study, hence the number of volunteers is less than the cumulative number of study participants.) 556 received Moxifloxacin (126 of whom received both Moxifloxacin and placebo in crossover designs), and 57 received only placebo.
Drug exposure:
782 treatment courses were administered. 685 were single doses
Oral Moxifloxacin was given to 499 subjects (117 received intravenous drug as well) and oral placebo only was given to 37.
Intravenous Moxifloxacin was given to 117 subjects, (9 received placebo as well) and 19 received placebo only.
Subjects taking at least one dose of Moxifloxacin were considered valid for a safety evaluation.
24 subjects involved in phase II studies did not receive Moxifloxacin and were not included in the safety analysis. Sixteen withdrew prior to treatment with Moxifloxacin and 9 others received a comparator other than placebo.
Oral treatment was given for one day to 188 (37.7%) subjects, 2-7 days to 258 (51.7%) and 8-30 days to the remaining 53 (10.6%).
Intravenous Moxifloxacin was given to 89 (76.1%) for one day, 20 (17.1%) for 2-7 days and 8 for 8 or more days.

In the sponsor's analysis:

- The total number of days of exposure did not necessarily mean that those days were continuous.
- Exposure data were pooled for all preparations of Moxifloxacin (IV and oral).
- Treatment emergent events were those either starting or worsening in intensity only after the drug was started.
- COSTART terms were used to code adverse events. Repeated occurrences were only counted once.
- All treatment-emergent events occurring within 30 days of treatment were included.
- 18 subjects in study 0158 were excluded from the safety pool as the results were obtained late. No adverse events were reported in these 18 patients.

MO comment: Those receiving non-continuous doses of medication are likely less prone to adverse events than those on continuous medication. Long term safety beyond 30 days is not addressed.

The demographic characteristics of patients treated with IV and oral Moxifloxacin in phase II studies are shown below.

Table 30: Demographic characteristics of patients treated with oral moxifloxacin.

Table 1 Demographic Characteristics of Subjects Receiving Oral Moxifloxacin, by Dose Group						
Demographics			<400 mg/d	400 mg/d	> 400 mg/d	Placebo
Set	Subset	Data	N=89 (18%)	N=363 (73%)	N=47 (9%)	N=37
Gender	Male	N (%)	81 (91.0)	323 (89.0)	36 (76.6)	31 (83.3)
	Female	N (%)	8 (9.1)	40 (11.0)	11 (23.4)	6 (16.2)
Race	Caucasian	N (%)	71 (79.8)	298 (82.1)	21 (44.7)	32 (86.5)
	Black	N (%)	4 (4.5)	3 (0.8)	0	2 (5.4)
	Asian	N (%)	13 (14.6)	14 (3.9)	6 (12.8)	3 (8.1)
	Other	N (%)	1 (1.1)	6 (1.7)	0	0
	Unknown	N (%)	0	42 (11.6)	20 (42.6)	0
Age	Year	Mean	37.8	37.8	27.3	38.5
		Range	18-81	19-78	25-45	19-79
	<65 years	N (%)	73 (82.0)	340 (93.7)	47 (100)	29 (78.4)
	≥65 years	N (%)	16 (18.0)	23 (6.3)	0	8 (21.6)
Weight	Kg	Mean	74.82	77.58	73.59	75.49
		Range	50.8-111	50-129.7	53.5-101	51.1-101.3
Height	cm	Mean	177.2	177.4	175.7	178.0
		Range	157-197	155-200	159-193	157-194

Table 31: Demographic details of patients treated with IV medication

Table 3 Demographic Characteristics of Subjects Receiving Intravenous Moxifloxacin, by Dose Group						
			< 400 mg/day	400 mg/day	>400 mg/day	Placebo
Set	Subset	Data	N=22 (19%)	N=86 (74%)	N=9 (8%)	N=19
Gender	Male	N (%)	22 (100)	73 (84.9)	9 (100)	16 (84.2)
	Female	N (%)	0	13 (15.1)	0	3 (15.8)
Race	Caucasian	N (%)	20 (90.9)	65 (75.6)	9 (100)	18 (94.7)
	Black	N (%)	2 (9.1)	2 (2.3)	0	1 (5.3)
	Asian	N (%)	0	1 (1.2)	0	0
	Unknown	N (%)	0	18 (20.9)	0	0
Age	Yr	Mean	33.4	34.8	32.9	43.2
		Range	19-43	19-75	20-44	20-70
	< 65	N (%)	22 (100)	76 (88.4)	9 (100)	14 (73.7)
	≥65	N (%)	0	10 (11.6)	0	5 (26.3)
Weight	Kg	Mean	83.56	78.89	78	75.78
		Range	66-113	50-112	61-91	56-91.6
Height	cm	Mean	181.2	176.6	179.9	171.0
		Range	170-198	147-197	172-187	147-192

MO comment: The majority of subjects in this data pool were young white men. Limited conclusions can be derived for women and elderly patients. No pediatric data are included

Adverse events:

Adverse events were reported in 209 of the 499 subjects (41.9%) on oral Moxifloxacin compared with 15 of 37 (40.5%) on oral placebo. The most common of these adverse events are shown below.

Table 32: Adverse events occurring in more than 2% of the population treated with oral Moxifloxacin:

Table 4 Incidence Rates of Adverse Events During and After Oral Moxifloxacin by Dosage Group, N (%)				
COSTART	Moxifloxacin			Placebo
	< 400 mg/day	400 mg/day	>400 mg/day	
	N=89 (17.8)	N=363 (72.7)	N=47 (9.4)	N=37
Headache	13 (46)	46 (12.7)	7 (14.9)	3 (8.1)
Abdominal Pain	0 (0)	19 (5.2)	5 (10.9)	1 (2.7)
Asthma	1 (1.1)	11 (3.0)	3 (6.4)	1 (2.7)
Lab Test Abnormal	0 (0)	3 (0.8)	3 (6.4)	0 (0)
Arm Pain	2 (2.2)	2 (0.6)	0 (0)	0 (0)
Back Pain	0 (0)	3 (0.8)	0 (0)	2 (5.4)
QT Interval Prolonged	0 (0)	1 (0.3)	2 (4.3)	0 (0)
Diarrhea	6 (6.7)	30 (8.3)	6 (12.8)	3 (8.1)
Nausea	3 (3.4)	24(6.6)	3 (6.4)	2 (5.4)
Flatulence	6 (6.7)	17 (4.7)	1 (2.1)	1 (2.7)
Ecchymosis	5 (5.6)	2 (0.6)	0 (0)	1 (2.7)
Dizziness	1 (1.1)	14 (3.9)	4 (8.5)	2 (5.4)
Somnolence	0 (0)	8 (2.2)	0 (0)	0 (0)
Rhinitis	3 (3.4)	9 (2.5)	1 (2.1)	2 (5.4)
Pharyngitis	1 (1.1)	8 (2.2)	0 (0)	0 (0)
Ear Disorder	2 (2.2)	0 (0)	0 (0)	0 (0)
Total	39 (43.8)	145 (39.9)	25 (53.2)	15 (40.5)
Note: Only adverse events with an incidence ≥ 2% are shown in Table 4				

When all doses were pooled, the most common adverse events were headache 66/499 (13%), diarrhea 42/499, nausea 30/499, abdominal pain 24/499, flatulence 24/499,dizziness 19/499
Adverse events showing a dose relation included abdominal pain, prolongation of QT interval, diarrhea nausea, asthenia, dizziness and "abnormal laboratory tests".
Multiple doses were associated with higher overall adverse event rates than single doses (61/118 (51.7%) versus 90/292 (30.8%))

In a subset of patients involved in placebo-controlled and placebo crossover studies, including 128 moxifloxacin treated patients and 75 placebo recipients, gastrointestinal events were again significantly more common in patients treated with moxifloxacin (see below)

Table 33: Adverse events in placebo controlled phase II studies

Table 5 Incidence Rates of Adverse Events During or After Oral Moxifloxacin: Placebo-Controlled and First Period of Crossover Studies		
Adverse Event/	Moxifloxacin, N=128	Placebo, N=75
COSTART	N (%)	N (%)
Headache	17 (13.3)	10 (13.3)
Abdominal Pain	8 (6.3)	1 (1.3)
Asthenia	4 (3.1)	2 (2.7)
Back Pain	0 (0)	2 (2.7)
Diarrhea	17 (13.3)	3 (4.0)
Nausea	12 (9.4)	2 (2.7)
Flatulence	7 (5.5)	4 (5.3)
Ecchymosis	4 (3.1)	1 (1.3)
Hyperglycemia	5 (3.9)	4 (5.3)
Dizziness	4 (3.1)	2 (2.7)
Rhinitis	4 (3.1)	6 (8.0)
Pharyngitis	3 (2.3)	1 (1.3)
Note: Only adverse events with an incidence ≥ 2% are shown in Table 5		

Adverse events related to intravenous dosing: Although less frequent than in patients on oral treatment, diarrhea and nausea were more common in patients treated with Moxifloxacin than placebo (see below).

Table 34: Adverse event rates during intravenous treatment

Table 7 Incidence Rates for Adverse Events During and After Intravenous Moxifloxacin: Placebo-Controlled and First Period of Crossover Trials		
Adverse Event	Moxifloxacin N=52	Placebo N=23
COSTART	N (%)	N (%)
Headache	3 (5.8)	4 (17.4)
Asthenia	3 (5.8)	1 (4.3)
Injection Site Hypersensitivity	3 (5.8)	1 (4.3)
Injection Site Reaction	3 (5.8)	0 (0)
Back Pain	0 (0)	2 (8.7)
Thrombophlebitis	2 (3.8)	0 (0)
Vasodilatation	0 (0)	2 (8.7)
Diarrhea	6 (11.5)	0 (0)
Liver Function Tests Abnl	3 (5.8)	1 (4.3)
Nausea	2 (3.8)	0 (0)
Leukocytosis	4 (7.7)	0 (0)
Dizziness	2 (3.8)	2 (8.7)
Paresthesia	2 (3.8)	1 (4.3)
Rhinitis	2 (3.8)	1 (4.3)
Pruritus	3 (5.8)	0 (0)
Creatinine Clearance Decreased	2 (3.8)	1 (4.3)
Note: Only adverse events with an incidence > 2% (and > 1 event) are shown in Table 7		

Laboratory abnormalities:
Treatment emergent laboratory abnormalities were presented for patients participating in placebo controlled or placebo crossover trials (see below). (Incidence was only reported for patients whose pre-treatment laboratory results were normal.)

Table 35: Laboratory test abnormalities in placebo controlled trials

Table 8 Incidence Rates for Selected Laboratory Abnormalities in Oral Moxifloxacin and Placebo Treated Subjects, Placebo-Controlled Data Set, Incidence/# at Risk (Percent)		
Laboratory Test	Moxifloxacin	Placebo
Clinical Chemistry		
Elevated Alkaline Phosphate	2/110 (1.8%)	0/66 (0.0%)
Elevated Amylase	1/57 (1.8%)	0/36 (0.0%)
Elevated Bilirubin	5/109 (4.6%)	1/66 (1.5%)
Elevated Creatine Kinase	6/104 (5.8%)	4/65 (6.2%)
Elevated GLDH	7/53 (13.2%)	3/35 (8.6%)
Elevated LDH	2/103 (1.9%)	0/61 (0.0%)
Elevated Lipase	0/50 (0.0%)	1/34 (2.9%)
Elevated Phosphorus	11/64 (17.2%)	0/34 (0.0%)
Elevated Potassium	13/124 (10.5%)	5/71 (7.0%)
Elevated PTT	7/65 (10.8%)	4/39 (10.3%)
Elevated SGOT/AST	7/127 (5.5%)	4/75 (5.3%)
Elevated SGPT/ALT	12/122 (9.8%)	13/74 (17.6%)
Elevated Urea	6/55 (10.9%)	5/35 (14.3%)
Elevated Uric Acid	3/106 (2.8%)	1/64 (1.6%)
Low Urea/BUN	8/100 (8.0%)	0/63 (0.0%)
Hematology		
Low Hematocrit	32/102 (31.4%)	18/64 (28.1%)
Low Hemoglobin	8/104 (7.7%)	6/67 (9.0%)
Low Platelets	6/104 (5.8%)	1/65 (1.5%)
Low RBC	9/104 (8.7%)	5/67 (7.5%)
Low WBC	5/98 (5.1%)	1/63 (1.6%)

Elevated bilirubin, GLDH, phosphorus and potassium and low BUN were notably more frequent in Moxifloxacin treated patients. (Potassium changes were all <1.3 ULN and phosphorus <2 ULN.)
Low hematocrit was also more frequent in Moxifloxacin treated patients although a low Hemoglobin was more common among placebo recipients. Both thrombocytopenia and leukopenia were substantially more common in Moxifloxacin treated patients.

MO comment: It is unclear whether the hematological changes described reflect a general suppressive effect on the bone marrow. (Possible marrow toxicity was encountered in preclinical studies on Rhesus monkeys (PH25970, PH 25354 and T5060045) as detailed in an FDA review by T Peters May 13, 1997 .)
While anemia was also frequent in placebo recipients and numerous blood draws may have been responsible in part, the leukopenia and thrombocytopenia appear only to be related to Moxifloxacin use in this healthy population of study volunteers. Leukopenia and thrombocytopenia were however not substantially more frequent in moxifloxacin treated than comparator treated patients among more than 3500 evaluable patients in phase 3 studies (see table 17)

Two patients with concurrent elevation of trasaminases and GLDH are described below.

- In this subject treated with Moxifloxacin, elevations of ALT, AST and GLDH peaked on day 5-7 and declined spontaneously despite continued Moxifloxacin therapy for 10 days.

- In a study investigating the effect of fasting or food on the pharmnacokinetics of a single 200mg dose of moxifloxacin one 21 year old Japanese male developed a treatment emergent elevation of SGOT 184U/L and SGPT 435U/L 6 days after a single dose. The patient was withdrawn from further study and SGOT and SGPT were normal by day 28. The investigator ascribed the changes to an intercurrent viral infection viral studies. Tests for CMV IgM and IgG, EBV-VCA IgG and IgM, EBNA, adenovirus, HBS antigen and antibody and HCV antibody were negative on day 7.

MO comment: The information provided suggests these events may be drug related (although a longer period of follow up would be needed to confirm negative hepatitis serologies).

Of the hematological tests, low hematocrit, low platelets and leukopenia were more frequent among Moxifloxacin treated subjects and all appeared to show some dose relation (see table below).

