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RESEARCH**

APPLICATION NUMBER:

21-404

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21-061/s010, s016

21-062/s011, s017

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-061; SLR 010 21-062; SLR 011	Submission Dates:	July 20, 2001 May 28, 2002
NDA:	21-061; SLR-016 21-062; SLR-017	Submission Date:	May 10, 2002
NDA:	21-404 21-405	Submission Dates:	June 29, 2001 February 6, 2002
Drug Product:	Gatifloxacin Tablets (400 mg) and Injection		
Trade Name:	TEQUIN®		
Sponsor:	Bristol-Myers Squibb Wallingford, CT 06492		
Submission Type:	Special Labeling Supplement: Changes Being Effected - Studies of Effect of Gatifloxacin on Glucose Homeostasis in Humans (Clinical Study Report – Study AI420-105) New Indication – Uncomplicated Skin and Skin Structure Infections		
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.		

I. EXECUTIVE SUMMARY

Study AI420-105 was an open-label, non-randomized study designed to investigate the effects of gatifloxacin (400 mg QD x 14 days) on glucose homeostasis and insulin and c-peptide secretion in 69 Type 2 diabetic patients in whom their diabetes is controlled with either a glyburide containing oral antidiabetic drug regimen (N=35) or a non-glyburide containing oral antidiabetic drug regimen (N=34). The impetus for the sponsor to conduct this study has apparently been the post-marketing reports of symptomatic hypo- and hyperglycemia associated with gatifloxacin therapy for treatment of infections, particularly in Type 2 diabetics controlled with oral antidiabetic agents, with or without insulin. While the mechanism for these occurrences is currently not known, these reports have raised the possibility of a pharmacodynamic interaction between gatifloxacin and the currently prescribed oral antidiabetic agents.

The results indicated that in the well-controlled Type 2 diabetics studied, repeat dose administration of gatifloxacin (400mg QD x 14 days) appears to have a dual effect on glucose and insulin control. Upon initiation of gatifloxacin treatment (within the 1st two days of dosing), there appears to be a hypoglycemic effect, with an increase in serum insulin and the resultant reduction in blood glucose by approximately 50 to 70 mg/dL of baseline glucose values. With continued gatifloxacin treatment (beyond the 3rd day of dosing) there appears to be a hyperglycemic effect, with a persistent increase in serum glucose concentrations in both the glyburide and non-glyburide treated diabetics of up to

approximately 40 mg/dL, from baseline. *This effect of increased glucose did not appear to have been completely reversed at 28 days after completion of gatifloxacin administration, particularly in the glyburide treated diabetics.*

II. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the study report for gatifloxacin **Study AI420-