Table 36: Abnormally low laboratory results – Phase 1 and II studies (Dosage range 200mg to 800mg QD)

LABORATORY TEST	BAY 12-8039 < 400 MG/DAY	BAY 12-8039 400 MG/DAY	BAY 12-8039 > 400 MG/DAY
CHEMISTRY			
LOW ALBUMIN	0/ 49(0.0%)	2/ 79(2.5%)	0/ 8(0.0%)
LOW ALKALINE PHOSPHATASE	1/ 82(1.2%)	10/ 261(3.8%)	0/ 28(0.0%)
LOW AMYLASE	0/ 46(0.0%)	1/ 186(0.5%)	0/ 27(0.0%)
LOW BILIRUBIN. TOTAL	0/ 80(0.0%)	4/ 258(1.6%)	0/ 29(0.0%)
LOW BUN	0/ 41(0.0%)	1/ 45(2.2%)	0/ 6(0.0%)
LOW CALCIUM	3/ 84(3.6%)	8/ 242(3.3%)	3/ 29(10.3%)
LOW CHOLESTEROL. TOTAL	0/ 59(0.0%)	9/ 195(4.6%)	1/ 27(3.7%)
LOW CREATINE KINASE (CK.CPK)	0/ 75(0.0%)	1/ 202(0.5%)	0/ 27(0.0%)
LOW CREATININE	0/ 81(0.0%)	3/ 255(1.2%)	0/ 29(0.0%)
LOW GGT	4/ 58(6.9%)	15/ 244(6.1%)	1/ 28(3.6%)
LOW GLUCOSE. UNSPECIFIED	1/ 80(1.3%)	19/ 235(8.1%)	0/ 29(0.0%)
LOW LDH	16/ 75(21.3%)	39/ 182(21.4%)	6/ 21(28.6%)
LOW LEUCINAMINOPEPTIDASE (LAP)	4/ 25(16.0%)	10/ 85(11.8%)	2/ 16(12.5%)
LOW PHOSPHORUS. INORG.	1/ 48(2.1%)	19/ 130(14.6%)	0/ 7(0.0%)
LOW POTASSIUM	0/ 84(0.0%)	5/ 257(1.9%)	1/ 46(2.2%)
LOW PROTEIN. TOTAL	11/ 77(14.3%)	42/ 239(17.6%)	6/ 25(24.0%)
LOW PT RATIO	0/ 34(0.0%)	2/ 165(1.2%)	2/ 23(8.7%)
LOW PTT	7/ 47(14.9%)	30/ 188(16.0%)	2/ 20(10.0%)
LOW SGOT/AST	0/ 84(0.0%)	2/ 264(0.8%)	0/ 47(0.0%)
LOW SGPT/ALT	0/ 83(0.0%)	2/ 254(0.8%)	0/ 47(0.0%)
LOW SODIUM	2/ 84(2.4%)	3/ 272(1.1%)	0/ 29(0.0%)
LOW TRIGLYCERIDES	0/ 63(0.0%)	7/ 175(4.0%)	1/ 27(3.7%)
LOW UREA	4/ 36(11.1%)	29/ 202(14.4%)	4/ 21(19.0%)
LOW URIC ACID	1/ 81(1.2%)	14/ 238(5.9%)	2/ 26(7.7%)
HEMATOLOGY			
LOW HEMATOCRIT	15/ 79(19.0%)	85/ 237(35.9%)	7/ 27(25.9%)
LOW HEMOGLOBIN	5/ 78(6.4%)	43/ 251(17.1%)	4/ 27(14.8%)
LOW PLATELETS	2/ 79(2.5%)	11/ 218(5.0%)	2/ 29(6.9%)
LOW RBC	5/ 81(6.2%)	26/ 223(11.7%)	4/ 29(13.8%)
LOW WBC	3/ 73(4.1%)	19/ 209(9.1%)	0/ 27(0.0%)

While the above data confirm a dose-related effect on hematocrit, hemoglobin, platelet count and white cell count in phase 1 studies, these changes were not confirmed in phase 3 studies (see table 17).

Table 37: Abnormally high laboratory results (Phase I and II studies)

LABORATORY TEST	BAY 12-8039 < 400 MG/DAY	BAY 12-8039 400 MG/DAY	BAY 12-8039 > 400 MG/DAY
CHEMISTRY			
ELEVATED ALBUMIN	2/ 49(4.1%)	3/ 79(3.8%)	0/ 8(0.0%)
ELEVATED ALKALINE PHOSPHATASE	1/ 82(1.2%)	3/ 261(1.1%)	0/ 28(0.0%)
ELEVATED AMYLASE	1/ 46(2.2%)	7/ 186(3.8%)	0/ 27(0.0%)
ELEVATED BILIRUBIN. TOTAL	3/ 80(3.8%)	19/ 258(7.4%)	1/ 29(3.4%)
ELEVATED CALCIUM	1/ 84(1.2%)	17/ 242(7.0%)	0/ 29(0.0%)
ELEVATED CHLORIDE	2/ 84(2.4%)	9/ 262(3.4%)	0/ 28(0.0%)
ELEVATED CHOLESTEROL. TOTAL	2/ 59(3.4%)	16/ 195(8.2%)	1/ 27(3.7%)
ELEVATED CREATINE KINASE (CK.CPK)	2/ 75(2.7%)	19/ 202(9.4%)	2/ 27(7.4%)
ELEVATED CREATININE	0/ 81(0.0%)	14/ 255(5.5%)	1/ 29(3.4%)
ELEVATED GGT	0/ 58(0.0%)	6/ 244(2.5%)	0/ 28(0.0%)
ELEVATED GLDH	3/ 47(6.4%)	9/ 126(7.1%)	2/ 27(7.4%)
ELEVATED GLUCOSE. UNSPECIFIED	4/ 80(5.0%)	23/ 235(9.8%)	4/ 29(13.8%)
ELEVATED LDH	1/ 75(1.3%)	1/ 182(0.5%)	0/ 21(0.0%)
ELEVATED LEUCINAMINOPEPTIDASE (LAP)	0/ 25(0.0%)	3/ 85(3.5%)	0/ 16(0.0%)
ELEVATED LIPASE	1/ 46(2.2%)	7/ 174(4.0%)	1/ 26(3.8%)
ELEVATED PHOSPHORUS. INORG.	5/ 48(10.4%)	19/ 130(14.6%)	2/ 7(28.6%)
ELEVATED POTASSIUM	11/ 84(13.1%)	43/ 257(16.7%)	5/ 46(10.9%)
ELEVATED PROTEIN. TOTAL	2/ 77(2.6%)	7/ 239(2.9%)	0/ 25(0.0%)
ELEVATED PT RATIO	0/ 34(0.0%)	2/ 165(1.2%)	0/ 23(0.0%)
ELEVATED PTT	6/ 47(12.8%)	4/ 188(2.1%)	1/ 20(5.0%)
ELEVATED SGOT/AST	5/ 84(6.0%)	6/ 264(2.3%)	1/ 47(2.1%)
ELEVATED SGPT/ALT	7/ 83(8.4%)	20/ 254(7.9%)	4/ 47(8.5%)
ELEVATED SODIUM	0/ 84(0.0%)	36/ 272(13.2%)	3/ 29(10.3%)
ELEVATED TRIGLYCERIDES	4/ 63(6.3%)	36/ 175(20.6%)	3/ 27(11.1%)
ELEVATED UREA	4/ 36(11.1%)	21/ 202(10.4%)	3/ 21(14.3%)
ELEVATED URIC ACID	4/ 81(4.9%)	20/ 238(8.4%)	1/ 26(3.8%)
HEMATOLOGY			
ELEVATED HEMOGLOBIN	0/ 78(0.0%)	1/ 251(0.4%)	0/ 27(0.0%)
ELEVATED PLATELETS	0/ 79(0.0%)	2/ 218(0.9%)	0/ 29(0.0%)
ELEVATED RBC	0/ 81(0.0%)	2/ 223(0.9%)	0/ 29(0.0%)
ELEVATED WBC	2/ 73(2.7%)	12/ 209(5.7%)	2/ 27(7.4%)

Several elevated laboratory test results appeared dose related including total bilirubin, calcium, total cholesterol, creatine kinase, glucose, phosphorus, triglycerides and WBC count.

Other clinical investigations: Review of vital signs, Romberg tests (in 4 studies) and opthalmologic findings on slit lamp examination in 4 studies did not demonstrate any treatment emergent abnormalities. No deaths were reported in the clinical pharmacology studies.

Discontinuations due to adverse events:
Ten subjects discontinued participation in phase I studies due to adverse events (1 placebo, 5 after oral Moxifloxacin and 4 after intravenous Moxifloxacin) as shown below.

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Table 38: Premature discontinuation of therapy due to adverse events (Phase 1 studies)

Table 11A
Adverse Event Discontinuations by Patient
Source Datapool of Oral and Intravenous Moxifloxacin Phase I Trials
Treatment: Moxifloxacin, Oral or I.v.)

Trial	Center	Patient #	Age (Yrs)	Gender	Dose (mg)	Time* (Days)	Body System	Preferred Term	Adverse Event	Serious	Outcome
0117	1	11	35	M	400	6	Urogenital	Epididymitis	Epididymitis Right	N	Referral to Urologist
0120	4	2	21	M	200	6	Digestive	Liver Function Tests Abnormal	GLDH Abnormal GPT Abnormal	N	R
0145	12	1	41	M	400 (i.v.)	1	Skin and Appendages	Macular Rash	Macular Rash on Trunk and Arms	N	R
0149	3	4	25	M	400 (i.v.)	1	Body as a Whole	Injection Site Hypersensitivity	Swelling, Pruritus, Erythema	N	R (+ Rechallenge)
0149	3	7	35	M	400 (i.v.)	1	Cardiovascular	Arrhythmia	Vasovagal Syncope	Y	R
0156	11	4	26	M	400 (i.v.)	1	Body as a Whole	Injection Site Hypersensitivity	Itching, Rash of Veins prox to Injection Site	N	R
0162	17	6 ("S/A/T")	52	M	400	2	Digestive	Diarrhea	Diarrhea	N	R
0163	13	7	27	F	800	1	Nervous	Dizziness	Fuzziness	N	R
0163	13	15	21	F	800	7	Body as a Whole	Flu Syndrome	Flu, Beta HCG Increased (Falsely)	N	R

Abbreviations: M, male; F, female; N, no; Y, yes; R, recovered
*Time: Day of onset of adverse event relative to first day of therapy

Adverse Event Discontinuations by Patient
Source: Datapool of Oral and Intravenous Moxifloxacin Phase I Trials
Treatment: Placebo

Trial	Center	Patient #	Age (Yrs)	Gender	Dose (mg)	Time* (Days)	Body System	Preferred Term	Adverse Event	Serious	Outcome
0104	1	8	43	M	Placebo	9	Body as a Whole	Flu Syndrome	Cold is getting Worse, more Flu-like	N	R

Abbreviations: M, male; F, female; N, no; Y, yes; R, recovered
*Time: Day of onset of adverse event relative to first day of therapy

Study 0120, patient # 2 appeared to have developed hepatotoxicity on day 6 and has been reviewed under the discussion of liver function abnormalities.
Study 0149 patient #7 has been reviewed under the cardiac safety section and was thought to have had a syncopal episode accounting for a brief period of asystole rather than a primary arrhythmia.
Three subjects developed probable allergic cutaneous reactions within the first day of drug administraion, two localized and one generalized. They were described as "not serious" and all resolved.

Serious adverse events:
Serious adverse events occurred in two patients treated with moxifloxacin. One was a fall in a 61 year old patient 6 days after receiving three 400mg doses of moxifloxacin orally. The event appears not to be related to study drug. The case of vasovagal syncope with arrhythmia was reported above.

Fluoroquinolone associated adverse events:

Central nervous system:
Studies examining the propensity for Moxifloxacin to cause electroencephalographic changes are described below:

Table 39: Summary of EEG findings in phase 1 and II studies

Study #	dose	N	Description	Outcome
0102	100-200mg bid x 5days PO	16	Dose escalation, EEG's performed	No EEG changes or seizures
0115	100-600mg PO single doses	18	Dose escalation single dose EEG 's performed	No EEG changes or seizures
0101	50-600mg PO single doses	38	Dose escalation, EEG's performed	No EEG changes or seizures
0137	400mg QD x 7 days PO	6	Repeated doses EEG's performed	No EEG changes or seizures
0132	100-400mg IV as single doses	24	Dose escalation IV. Each administered over 30 min. EEG's	No EEG changes or seizures
0143	400mg daily IV x 10 days	8	Repeat IV dosing	No EEG changes or seizures
0154	400mg daily IV x 5days	12	Repeat IV dosing in elderly subjects, EEG telemetry	No EEG changes or seizures

MO comment: Of the 122 patients referred to above, 12 were elderly, the rest were healthy young males. Dose ranges were representative of clinical use. However the risk of seizures in individuals with a history of epilepsy or on other concomitant medications is not known.

Dizziness was reported in 24/616 (3.9%) of Moxifloxacin treated patients and 4/94 (4.3%) of placebo treated patients.

Phototoxicity:
Photosensitizing effects of Moxifloxacin at doses of 200mg and 400mg daily for 7 days were compared with placebo and lomefloxacin (known to cause photosensitivity). Diminution in the minimal erythema dose (MED) over a range of UV wavelengths was determined for each treatment group. While MED diminution was documented with Lomefloxacin no photosensitizing effect was detected with Moxifloxacin.

Drug interaction:
Moxifloxacin was not shown to be a substrate for phase I (Cytochrome P450) metabolism. Drug interactions with other agents metabolized by P450 were studied and supported this claim. No interactions were found between Moxifloxacin and theophylline.
Glyburide: In diabetic patients, Moxifloxacin resulted in a 21% and 12% reduction of C max and AUC for glyburide, and 7% and 6% reductions in glucose AUC (0-6hrs) and C max (0-6hrs). Plasma insulin, fasting, and 24hr AUC glucose values were not affected. The sponsor concluded that reductions in glyburide were not associated with loss of glucose control.
Glyburide is known to block the Ik ATP channel in pancreatic islet cells. A theoretical interation with cardiac Ikr channnels was not confirmed. The mean QTc prolongation in patients treated with both glyburide and Moxifloxacin was 2.3Ms; less than that on Moxifloxacin alone.

Warfarin: Moxifloxacin studied concurrently with warfarin did not result in significant changes of C max, AUC 0-4 and T ½ when compared with subjects treated with warfarin alone.

Ranitidine did not affect the plasma and urinary pharmacokinetics of Moxifloxacin.

Digoxin: Moxifloxacin resulted in a significant (49.6%) increase in the Cmax of digoxin, although the AUC 0-24 hrs was unchanged. The sponsor claims that since this occurs in the distribution phase it is unlikely to have a clinical effect. ECG monitoring during the study did not detect digoxin toxicity. Adverse

events and laboratory test abnormalities were equally frequent among those patients given or not given digoxin.

Other fluoroquinolone associated toxicities:
Cataracts/lens opacities
Despite reports of cataracts in animals treated long term with fluoroquinolones, no reports of cataracts in humans have been published. Four phase I studies of Moxifloxacin included slit lamp examination, fundoscopy and tests of visual acuity before and after courses of Moxifloxacin (200mg – 600mg /day for up to 10 days). No cataracts or retinal changes were detected in these studies.

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Special cardiac safety study:

Evaluation of the effects of moxifloxacin on the QT interval.

Background: Prolongation of the QT interval was first detected during safety pharmacology studies for IV moxifloxacin in human subjects. Subsequently, dogs treated with high doses of Moxifloxacin were also shown to develop prolonged QT intervals.

Table 40: Summary of preclinical animal data

Species & study design	Route of admin	Dose range (mg/kg)	Increase in Δmean QTc	Ventric arrhythmias	Study
Beagles	Intraduodenal	10-100	2 ms	-	PH 24362
Beagles (4 weeks)	Oral	0-90	25 ms at high dose *	-	PH 27061
Monkeys	Intraduodenal	10-100	0	-	R 7104
Beagles	IV bolus	1-30	8-69ms	-	PH 25622
Beagles	IV infusion	30 over 30 min	<21ms	-	PH 25854
Beagles	IV varying infusion rates	30 over 15 to 60 min	64 ms at highest rate	-	PH26684
Beagles (Hypokalemia)	IV infusion	30 over 30 min	20ms	-	PH27428
Dogs (+sotalol)	IV infusion	30 over 30 min	113ms	-	PH27430
Beagles (vs Sparflox)	IV infusion	30 over 30 min	28ms (vs 58ms)	-	PH27427
Rabbits (vs Sparflox)	IV infusion	120	50ms (vs 140)	1/6 PVC (vs 4/6 PVC, 1/6 VT)	R7264
Beagles (overdose)	IV infusion	Up to 360 over 60-90 min	600ms	VEs & TdP	PH27429

*QT rather than QTc

A consistent QT prolonging effect of Moxifloxacin was noted in beagle dogs that was related to dose and to the rapidity of infusion. (Note that a 30mg/kg dose over 30 minutes in beagle dogs resulted in a Cmax approximately 25 times the anticipated human Cmax after a 400mg oral dose.)
Sotalol substantially increased the effects of Moxifloxacin on the QTc prolongation. Sparfloxacin was more potent than Moxifloxacin in inducing QT prolongation. Ventricular arrhythmias only appeared during massive overdoses of Moxifloxacin.

In vitro studies
On guinea pig papillary muscle, action potential duration (APD90) was measured using intracellular microelectrodes. Moxifloxacin did not influence the rate of rapid repolarization (inward rectifier current was not affected). APD90 was prolonged by a 50μM threshold concentration of Moxifloxacin and a 3μM threshold concentration of Sparfloxacin.

The whole cell voltage clamp technique was use on guinea pig ventricular myocytes to measure outward currents. Moxifloxacin did not block the rapidly activating component of the delayed rectifier current (Ikr) when compared to E-4031 (used as a positive control) but appeared to block the slowly activating component (Iks) at a concentration of 50uM.
Conflicting results were obtained using whole-cell- patch-clamp studies on mouse atrial cells. Moxifloxacin blocked Ikr with an IC50 of 0.75μM. (The comparable IC50 for sparfloxacin was 0.23μM.)

A third approach used a CHO cell line transfected with KvLQT1+minK (the molecular basis for Iks). Rubidium efflux from these cells reflected the Iks. Neither Moxifloxacin nor Sparfloxacin inhibited depolarization or mefanemic-acid-induced ion flux in these preparations.

These results indicated some effect of Moxifloxacin on both Iks and Ikr depending on the experimental technique that was used.

Clinical pharmacology:

Following an initial observation that human subjects developed a prolongation of the QT interval during safety studies of intravenous Moxifloxacin, QT intervals and other ECG changes were examined in the intravenous dose escalation program.

Subjects included mainly healthy males, 18-55 years in age. Small numbers of elderly and young males and females, and patients with renal and hepatic dysfunction were also examined.

With the exception of one study, baseline ECG's were taken after a lie-in period of 15 minutes. Digitised automated analysis was performed using [redacted] formula for the calculation of QTc.
Manually read tracings were blinded, though sequential ECG's from the same subject were read by the same reviewer.

Review criteria:
All ECG leads were examined
QT was measured first in lead II, then if not feasible in lead V5, then the longest available QT was selected.
QRS ad RR intervals were recorded form the same lead that the QT was measured.

Abnormal T and U waves and prominent U waves were reported.

Methods:
Manual evaluation of ECG's: Paper copies were blinded for the reviewers. Measures were taken to assign the pairs of ECG's from each subject to the same reviewer.

All leads were to be looked at.
Lead II would be examined first, if not feasible, then lead V5, and if still not feasible the longest QT in any lead would be examined.
The end of the QT was the point of intersection between the tangent to the downslope of the T wave , and the TP baseline.
U waves were excluded from the measurement.

[redacted]

The following classification of abnormalities was employed:

1) abnormal QT intervals

Table 41: Classification of abnormal QT intervals.

	Adult Males (msec)	Adult Females (msec)
Normal	< 430	< 450
Borderline	431 - 450	451 – 470
Prolonged[2]	> 450	> 470
Raise clear concerns about thepotential risk of inducing arrhythmias including Torsades de Pointes	> 500[2]	> 500[2]

[1] according to the CPMP. Points to consider [5]
[2] will be referred to in the text as "abnormal"

2) Dispersion
Abnormalities in dispersion (the maximum difference of QT intervals between all 12 leads) were classified as causing concern if the value was > 100 msec or more than 100%
3) significant outliers were identified according to the following criteria

Table 42: CPMP criteria for the identification of "significant outliers"

Significant Outliers
QTc > 450 msec in males[1] OR QTc > 470 msec in females[1]
Δ QTc > 60 msec[1]
QTc > 450 msec in males AND Δ QTc > 30 msec OR QTc > 470 msec in females AND Δ QTc > 30 msec
Δ QTc divided by baseline QTc > 15%

[1] according to the CPMP. Points to consider [5]

The QTc changes relative to baseline were categorized as shown below.

Table 43: categorization of changes from baseline in the QTc.

QTc changes (msec)	Implications of these changes
< 30	Unlikely to raise significant concern about the potential risk of inducing arrhythmias including Torsades de Pointes
31 – 60	More likely to represent a drug effect and raise concern about the potential risk of inducing arrhythmias including Torsades de Pointes (referred to as "borderline")
> 60 *	Raise clear concerns about the potential risk of inducing arrhythmias including Torsades de Pointes

* according to the CPMP. Points to consider [5]

Results:
Following the observation that Moxifloxacin caused a prolongation of the QTc interval, an initial retrospective analysis was performed where paired ECGs from treated patients were read manually by a single cardiologist. All ECG's obtained during studies were read manually by a single cardiologist. A total of 931 ECG's from 304 treatment periods among 197 subjects were analyzed from a pool of 14 studies. These included studies of dose escalation, drug and food interaction, bio-equivalence and pharamcokinetics.

ECG results for the pool of 14 pre-clinical studies.
Among placebo recipients, no patient (0/46) had a QTc >450ms pretreatment whereas 2/46 (4.3%) had post treatment values > 450ms at the assumed C max. Among moxifloxacin treated subjects 3/182 (1.6%) had a QTc > 450mS pre-treatment which was <450mS after treatment, and 4/182 (2.1%) had a normal pre-treatment QTc with was > 450mS after treatment. One moxifloxacin treated patient developed a QTC >500 (502ms) at presumed C max, 2 hours after a single 400mg dose.

The influence of pre-treatment prolongations of QTc on post-treatment effects
The three patients with pre-treatment QTc intervals >450ms were shown to shorten the QTC interval after drug administration. Conversely, patients with prolonged QTc intervals post-treatment began with normal QTc intervals pre-treatment.

Table 44: Relationship between pre-treatment and post-treatment QTc interval (all doses used in pre-clinical studies)

QTc (msec)	At C_{max}*			
	< 430	430 - 450	> 450	Total
Pre-Treatment BAY 12-8039	N	N	N	N
< 430	140	18	4	162
430 - 450	12	5	0	17
> 450	1	2	0	3
Total	153	25	4	182
Pre-Treatment Placebo				
< 430	39	1	1	41
430 - 450	3	1	1	5
> 450	0	0	0	0
Total	42	2	2	46

* assumed C_{max} i.e. 2 hours after oral drug administration. In case of multiple dosing only data of day 1.

MO comment
While there was no clear relationship between pre- and post- treatment values, the number of patients with abnormalities at either time-point was small.

ECG results for pooled oral studies using a standard 400mg dose.

Of the 119 patients treated with a 400mg dose, all had normal QTc values before treatment, and 3 (2.5%) developed QTc intervals > 450mS after treatment. The mean increase in QTC among 112 patients was 6.9mS [redacted] compared with 2.5 mS [redacted] among 27 placebo treated patients.

Table 45: QTc results among pooled subjects treated with Moxifloxacin 400mg PO

QTc (msec)	At C_{max}*			
	< 430	430 - 450	> 450	Total
Pre-Treatment BAY 12-8039	N	N	N	N
< 430	94	10	3	107
430 – 450	9	3	0	12
> 450	0	0	0	0
Total	103	13	3	119

* assumed C_{max} i.e. 2 hours after oral drug administration. In case of multiple dosing only data of day 1.

Repeat dosing

With time, 7 patients on courses of Moxifloxacin showed an initial increase in the mean QTc followed by a trend to decreasing QTc intervals over 5 days of treatment (from a mean increase from baseline of 24.3mS, [redacted] to a mean of 14.4mS, [redacted]

Intravenous administration and QT prolongation

Among 28 subjects given a single intravenous dose of 400mg of Moxifloxacin over 15 to 60 minutes, there was a mean QTc prolongation of 12.1msec In 7 subjects given repeated daily doses, the mean prolongation of QTc on day 10 at steady state was 12.6 mS , effectively no different from the change after the first dose.

Baseline QTc intervals in all 56 volunteers for intravenous study were <450mS. Two developed QTc intervals of >450 mS at Cmax, one after 400mg over 33 minutes and one after 600mg over 100 min. QTc in 18 IV-placebo treated subjects were all ≤450mS both before and after treatment.

After oral doses a change in QTc >60mS was seen in 4/182 moxifloxacin treated subjects and 1/46 placebo treated subjects. After intravenous doses no subjects showed a change in QTc >60mS.

Other parameters to detect prolongation of the QT interval included a change of >30 msec in the QTc. Five such patients were identified and all five were previously identified with a post-treatment QTc of > 450mS.

The frequency of outliers defined by four different parameters are shown below for patients treated with various oral doses of Moxifloxacin and placebo.

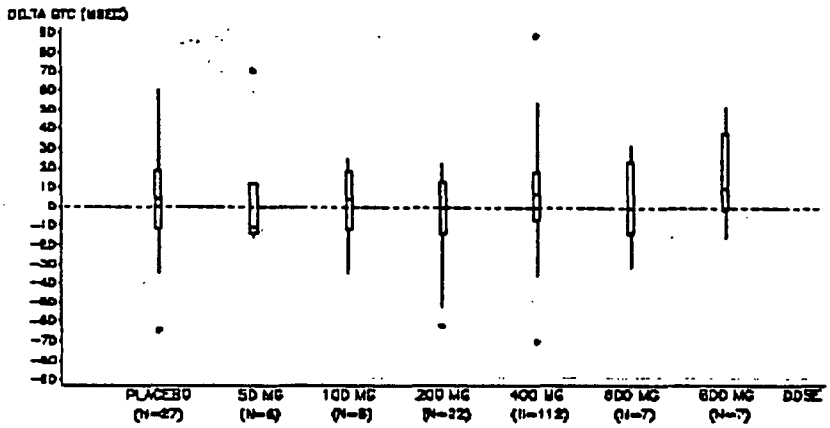
Table 46: Frequency of significant outliers in Moxifloxacin and placebo treated subjects

"Significant outliers"	BAY 12-8039	Placebo
QTc > 450* msec		
... all subjects	2.7 %	2.1 %
Δ QTc > 60 msec		
... all subjects	2.7 %	2.1 %
QTc > 450*msec AND Δ QTc > 30 msec		
... all subjects	2.1 %	2.1%
Δ QTc divided by baseline QTc ≥ 15 %		
... all subjects	3.2 %	2.1 %

* only male volunteers were part of this analysis

The relationship between QTc prolongation and a single oral dose was inconsistant. Doses of 400mg and 800mg resulted in a mean prolongation of the QTc of 6.9 and 16.7mS whereas doses of 50, 100, 200 and 600 mg did not result in a prolongation of the mean QTc as shown below.

Figure 1: Changes in QTc after oral Moxifloxacin at various doses

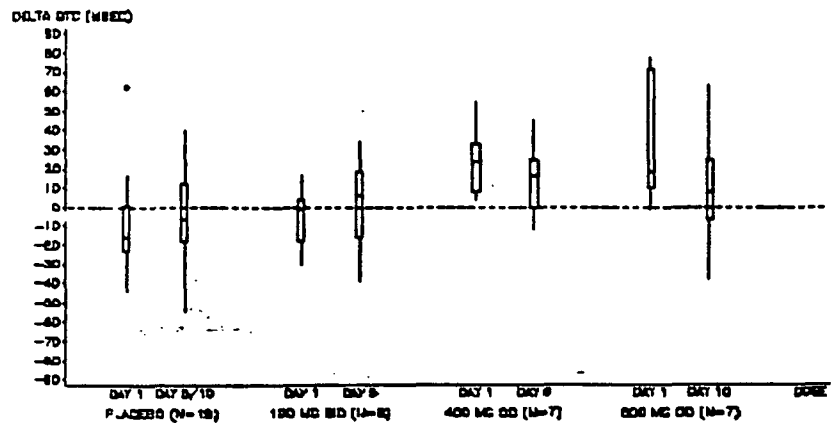


Box: 25th percentile; horizontal line: median; vertical line extended from the box as far as the data extend, to a distance of at most 1.5 interquartile ranges. Any value more extreme is plotted separately.

MO comment: The very small number of subjects in most groups other than the 400mg group do not allow a reliable comparison in the frequency of outliers. Of note, in the highest dosing group, the entire interquartile range showed a postive increase in mean QTc unlike any of the other doses.

Small numbers of volunteers were investigated at day 1 and day 5 of a daily regimen with doses ranging between 0 and 600 mg QD as shown below.

Figure 2: Change in QTc at day 1 and day 5 on daily treatment regimens

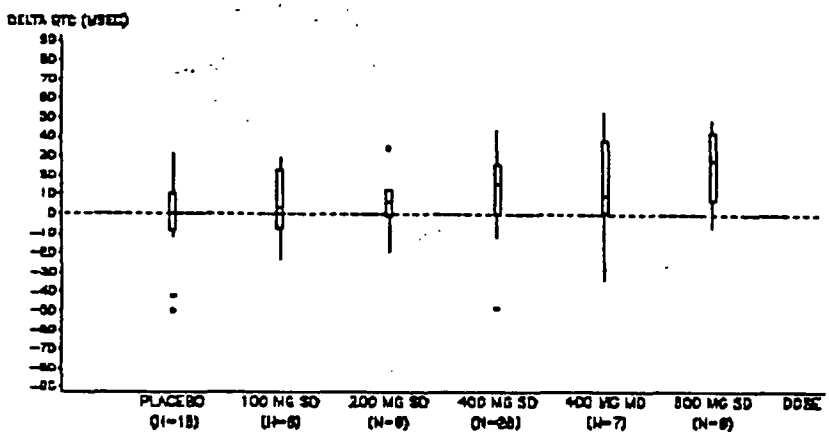


Box: 25th percentile; horizontal line: median; vertical line extended from the box as far as the data extend, to a distance of at most 1.5 interquartile ranges. Any value more extreme is plotted separately

MO comment: Despite small numbers of participants, this study demonstrates a compelling dose related effect of Moxifloxacin on the change in QTc from baseline. The effects of single and repeated dosing appear similar.

A range of intravenous doses were tested on small numbers of patients again demonstrating a clear dose effect on the change in QTc as shown below.

Figure 3: The effect of various intravenous doses (single and multiple over 15 to 60 minutes) on the change from baseline in QTc



Box: 25th percentile; horizontal line: median; vertical line extended from the box as far as the data extend, to a distance of at most 1.5 interquartile ranges. Any value more extreme is plotted separately

MO comment: Prolongation of QTc was related to the dose of intraveous Moxifloxacin. This figure and the previous demostrate a tendency for the effect to be more pronounced after the first dose than after multiple doses.

Changes in T wave morphology, U waves and duration of QRS

U waves: New U waves were not detected in any of the subjects on treatment.
T waves: A pre-existing pre-terminal negative T wave in one subject did not change on treatment.
In another subject, biphasic T waves in V2-3 were found before and after treatment with single oral and IV doses of 400mg and a single oral dose of 800mg. Since these changes were present at baseline, the investigator did not consider them treatment related.

QRS duration: This was analyzed by dose, duration, and route of administration. Compared to baseline, no effects of Moxifloxacin on the QRS duration were detected. Below are the data for QRS responses following a variety of single doses of Moxifloxacin.

Table 47: QRS duration pre- and post administration of a single oral dose of Moxifloxacin

DOSE	TIME	N	MEAN	SD	MINIMUM	MEDIAN	MAXIMUM	CHANGE TMAX VS. PRE-TREATMENT N	MEAN	SD	MINIMUM	MEDIAN	MAXIMUM
PLACEBO	PRE-TREATMENT	27	83.7	10.4	60.0	80.0	100.0						
	AT TMAX*	27	82.6	10.2	60.0	80.0	110.0	27	-1.1	9.3	-20.0	0.0	20.0
50 MG	PRE-TREATMENT	6	85.0	8.4	80.0	80.0	100.0						
	AT TMAX*	6	85.0	8.4	80.0	80.0	100.0	6	0.0	0.0	0.0	0.0	0.0
100 MG	PRE-TREATMENT	6	88.3	7.5	80.0	90.0	100.0						
	AT TMAX*	6	81.7	4.1	80.0	80.0	90.0	6	-6.7	10.3	-20.0	-10.0	10.0
200 MG	PRE-TREATMENT	22	86.4	9.5	70.0	85.0	100.0						
	AT TMAX*	22	85.5	8.6	70.0	80.0	110.0	22	-0.9	5.3	-10.0	0.0	10.0
400 MG	PRE-TREATMENT	112	85.4	10.6	60.0	90.0	110.0						
	AT TMAX*	112	84.5	12.0	50.0	80.0	110.0	112	-0.9	7.9	-20.0	0.0	20.0
600 MG	PRE-TREATMENT	7	91.4	12.1	80.0	90.0	110.0						
	AT TMAX*	7	87.1	12.5	80.0	80.0	110.0	7	-4.3	7.9	-20.0	0.0	0.0
800 MG	PRE-TREATMENT	7	85.7	11.3	70.0	80.0	100.0						
	AT TMAX*	7	82.9	9.5	70.0	80.0	100.0	7	-2.9	12.5	-20.0	0.0	20.0

MO comment: Compared to baseline, the mean QRS duration was unchanged or lower following all doses tested. The maximum value was only found to increase in the 200mg dose, and this increase was no different from that seen with placebo.

Repeated oral administration in 22 subjects and 19 controls over 5 to 10 days, and intravenous administration of between 0 and 600mg of Moxifloxacin as a single dose (56 drug treated subjects and 18 controls) also did not demonstrate any significant differences between drug-treated and placebo-treated subjects in the duration of the QRS complex.

A number of patient dependent factors were investigated to see if these contributed to QT prolongation. They included "reverse rate dependency" gender, QT dispersion

To investigate reverse rate dependency, 18 volunteers given various doses of oral Moxifloxacin were subjected to an exercise treadmill test, two hours after drug dosing. Projected QTc intervals were then calculated and reverse rate dependency was not detected.

QT dispersion was measured at the end of IV infusions, and 2 hours after oral doses as shown below for 18 valid subjects. All QT dispersions after oral doses were normal (less than 60mS). QT dispersion was above the upper limit of normal for two subjects treated IV. Their results (71mS and 78mS) were below 100mS (deemed the upper limit of normal by CPMP in their points to consider document).

Table 48: QT and QTc interval dispersion (mSec) at expected Cmax
(Arithmetic mean/std dev (Range)

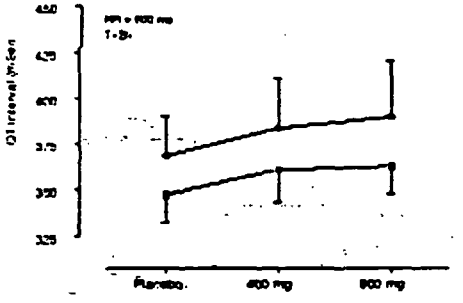
Parameter	Placebo	BAY 12-8839 400mg p.o.	BAY 12-8839 800mg p.o.	BAY 12-8839 400mg I.V.
QT dispersion	27.1/12.6	25.2/11.0	27.7/11.0	37.8/17.8
QTcB ** dispersion	27.9/13.9	26.0/11.6	28.3/11.1	37.1/17.4
QTcI ** dispersion	27.6/13.4	25.7/11.3	28.2/11.1	37.1/17.2

* 2 hours post oral dosing and end of the I.V. infusion
** QTcB : QT corrected by
*** QTcI : QT corrected by

Small numbers of males (9) and females (11) were compared to investigate the effect of gender on QT prolongation as shown below.

Figure 4: Comparison of predicted mean QT intervals for males and females

Mean calculated* QT interval values (mSec) in male and female subjects 2 hours after administration of placebo, 400 mg and 800 mg of moxifloxacin RR = 800 mSec) (all subjects valid for QT_{ac} analysis, n=18)



male subjects, — female subjects

Values were higher in females than males but all remained within the normal range.

MO comment: Given the small numbers of patients in this analysis and the wide variation of QTc intervals between patients, this analysis cannot be relied on to predict dose related frequencies of outliers.

Age: Elderly volunteers given infusions of 400mg Moxifloxacin over 15 or 60 minutes were compared with the results of a similar 15 minute infusion in young volunteers as shown below.

Table 49: Mean changes in QTc for elderly and young volunteers at different infusion rates

Population	N	Day of Treatment	Time of administration*	BAY 12-8039 Mean Δ QTc (range) [msec]	Placebo Mean Δ QTc (range) [msec]
Young Males	9	Day 1	0.25 hr to predose day 1	25.7 (N=9)	19.3 (N=3)
Elderly Males and Females	18	Day 1	0.25 hr to predose day 1	17.8 (N=12)	1.8 (N=6)
		Day 5	1 hr to predose day 1	5.1 (N=12)	- 13.7 (N=6)

* 0.25 hr is end of 15 minute infusion. 1 hr is end of 60 minute infusion

Changes in the QTc were less marked in the elderly than in the young and it was concluded that age did not influence the QT response.
MO comment: The small number of subjects in this study does not allow an adequate consideration of outlier responses among the elderly.

Evaluation of the relationship between plasma moxifloxacin concentration and QTc
The relationship between plasma concentration and prolongation of the QTc was investigated using the pooled data from the studies listed below.

Table 50: Synopsis of studies included in the analysis of dose versus QT prolongation

Study number	MKR no.	Description	N placebo	N active	Dose range [mg]	t_{max} range [h]	C_{max} range [ng/ml]
Oral data U.S./Europe							
101*	PH-20012	Dose escalation, SD, PO	20	32	50-800	0.5-4	220-5090
102*	PH-20035	Dose escalation MD, BID, PO	16	16	100-200	0.5-4	540-2730
104*	PH-20107	Food interaction	--	16	200	0.5-8	804-1720
105*	PH-20549	MD, QD PO	8	7	400	0.5-4	1780-4370
111*	PH-20477	SD, PO	8	8	800	2-4	3060-5410
113*	PH-20301	MD, QD, PO	3	7	600	0.5-3	3260-7190
114*	PH-20615	Ranitidine interaction	--	20	400	0.5-4	2090-4280
123	PH-20911	Maalox interaction	--	48	400	0.25-8	480-3650
133	PH-20852	8x50 vs 1x400 mg tablet	--	12	400	0.5-3	1760-3570
135	PH-20980	Pharmacokinetic interaction	--	24	400	0.5-4	1740-3890
139*	PH 27517	400mg PO vs IV-inf., mass balance	--	24	400	0.5-6	1620-5980
141*	PH-27304	Bioequivalence	--	48	400	0.5-4	1610-4090
142	PH-27385	Digoxin interaction	11	22	400		
149*	PH-27491	Different infusion rates	--	12	400-600	0.25-1.66	1170-6470
154	MOXRR 1456	Elderly volunteers	9	18	400	0.25-1	4760-10750
146*	PH-27392	Iron interaction	--	24	400	0.5-4	660-4630
157*	PH-27490	Dairy products interaction	--	24	400	0.5-4	1560-4780
Oral data Japan							
115	PH-27443	Dose escalation, SD, PO	--	18	100-600	0.5-3	2350-8444
120	PH-27445	Food effect	--	6	400	0.5-2	2120-3010
121	PH-27484	MD, QD, PO	3	6	400	0.5-3	3030-7560
IV data U.S./Europe							
132*	PH-27288	Dose escalation, SD, 30 min, IV-infusion	6	18	100-400	0.5-0.5	880-6540
139* (see above)	PH 27517	400mg PO vs IV-inf, mass balance	--	24	400	0.5-6	1620-5980
144*	PH-R 2007	MD, QD, 60 min IV-infusion	4	8	400	1-1.75	2660-5070

* automated and "manual" reading available

Subgroup analysis of oral data showed manual and automated readings to be similar.

The presumed time to reach Cmax (the time at which a concentration value was obtained in combination with a QTc measurement) was 2 hours after oral administration in European and American studies and 2 ½ hours in Japanese studies. For intravenous studies, C max was assumed at the end of infusions given over 0.25 to 1.67 hours in different studies.

Effects that were examined:

- Influence of rate of infusion on QT
- Influence of baseline QT on QT prolongation- Regression lines were compared for patients with baseline QTc in the upper 25% of all QTc's with the regression line for patients with baseline QTc in the lower 25% of all QTc's

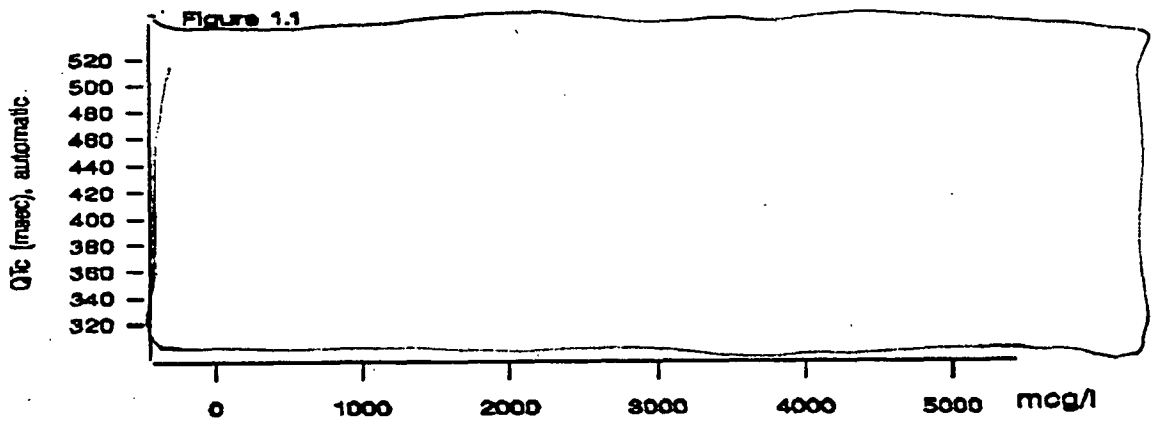
Four plots were made including

1) QTc at presumed T max
2) Change in QTc from baseline
3) Percentage change in QTc versus concentration
4) QTc pre-medication versus QTc at presumed Tmax for the following concentration groups >0-1500, >1500-2500,>2500-3500, <3500)

Results:

The QTc intervals of US/EU patients (n=199) were plotted in relation to plasma concentration in the figure below.

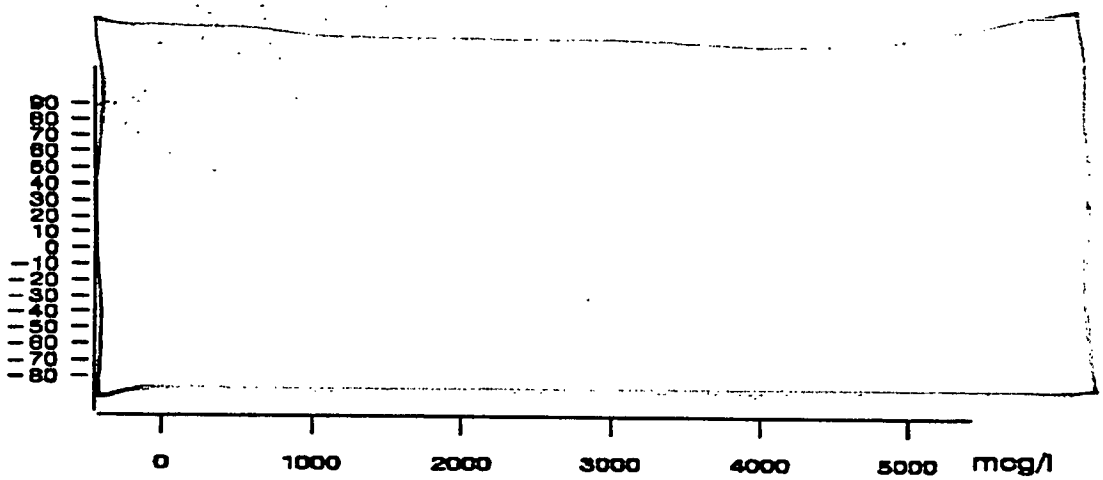
Figure 5: QTc versus Moxifloxacin concentration in US/EU patients PO (n=199) Linear regression and 5th and 95th percentile



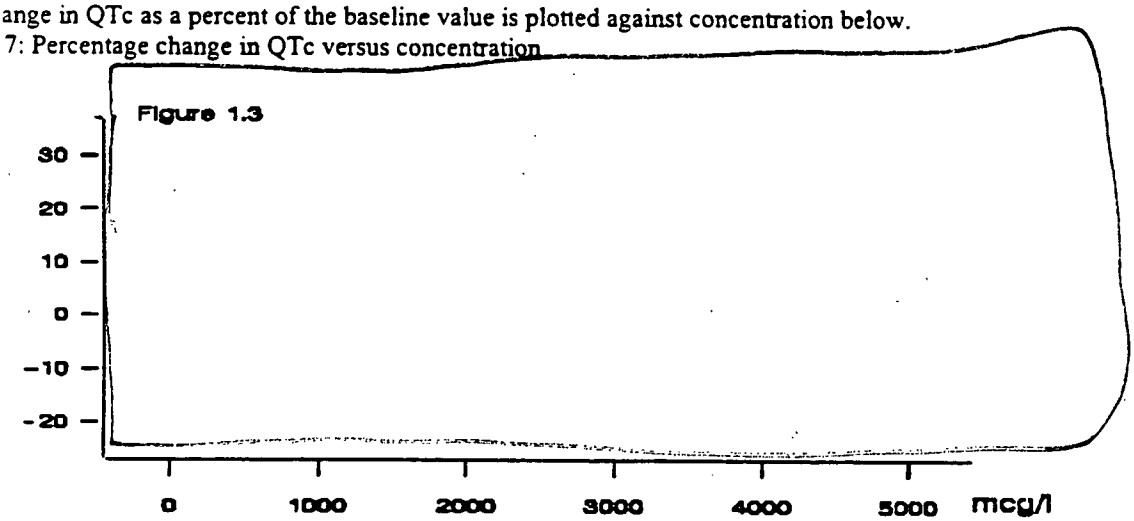
MO comment: **The analysis has incorporated repeat readings on each subject. These are potentially mutually dependent e.g. subjects with a high reading at one concentration may have a higher reading at the next concentration.**

The absolute change in QTc from baseline versus concentration is shown below

Figure 6: Change in QTc versus concentration

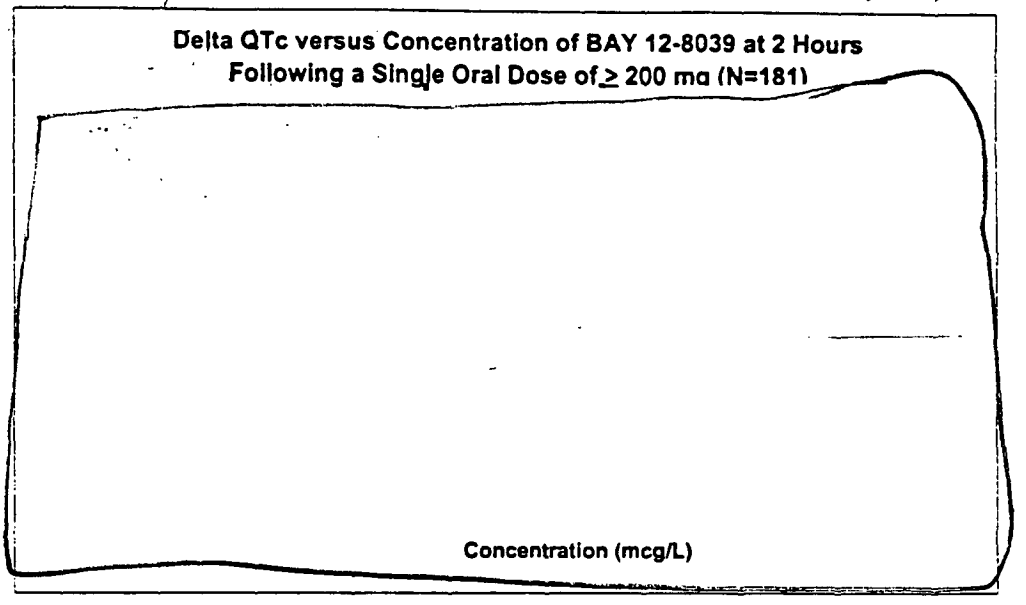


The change in QTc as a percent of the baseline value is plotted against concentration below.
Figure 7: Percentage change in QTc versus concentration



Since patients in the above analyses provided more than one data point each, a separate analysis was requested from the sponsor using only one value for each patient. The result of this analysis, (shown below) was similar.

Figure 8: Change in QTc versus plasma concentration of Moxifloxacin. (The Cmax (dotted line) ±SD (solid lines) for a population treated with a single dose of moxifloxacin 400mg is superimposed.)



Analysis of QTc responses grouped by concentration ranges.

QTc pre-medication versus QTc at presumed Tmax for the following concentration groups >0-1500, >1500-2500,>2500-3500, <3500 was plotted as shown below (n=189).

Figure 9: QTc versus concentration pre- and post- treatment per "concentration group"

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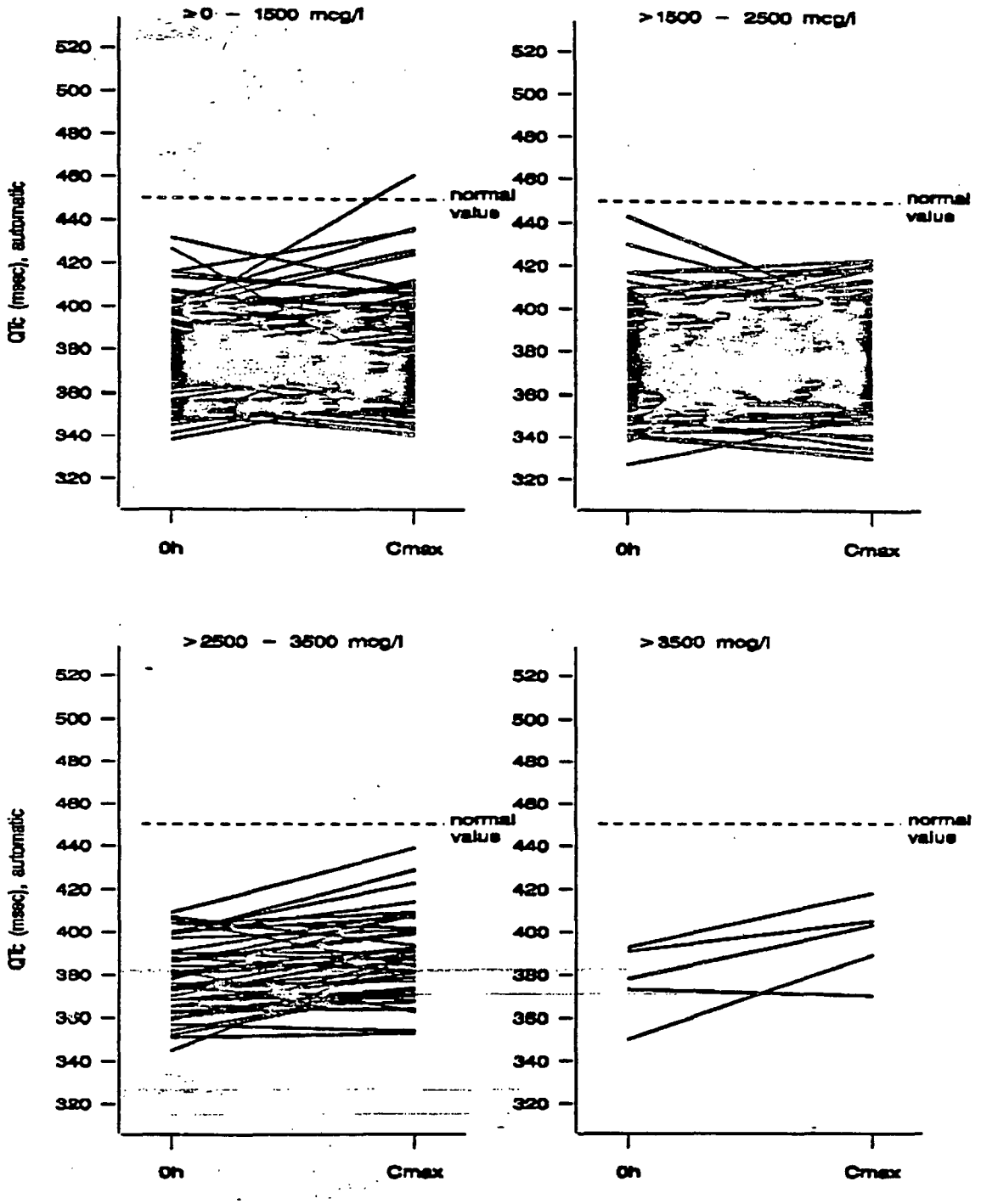
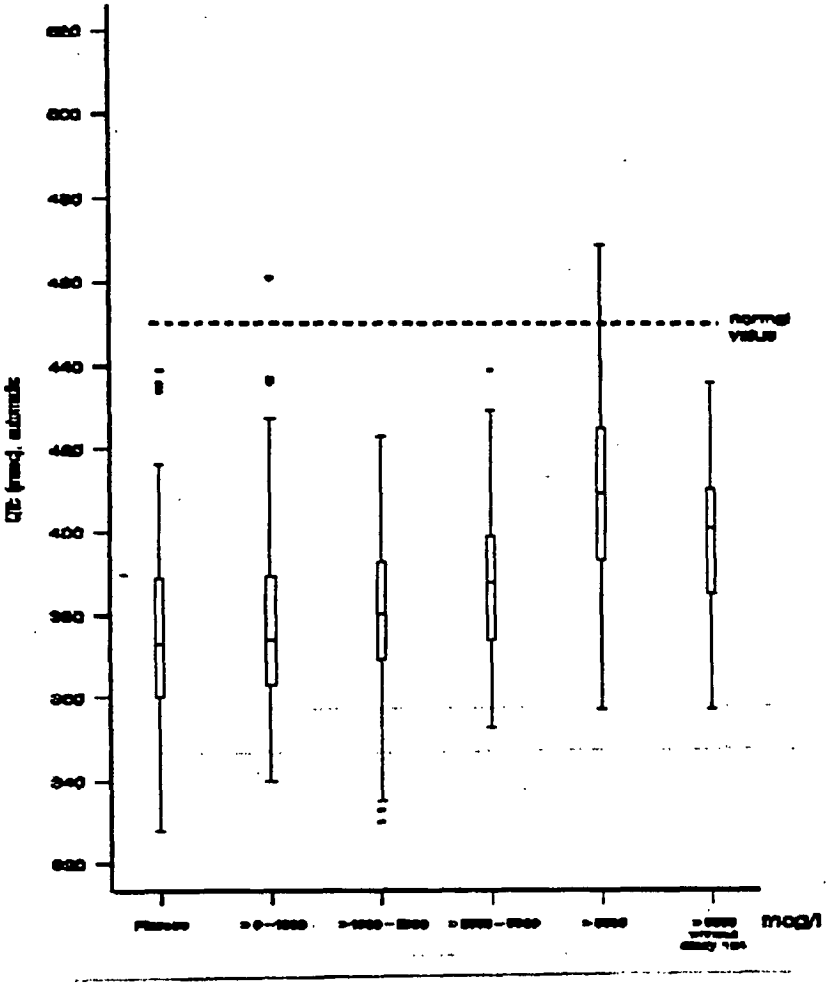


MO comment: In the lower concentration ranges upward and downward changes in QTc occur frequently. At concentrations >2500 increases in the QTc predominate suggesting a pharmacological threshold for QT changes in response to Moxifloxacin. At steady state, the mean Cmax is 4500µg/ml. Although limited data indicate a decrease in QTc with repeat dosing (see fig 2) the high Cmax at steady state suggest that most individuals would show an increase in QTc.

A box plot of the distribution of QTc intervals for six different serum concentration ranges among 319 experimental subjects was performed.

Figure 10: Box plot of QTc per concentration Group (n=319) median, 25th and 75th percentiles, 1.5 interquartile ranges and single points outside 1.5 interquartile ranges

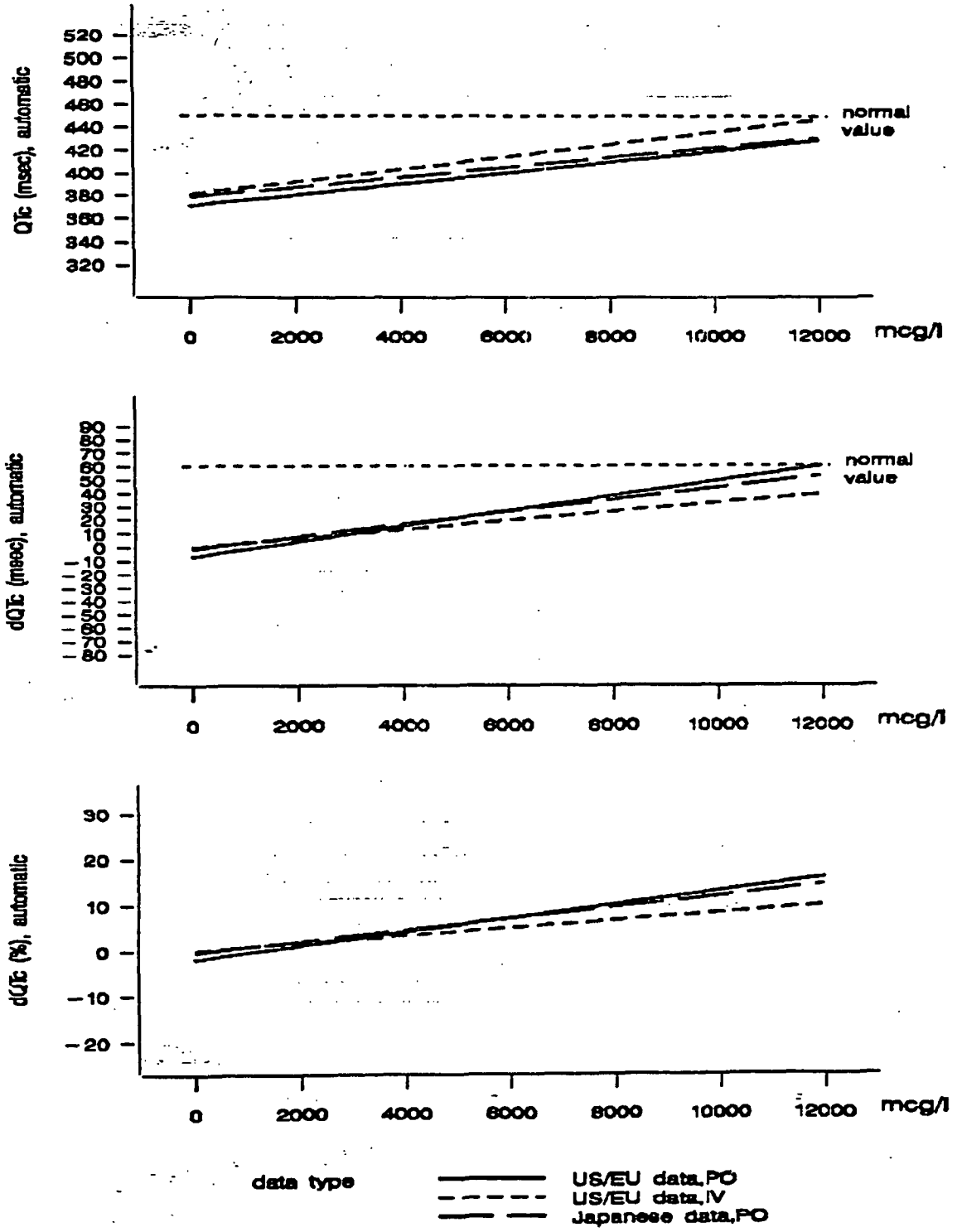


MO comment: Mean QTc rose with concentration and the interquartile range exceeded the normal when subjects in study 154 with concentrations >3500mcg/l were included.

Equivalent analyses were performed for the IV data set, for oral treatment in Japanese subjects, and for manually read ECGs in patients treated orally and intravenously.

A comparison of the regression lines from each of these data sets is shown below:

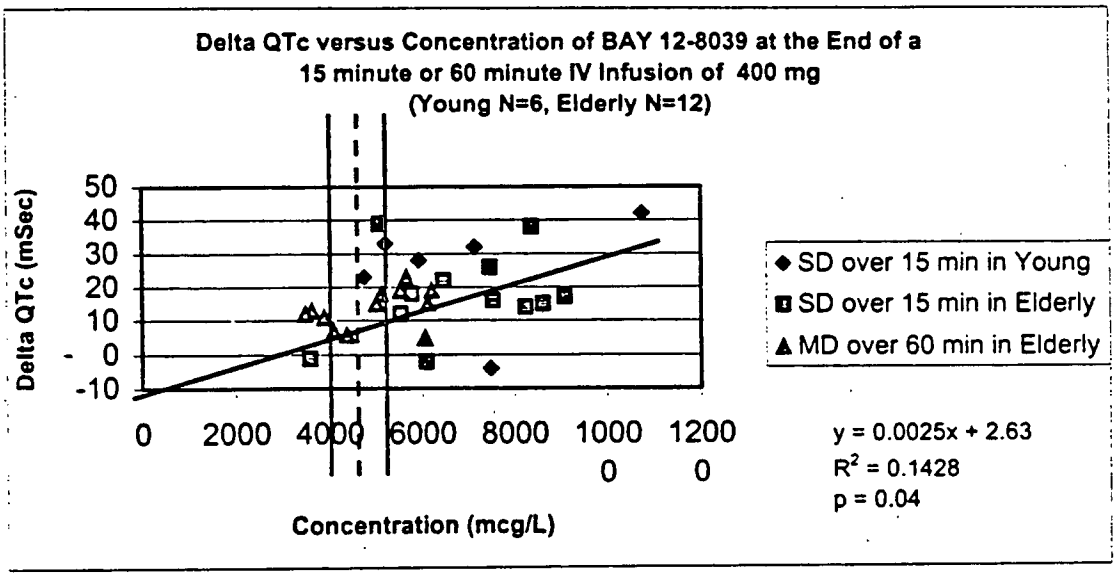
Figure 11: A comparison of regression lines for the oral, IV, and oral Japanese datasets using 3 analyses of QTc prolongation.


QTc (msec), automatic
520
500
480
460
440
420
400
380
360
340
320
normal value
0
2000
4000
6000
8000
10000
12000
mcg/l
dQTc (msec), automatic
normal value
dQTc (%), automatic
30
20
10
0
−10
−20
data type
US/EU data,PO
US/EU data,IV
Japanese data,PO

MO comments: All regression analysis in these different experimental populations showed shallow but very significant correlations between QTc increases and serum concentration. Regression slopes were very similar for the different study pools. Analysis of QTc prolongations according to concentration group suggest that the effects on QTc become more marked with concentrations above 2500mcg/l.

Study #154 consisting of 27 elderly US/EU volunteers was excluded by the sponsor from the combined analysis, based on the reasoning that baseline QTc's were longer than for other studies. It is notable that the concentration range in this oral treatment group reached 10750mcg/l, the highest concentration in this database. The results of this study are shown below.

Figure 12: Relationship between plasma moxifloxacin levels and the change in QTc for iv Moxifloxacin infused at various rates to elderly and young subjects. (The Cmax (dotted line) ±SD (solid lines) for a population treated with a single iv dose of moxifloxacin 400mg is superimposed.)



Influence of baseline QTc on the QTc prolongation:
Subjects with baseline QTc's below the 25th percentile (n=76) were compared with subjects with baseline QTc's above the 75th percentile (n=79)for prolongation of QTc.

Figure 13: Effects of baseline QTc on QTc prolongation. Subjects with baseline QTc <25th percentile (n=76)

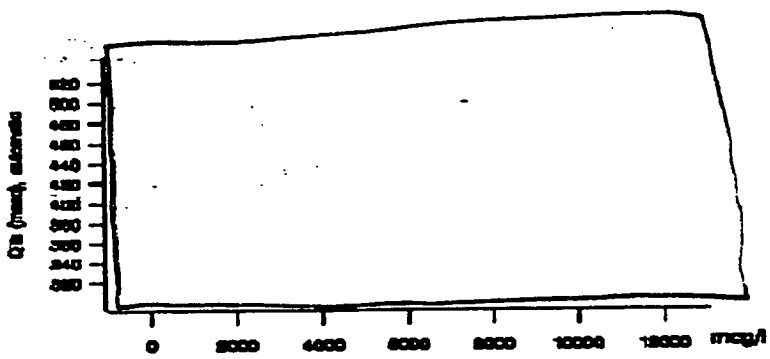
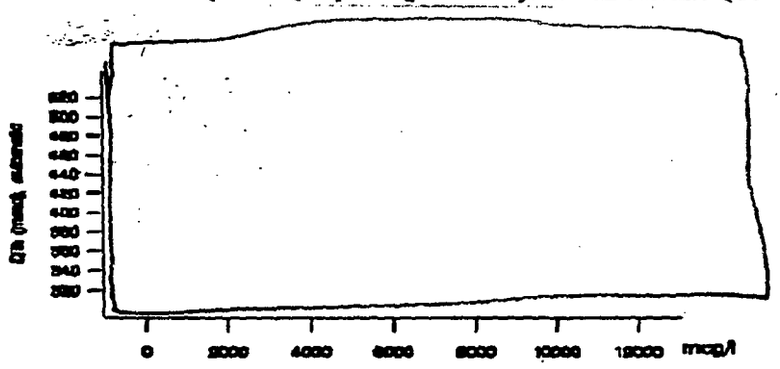


Figure 14: Effects of baseline QTc on QTc prolongation. Subjects with baseline QTc >75th percentile (n=79)



The slope of the regression line was steeper for subjects with a low baseline QTc than a higher one (for QTc, 0.0064 vs 0.0053, for change in QTc 0.0057 versus 0.0038 and for percentage change in QTc 0.0016 versus 0.0009).
More significantly, 6/79 individuals with higher baseline QTc's developed abnormal QTc's (>450mS) on treatment compared with 0/76 with lower baseline QTc's

Outliers in the regression analyses:
QTc>450 This was most apparent in the IV data pool where 6/87 subjects with concentrations above 4000mcg/ml developed QTc>450mS. Among 199 orally treated patients from the EU/US data pool and 33 from the Japanese pool,, one subject had an abnormally prolonged QTc at a drug concentration of less than 2500mcg/ml.

MO comment: Since outliers were no more frequent in orally versus IV treated subjects when concentrations were less than 4000mcg/ml, it appeared that concentration rather than route of administration contributed to the appearance of outliers.

Influence of infusion time on QTc
68 subjects were divided into four groups based on infusion times of 15, 30 60 and 100 minutes. In each group the change of QTc from baseline to end of infusion was examined for 4 different ranges of serum drug concentrations.

Figure 15: Influence of infusion time on the change in QTc from baseline shown for four ranges of serum concentration (n=68)

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MO comment: Increases in QTc predominated for all serum concentrations >2500mcg/ml. The rate of increase appeared similar regardless of infusion time. The small number of subjects in each group did not demonstrate a difference in maximum QTc when infusion times ranging from 15 minutes to 100 minutes were visually compared

Multiple dosing was used in 49 subjects over periods of 5 to 10 days. In these subjects there was no discernable trend when QTc's after the first dose were compared with QTc's after multiple doses.

Conclusions:
Prolongation of QTc was related to serum concentration
A threshold for QTc prolongation appeared at serum concentrations of approximately 2500mcg/l
The route of administration (PO or IV) did not affect the QTc
Multiple dosing did not affect the QTc
Subjects with higher baseline QTc's were more likely to enter the abnormal range after drug administration than subjects with low baseline QTc's

Metabolism
Moxifloxacin is eliminated by the liver and kidney. The drug is metabolized by sulfation the M1 metabolite) and glucuronidation (the M2 metabolite) in the liver and is not metabolized by the P 450 system. Plasma profiles of the two metabolites run in parallel with those of the parent drug hence the effect of the metabolites on QT cannot be distinguished from those of the parent drug.

M1 metabolites are increased in patients with renal failure and M2 metabolites are increased in patients with hepatic impairment. These two populations were examined for effects on the QTc

Hepatic impairment:
10 healthy and 8 hepatically impaired patients (6 Child Pugh A and 2 Child Pugh B) were compared. M1 was increased in hepatically impaired subjects compared to age matched normals, M2 was slightly increased and the parent drug concentrations were lightly decreased.

Table 51: Point and interval (90%CI) estimates of the true ratios of Cmax and AUC for patients with hepatic dysfunction relative to healthy subjects

	M1		M2	
Variable	Point Estimate (%)	90% Confidence Interval	Point Estimate (%)	90% Confidence Interval
Cmax	335.69	204.4 to 551.1	156.09	72.4 to 336.2
AUC	436.80	269.4 to 708.1	108.43	56.4 to 208.3

The baseline QTc of hepatically impaired subjects was higher than normals (a recognized phenomenon). This was thought to account for sporadically higher QTc levels (450-460mS) in the hepatically impaired over the 8 hour dosing interval. Mean QTc changes and number of QTc changes were no different between the groups (see table)

Table 52: Mean values of QTc from time 0 to time 8.00 hours after dose

	time (hh:mm) relative to dosing				
Subjects	0:00	0:30	1:00	2:00	8:00
Healthy	399 (361-431)	402 (363-446)	407 (363-437)	406 (363-429)	403 (369-438)
Hepatic Dysfunction	413 (380-444)	419 (382-469)	418 (377-473)	417 (385-469)	413 (355-474)

MO comment: It was noted that outer extremes in hepatically impaired subjects entered the abnormal range after dosing (predose maximum 444, post dose maximum 474) suggesting that hepatic impairment might result in an increase in the number of outliers. (Changes in QTc were similar for healthy and hepatically impaired subjects with no volunteer experiencing a change in QTc of >60Ms)

Renal impairment:
8 healthy and 24 patients with impaired renal function were treated with a single oral dose of 400mg. 8 subjects were selected for each renal failure group as shown in the figure below. Concentrations of M2 metabolite were increased in renally impaired subjects.

Table 53: Point estimates (PE% and 90% confidence intervals (CI) of true mean ratios for C max and AUC of M1 over a range of renal dysfunction (n=32)

	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
Variable	PE	90% CI	PE	90% CI	PE	90% CI
AUC	76.9	46.9 to 126.4	82.3	50.1 to 135.2	152.5	92.9 to 250.4
Cmax	90.6	61.6 to 133.4	81.6	55.4 to 120.1	101.2	68.7 to 149.0

group 1: creatinine clearance >90 ml/min/1.73m² (young healthy subjects)

group 2: creatinine clearance >60 and ≤ 90 ml/min/1.73m²

group 3: creatinine clearance >30 and ≤60 ml/min/1.73m²

group 4: creatinine clearance ≤30 ml/min/1.73m² (not on dialysis)

Table 54: Point estimates (PE% and 90% confidence intervals (CI) of true mean ratios for C max and AUC of M2 over a range of renal dysfunction (n=32)

	Group 2 : Group 1		Group 3 : Group 1		Group 4 : Group 1	
Variable	PE	90% CI	PE	90% CI	PE	90% CI
AUC	155.1	97.6 to 246.4	144.6	92.4 to 226.4	248.4	158.7 to 388.8
Cmax	172.4	106.4 to 279.5	132.6	83.1 to 211.4	140.2	87.9 to 223.5

group 1: creatinine clearance >90 mL/min/1.73m² (young healthy subjects)

group 2: creatinine clearance >60 and ≤ 90 mL/min/1.73m²

group 3: creatinine clearance >30 and ≤60 mL/min/1.73m²

group 4: creatinine clearance ≤30 mL/min/1.73m² (not on dialysis)

Although mean values of the QTc were not substantially different for normal and renally impaired subjects, maximum levels were noted to be higher in renally impaired subjects.

Table 55: Mean values (range) of the QTc interval (msec) from pre-dose to 8 hours after dose

	time (hh:mm) relative to dosing				
Subjects	0:00	0:30	1:00	2:00	8:00
Group 1	426	426	430	431	424
Group 2	424	431	431	430	432
Group 3	423	428	431	426	430
Group 4	430	434	435	436	437

group 1: creatinine clearance >90 mL/min/1.73m² (young healthy subjects)

group 2: creatinine clearance >60 and ≤ 90 mL/min/1.73m²

group 3: creatinine clearance >30 and ≤60 mL/min/1.73m²

group 4: creatinine clearance ≤30 mL/min/1.73m² (not on dialysis)

No subjects developed changes in the QTc interval of >60 mS

Analysis of arrythmias (Phase 1 and II studies)

Two reports of arrhythmias were found among all patients in phase 1 and II studies.

1. An elderly woman treated with a single 200mg oral dose complained of an intermittent irregular heartbeat approximately 12 hours after dosing. An ECG at the time was reported normal and the symptoms ceased after the ECG. The relationship to drug was considered "remote" by the investigator.
2. A volunteer had completed a 33 minute infusion of 400mg of Moxifloxacin and was receiving an "IV extension" for 11 minutes to satisfy the single blind study design when he reported weakness and nausea. ECG showed a sinus bradycardia of 35 to 40 BPM. The patient turned pale and feinted with an asystole of several seconds on the monitor. Upon cardiac resuscitation the subject developed a ventricular rhythm of 20BPM. Upon treatment with adrenaline (3ml 1:10000 and Ringers) solution the subject developed a junctional rhythm, then a regular sinus rhythm. A transient change in the appearance of the QRS (resembling a LBBB) was seen initially (and attributed by the sponsor to the adrenaline). An hour after the event, ECGs were normal. An independent cardiologist saw the patient on the same day. A cardiac ultrasound, high resolution ECG exercise ECG and Chest Xray were reported normal as was the clinical examination. The event was evaluated as a vasovagal syncope and confirmed by a second cardiologist.

MO comment: While a relationship between the drug and a bradyarrhythmia cannot be excluded on the basis of the presented information, the clinical profile does not suggest TdP as a consideration.

Clinical phase III studies
Following the observation that Moxifloxacin produced QTc prolongations in clinical pharmacology studies, the protocols of active phase III studies were modified to acquire information on electrocardiographic changes while on treatment while excluding patients specifically perceived to be at greater risk for QTc elevations.
The following amendments were implemented to all clinical studies as of May 27, 1997
Exclusion of patients with known prolonged QTc.
Exclusion of patients on drugs known to prolong QTc (eg amidoarone, sotalol, dysopyramide, quinidine, procainamide, [redacted]
Performance of baseline and post-treatment 12 lead ECGs (1.5 to 2 hours after dosing).

Variation of data between countries:
Some non-US studies excluded patients at risk for QTc prolongation but did not require ECG's in all patients. The treatment day for the post-dose tracing was variable, and ECG machinery varied.
Electronic data acquisition was standardized in North American trials whereas studies outside of North America used a mixture of electronic and paper tracings.

Patients
Data valid for safety evaluation were available on 8341 patients, 4926 treated with Moxifloxacin and 3415 treated with comparative agents.

Of the 8341 patients, 2234 had ECGs
Based on the quality of ECG data, the sponsor identified two pools of subjects;

The "ITT" population required:
- Paired ECGs, one identified as pre-therapy
- Subjects with either ECG showing "long followed by short RR interval" were excluded

The "paired valid ECGs" population required:
Criteria for ITT population as well as
- Good technical quality of both ECGs
- A post dosing ECG 15 minutes to 6 hours after study drug dosing.

MO comment: while the difficulties in obtaining ECGs within narrow time limits are recognized, the wide range of timing allowed considerable variation in drug levels at the time the ECGs were measured.

The patients excluded from either of the ECG populations analyzed are described below.

Table56: Reasons for exclusion of patients with paired ECGs

Methodological Reasons	Technical Reasons	Clinical Reasons[2]
Excluded from ITT Analysis: • Baseline ECG not clearly identified (by date and time). • No post-dose ECG **Excluded from Paired Valid Analysis:** • Date or time of one of ECG pairs unknown • Second (post-dosing) ECG outside specified window (15 min to 6 hours after last dose)	**Excluded from Paired Valid Analysis** • Poor-quality or reduced-size copy • Poor-quality ECG recording (signal-to-noise ratio ≤ 0.5 and/or wandering baseline) • Missing leads or >2 poorly labelled leads • Number of recorded RR cycle lengths <3 with no accompanying (≥30 second) rhythm strip • Different machines used for ECG pair • Missing horizontal or vertical scale • QRS complexes truncated because of recording amplitude >20 mV	**Excluded from ITT and Paired Valid Analysis:** • VPCs (≥3 per 10 seconds) • Bigeminal or trigeminal rhythm • Salvos of ≥3 VPCs • Underlying atrial fibrillation or flutter • Atrial or supraventricular tachycardia

1 Coding of reasons for exclusion of ECGs is provided in Appendix D.
2 Although the ECG tracings themselves are excluded from the QT$_c$ effect analyses, these patients are still included in the evaluation of other ECG findings.

Analysis of ECGs from "ITT" population:

For the "paired valid ECG" and "ITT" populations, two data pools were examined, all studies and all comparative studies.
Of the 2113 patients with ECGs, 345 were excluded from the ITT population for the reasons listed above. The remaining 1768 included 76 patients on Moxifloxacin 200mg per day, 919 on Moxifloxacin 400mg per day, and a total of 773 patients treated with comparator agents of which 207 received clarithromycin.

a) Analysis of mean changes in the QTc (ITT population)

Table 57: Change in QTc

	N	Mean Δ QTc (mS)	95% CI (mS)
Moxifloxacin 200mg	76	2mS	-3 to 8
Moxifloxacin 400mg	919	5mS	3 to 7
Clarithromycin	207	2	-2 to 5
All comparators	773	0	-2 to 2

Table 58: Change in QT (uncorrected)

	N	Mean Δ QT (mS)	95% CI (mS)
Moxifloxacin 200mg	76	7	0 to 14
Moxifloxacin 400mg	919	14	12 to 16
Clarithromycin	207	12	8 to 17
All comparators	773	8	6 to 11

No significant differences were seen in the treatment emergent mean change of the QRS interval between the groups as shown below.

Table 59: Change in QRS on treatment

	N	Mean Δ QRS(mS)	95% CI (mS)
Moxifloxacin 200mg	76	-1	-4 to 2
Moxifloxacin 400mg	919	1	0 to 1
Clarithromycin	207	1	-1 to 2
All comparators	773	0	-1 to 1

b) Analysis of "outliers"

According to the points to consider document (March 1997) of the [redacted], prolongation of the QTc was classified as:

Normal: <430 mS (males) <450mS (females)
Borderline: 430-450mS (males) 450-470mS (females)
Prolonged: >450 (males) >470 (females)
Markedly prolonged: >500mS

Table 60a: Shift analysis of outliers
Moxifloxacin 200mg

		At C max				
		Normal	borderline	Prolonged	>500	Total
baseline	Normal	45	8 10.5%	3 3.9%	0	56
	Borderline	5	6	3 3.9%	0	14
	Prolonged	0	1	4	0	5
	>500	0	1	0	0	1
	Total	50	16	10	0	76

Table 60b
Moxifloxacin 400mg

		At C max				
		Normal	borderline	Prolonged	>500	Total
baseline	normal	576	107 11.6%	23 2.5%	1 .1%	707
	borderline	57	66	34 3.7%	2 0.2%	159
	prolonged	10	12	27	0	49
	>500	1	1	1	1	4
	Total	644	186	85	4	919

Table 60c
All comparators

		At C max				
		Normal	borderline	Prolonged	>500	Total
Bascline	normal	519	62 8%	14 1.8%	1 .1%	596
	borderline	54	45	23 3%	0	122
	prolonged	10	19	21	1 .1%	51
	>500	2	2	0	0	4
	Total	585	128	58	2	773

Table 60d
Clarithromycin

		At C max				
		Normal	borderline	Prolonged	>500	Total
baseline	normal	117	23 11%	7 3.4%	0	147
	borderline	10	18	10 4.8%	0	38
	prolonged	3	8	11	0	22
	>500	0	0	0	0	0
	Total	130	49	28	0	207

Underlying risk factors for treatment related QTc prolongation were examined below.

Table 61a: Risk factors for treatment related QTc prolongation
All Moxifloxacin (ITT)

	N	60>=DeltaQTc>=30	Delta QTc >60
<65 years	756	88 (11.6%)	12 (1.6%)
>=65 years	239	29 (12.1%)	5 (2.1%)
Male	468	57 (12.2%)	4 (0.8%)
Female	527	60 (11.4%)	13 (2.5%)
Normal K or Ca	897	94 (10.5%)	10 (1.1%)
Low K or Ca	94	23 (24.5%)	7 (7.4%)
No cardiac disease	947	114 (12%)	16 (1.7%)
Cardiac disease	48	3 (6.3%)	1 (2.1%)
Baseline QTc normal	763	112 (14.7%)	15 (2.0%)
Borderline	173	4 (2.3%)	2 (1.2%)
Prolonged	59	1 (1.7%)	0 (0%)

Table 61b: Risk factors for treatment related QTc prolongation
All comparators (ITT)

	N	60>=DeltaQTc>=30	Delta QTc >60
<65 years	598	45 (7.5%)	6 (1%)
>=65 years	175	20 (11.4%)	4 (2.3%)
Male	391	30 (7.7%)	4 (1%)
Female	382	35 (9.2%)	6 (1.6%)
Normal K or Ca	682	56 (8.2%)	8 (1.2%)
Low K or Ca	84	9 (10.7%)	2 (2.4%)
No cardiac disease	729	59 (8.1%)	9 (1.2%)
Cardiac disease	44	6 (13.6%)	1 (2.3%)
Baseline QTc normal	596	61 (10.2%)	10 (1.7%)
Borderline	122	2 (1.6%)	0 (0%)
Prolonged	55	2 (3.6%)	0 (0%)

MO comment: Greater treatment emergent prolongation of the QTc was more frequent in elderly patients, females, those with an indication of hypokalemia or hypocalcemia, and those with an indication of cardiac disease. This was seen both for Moxifloxacin and comparator groups. In both treatment groups, patients with normal QTc's at baseline were more likely to develop significant treatment emergent changes in QTc than those with prolonged QTc at baseline. A disproportionately large percentage of Moxifloxacin treated patients with an indication of hypokalemia or hypocalcemia showed marked treatment related prolongations of the QTc compared with patients given comparator agents. This suggests that Moxifloxacin should be avoided in patients likely to have these electrolyte abnormalities.

Analysis of ECGs from "paired valid ECG" population

Of 2113 patients with ECG's from comparative studies worldwide, paired valid ECGs were available for 1111 patients. The large number of patients with paired ECGs excluded from the "paired valid ECG" population was noted for reasons of technical quality, absent data on the timing of the ECGs and underlying abnormalities of rhythm as described below.

Table 62: Reasons for exclusion from analysis of paired valid ECGs in all comparative studies
Moxifloxacin (all) Total number of ECGs = 2255

NON-PAIRED ECGS (1)	RELATIVE TIME OF ECG NOT ASSESSABLE (2)	ON-STUDY ECG NOT IN DEFINED TIME-WINDOW (3)	POOR QUALITY OF PHOTOCOPY OF ECG (4)	POOR QUALITY OF ECG (5)	MISSING/UN-DEFINED LEADS (6)	INSUFFICIE-NT NUMBER OF CYCLES RECORDED (7)	DIFFERENT MACHINES USED (8)	SCALE(S) MISSING (9)	TRUNCATED QRS COMPLEXES (10)
104	131	122	19	92	12	9	10	65	3

(CONTINUED)

VENTRICULAR PREMATURE BEATS (11)	ATRIAL FIBRILLATI-ON (14)	ATRIAL FLUTTER (15)	ATRIAL TACHYCARDIA (16)
83	24	6	1

Comparator (all) Total number of ECGs=1936

NON-PAIRED ECGS (1)	RELATIVE TIME OF ECG NOT ASSESSABLE (2)	ON-STUDY ECG NOT IN DEFINED TIME-WINDOW (3)	POOR QUALITY OF PHOTOCOPY OF ECG (4)	POOR QUALITY OF ECG (5)	MISSING/UN-DEFINED LEADS (6)	INSUFFICIE-NT NUMBER OF CYCLES RECORDED (7)	DIFFERENT MACHINES USED (8)	SCALE(S) MISSING (9)	TRUNCATED QRS COMPLEXES (10)
91	132	101	10	65	16	9	14	74	3

(CONTINUED)

VENTRICULAR PREMATURE BEATS (11)	ATRIAL FIBRILLATI-ON (14)	ATRIAL FLUTTER (15)
53	19	1

Of the 1111 patients with paired valid ECGs, 559 received Moxifloxacin 400mg per day and 37 received 200mg per day as shown below:

Table 63: Numbers of patients included in each analysis pool

	No of Patients with ECGs		No of Patients with ECGs Valid for ITT Analyses		No of Patients with Paired Valid ECGs	
Indication	200 mg	400 mg	200 mg	400 mg	200 mg	400 mg
Sinusitis		58		55		19
Bronchitis	89	337	71	285	37	166
Pneumonia	9	297	5	231	0	163
Other		100		62		37
Total	98	1041	76	825	37	559

The demographic characteristics of patients in the global pool with paired valid ECG's was similar for those treated with Moxifloxacin and those treated with comparators as shown below.

MO comment: Recognizing the dose related effect of Moxifloxacin on the QT interval, the medical officer elected to examine the population receiving 400mg QD separately since patients on half the dose were likely to dilute the impact of treatment on the QT interval.

Table 64: Demographic characteristics at baseline of patients with paired valid ECG's in all comparative studies using Moxifloxacin 400mg QD.

VARIABLE	TREATMENT GROUP	N	MEAN	SD	MINIMUM	MEDIAN	MAXIMUM
AGE (YEARS)	BAY 12-8039 200 MG	37	54.38	15.26	26.00	56.00	86.00
	BAY 12-8039 400 MG	559	49.30	17.23	18.00	49.00	88.00
	BAY 12-8039 TOTAL	596	49.61	17.15	18.00	49.00	88.00
	CLARITHROMYCINE	136	51.55	16.15	19.00	51.50	88.00
	ALL COMPARATORS	515	47.76	17.04	18.00	47.00	88.00
BODY WEIGHT (KG)	BAY 12-8039 200 MG	37	79.40	22.22	45.50	78.60	127.30
	BAY 12-8039 400 MG	558	76.30	18.62	42.00	74.75	181.80
	BAY 12-8039 TOTAL	595	76.49	18.86	42.00	75.00	181.80
	CLARITHROMYCINE	136	75.40	18.04	38.60	75.00	136.40
	ALL COMPARATORS	513	76.18	18.94	33.00	74.00	185.00
HEART RATE (/MIN)	BAY 12-8039 200 MG	37	73.89	10.48	53.00	74.00	98.00
	BAY 12-8039 400 MG	559	79.46	16.12	47.00	77.00	141.00
	BAY 12-8039 TOTAL	596	79.11	15.88	47.00	77.00	141.00
	CLARITHROMYCINE	136	82.63	17.35	51.00	79.00	126.00
	ALL COMPARATORS	515	79.87	17.52	44.00	77.00	159.00
QTCB (SEC)	BAY 12-8039 200 MG	37	0.43	0.02	0.40	0.43	0.48
	BAY 12-8039 400 MG	559	0.42	0.03	0.00	0.42	0.55
	BAY 12-8039 TOTAL	596	0.42	0.03	0.00	0.42	0.55
	CLARITHROMYCINE	136	0.43	0.02	0.34	0.43	0.49
	ALL COMPARATORS	515	0.42	0.03	0.30	0.42	0.59

Two pools of comparator treated subjects were identified, 136 patients treated with clarithromycin and 515 patients treated with all comparators (including the clarithromycin treated patients).

The baseline characteristics of each treatment group are described below.

Table 65: Baseline characteristics of Moxifloxacin- and comparator- treated patients with valid paired ECGs

	Moxifloxacin (n=559)	Clarithromycin (n=136)	All comparators (n=515)
Past cardiac problem	4% (21)	7% (9)	5% (28)
Comedication causing prolonged QT	65% (362)	54% (74)	34% (174)
Indication of hypokalemia or hypocalcemia	11% (59)	2% (3)	10% (50)
<430mS (male) <450mS (female)	76% (424)	71% (97)	76% (392)
>= 430- 450mS (male) >= 450-470mS (female)	18% (100)	19% (26)	17% (90)
>= 450-500mS (male) >=470-500mS (female)	6.0% (33)	10% (13)	5% (30)
>=500mS	0.36% (2)	0	0.58% (3)

More Clarithromycin-treated patients had longer baseline QTc intervals and less had an indication of hypokalemia or hypocalcemia than the other treatment groups.

The change in the mean QTc and the change in the maximum QTc for each treatment group from baseline to presumed Cmax (30 minutes to 6 hours after drug administration) is shown below.

Table 66: Change in mean QTc (mS) and change in maximum QTc (mS) for each treatment group
Patients with "paired valid ECGs"
200mg/day n=37
400mg/day n=559
comparators n=515
clarithromycin n=136

Mean changes of QTCB (QT) in mS for patients with valid paired ECGs

	N	Mean change	95% CI	max
Moxi 200mg	37	4 (3)	-1 to 10 (-6 to 11)	41 (50)
Moxi 400mg	559	5 (12)	3 to 7 (9 to 15)	218 (277)
Clari	136	2 (12)	-2 to 6 (6 to 18)	56 (140)
All comparators	515	0 (7)	-2 to 2 (4 to 10)	80 (140)

Table 67: Maximum ΔQTc for each treatment group

	Maximum ΔQTc	
Moxifloxacin 200mg	**35**	**41**
Moxifloxacin 400mg	**96**	**218**
Clarithromycin	**41**	**56**
All comparators	**80**	**63**

For all Moxifloxacin treated patients, mean changes and maximum changes of QTc were greater in females than males. Overall, the mean change of QTc for Moxifloxacin was greater than the mean change for comparators. Notably, the largest changes in the maximum QTc occurred in patients treated with the higher dose of Moxifloxacin, particularly among the females.

In the global safety pool the mean QTc was increased by 4-5mS. For the ITT analysis, the mean change in QTc was 5 mS. (1.2% above the baseline mean).

Eight patients in the global pool were identified with a QTc > 500mS at some time during the study. The details are shown below.

Table 68: Characteristics of patients developing a post-treatment QTc >500mS.

Treatment group	Pre dose	Post dose	Confounders
Moxi 400	365	583	Hypokalemia
Moxi 400	439	535	RBBB
Moxi 400	452	519	
Comparator	>500	<500	
Comparator	>500	<500	
Comparator	>500	<500	
Comparator	494	>500	

3/559 patients treated with Moxifloxacin 400mg developed new QTc's > 500mg after treatment compared with 1/515 comparator treated patients.

A comparison of the percentage of patients with baseline and post-treatment QTc abnormalities is shown below.

Table 69: Frequency of QTc abnormalities (patients with valid paired ECGs)

Table 4 - Frequency Table of QT_c Abnormalities in Patients with Valid Paired ECGs in All Comparative Studies

		Abnormal		
	Normal[1]	Borderline[2]	Moderately Prolonged[3]	Markedly prolonged[4]
BAY 12-8039, 200 mg				
Baseline	27 (73%)	7 (19%)	3 (8%)	0 (0%)
Post-dosing[5]	25 (68%)	7 (19%)	5 (14%)	0 (0%)
BAY 12-8039, 400 mg				
Baseline	424 (76%)	100 (18%)	33 (6%)	2 (0.4%)
Post-dosing[5]	390 (70%)	114 (20%)	52 (9%)	3 (0.5%)
Clarithromycin				
Baseline	96 (71%)	27 (20%)	13 (10%)	0 (0%)
Post-dosing[5]	84 (62%)	30 (22%)	22 (16%)	0 (0%)
All comparators[6]				
Baseline	392 (76%)	90 (17%)	30 (6%)	3 (0.6%)
Post-dosing[5]	389 (76%)	81 (16%)	44 (9%)	1 (0.2%)

Reference: Table 7.1, Appendix C4

1 <430 msec for men and < 450 msec for women

2 ≥430 and < 450msec for men, and ≥450 and < 470 msec for women

3 ≥450 msec for men and ≥470 msec for women

4 ≥ 500 msec, both sexes

5 30 min to 6 h after last dose

6 All comparative drugs, including clarithromycin

Table 70: ECG changes for comparator treated patients excluding clarithromycin

Comparators excluding clarithromycin				
	Normal	Borderline	Moderately prolonged	Markedly prolonged
Baseline	296 (78%)	63 (17%)	17 (4.5%)	3 (0.7%)
Post dosing	305 (80%)	51 (13%)	22 (6%)	1 (0.3%)

A greater percentage of patients treated with moxifloxacin developed abnormal ECGs than did patients treated with all comparators. A greater percentage of patients treated with clarithromycin developed abnormal ECGs than did those treated with Moxifloxacin.

Table 71 Shift analysis of outliers in various treatment groups

a) Moxifloxacin 400mg (males)

		At C max			
		<430mS	430-450	>450	Total
baseline	<430	122	35	5	162
	430-450	20	29	22	71
	>450	7	6	18	31
	Total	149	70	45	264

b) Moxifloxacin 400mg (females)

		At C max			
		<450mS	450-470	>470	Total
baseline	<450	228	29	5	262
	450-470	12	13	4	29
	>470	1	2	1	4
	Total	241	44	10	295

For males and females 35 had significant QTc prolongations at baseline compared with 55 after treatment. 36/559 (6.4%) developed new significant QTc prolongation on treatment.

c) Clarithromycin (Males)

		At C max			
		<430mS	430-450	>450	Total
baseline	<430	22	10	4	36
	430-450	4	11	6	21
	>450	2	2	7	11
	Total	28	23	17	68

d) Clarithromycin (females)

		At C max			
		<450mS	450-470	>470	Total
baseline	<450	54	4	2	60
	450-470	1	3	2	6
	>470	1	-	1	2
	Total	56	7	5	68

For males and females, 13 had significant QTc prolongations at baseline compared with 22 after treatment. 14/136 (10.3%) developed new significant QTc prolongations on treatment

e) All comparators (Males)

		At C max			
		<430mS	430-450	>450	Total
baseline	<430	129	23	7	159
	430-450	24	25	14	63
	>450	4	8	14	26
	Total	157	57	35	249

f) All comparators (females)

		At C max			
		<450mS	450-470	>470	Total
baseline	<450	214	16	3	233
	450-470	15	7	5	27
	>470	3	1	2	6
	Total	232	24	10	266

For males and females, 32 had significant QTc prolongations at baseline compared with 45 after treatment.

29/515 (5.6%) developed new significant QTc prolongations on treatment.

g) comparators excluding clarithromycin (Males)

		At C max			
		<430mS	430-450	>450	Total
baseline	<430	117	13	3	123
	430-450	20	14	8	42
	>450	2	6	7	15
	Total	129	34	18	181

h) comparators excluding clarithromycin (females)

		At C max			
		<450mS	450-470	>470	Total
baseline	<450	160	12	1	173
	450-470	14	4	3	21
	>470	2	1	1	4
	Total	176	17	5	198

For males and females, 19 had significant QTc prolongations at baseline compared with 23 after treatment.

15/379 (4.0%) developed new significant QTc prolongations on treatment.

MO comment: New significant prolongations of QTc were most common following treatment with clarithromycin, then with moxifloxacin in comparison with other comparator drugs.

Patients with the most significant treatment emergent changes in QTc were identified in a consult from the cardio-renal division as those with QTc prolongations of >80mS and or a post treatment QTc > 500mS. A listing of such patients is shown below.

Table 72: Extreme outliers with ΔQTc>80mS or QTc>500mS

Patients with changes from baseline of >80mS or QTc>500mS (from Dr Gordon, cardiology)

patient	Baseline QTc	On drug QTc	Change from baseline
1	365	[redacted]	218
2	367	479	112
3	363	472	109
4	345	452	107
5	439	[redacted]	96
6	334	419	85
7	342	424	82
8	417	498	81
9	452	[redacted]	67

There were no patients in the Clarithromycin group and 1 patient in the other comparator group with QTc changes

Fisher's 2 sided exact p-value

Drug	incidence	P value compared to Moxifloxacin
Moxifloxacin	9/596 (1.51%)	
Comparators (all)	1/515 (0.19%)	0.024
Clarithromycin	0/136 (0%)	0.22

Line listings of these patients were reviewed and the patients are characterized in the table below:

Table 73: Features of patients with delta QTc of >80mS or QTc > 500mS

Patient	age	sex	QTc1 (rate)	QTc2 (rate)	K^+	Concom meds	Indic.	Underlying diseases	outcome
140/10544 p358 vol 353	60	f	365 (109)	583 (68)	3.4 at entry	[redacted]	CAP	CLL	Cure Delta QTc 68 post Rx
140/10368 p348	28	f	363 (115)	427 (79)	3.53	-	CAP	-	Cure
140/10669 p366	18	m	439 (115)	535 (137)	N	-	CAP	-	Cure
140/10074 p303	65	f	334 (73)	419 (77)	N	[redacted] propoxyphene	CAP	-	Clin failure Cured with ceftriaxone
140/10046 p301	72	f	452 (92)	519 (82)	-	Insulin, furosamide, amiodarone, ramipril	CAP	DM, LBBB	Cure QTc 465 (rate 79) after Rx
140/10255	82	m	417 (80)	498 (84)	3.4	Heparin, paracetamol,	CAP	Atrial fib.	Unknown

						digoxin		LBBB	
16128001	37	f	367 (78)	479 (81)	3.72	Oral contraceptives	Sinus -itis	-	Cure
81/31002	42	f	345 (79)	452 (64)	3.31	None	Sinus -itis	-	Cure
161/37016	26	m	342 (81)	424 (62)	4.15	[redacted]	Sinus -itis	-	Cure

QTc1=baseline QTc
QTc2=on treatment QTc
MO comment: There was considerable variation in the ages and sexes of the above patients. Although frank hypokalemia was not usually present, it was noted that 4 of the 5 potassium levels were <4 mEql/l at baseline. In two of the patients, underlying cardiac abnormalities and concomitant medications might have played a role in the observed QTc prolongation.

Following the reccomendations of the CPMP, outliers were identified with a treatment emergent prolongation of the QTc interval > 60mS. Nine such individuals were identified among 611 patients treated with moxifloxacin 400mg, as compared with 2/515 treated with comparator drugs.

Classification of electrocardiographic events possibly related to prolonged QT:
All electrocardiographic changes were classified according to the perceived strength of association with a prolongation of the QTc interval as shown below.

Table 74:Classification of ECG findings possibly associated with QTc prolongation
[1]
ECG Events
Type A
[2]
Significant QT_c events
- A-1: baseline or on-study QT_c value ≥ 500 msec, in particular any positive QT_c change from baseline to QT_c ≥ 500 msec.
- A-2: QT_c change from baseline ≥ 60 msec.
- A-3: positive change from baseline QT_c ≥ 30 msec with QT_c reaching ≥ 450 msec (men) or ≥ 470 msec (women) during study
- A-4: any positive percentage change ≥ 15%

Type B B-1
- Ventricular tachyarrhythmias
- Ventricular fibrillation
- Cardiac arrest/cardiac standstill/electrical asystole
- TDP
- Other ventricular premature contractions (VPCs), all frequencies
- Other serious (ventricular) events

B-2
- Prolonged QT interval

Type C • All nonventricular dysrhythmias
- T-wave morphologic changes
- Heart block
- Infarction, injury and ischemia patterns, ST segment elevation
- Nonspecific ST segment change
- ST segment depression
- Electrical alternans
- Early repolarization (normal variant)

1 Adapted from categories defined [redacted]
2 A listing of patients with Type A-1, A-2, A-3 and A-4 significant QT_c events is provided in Appendix E.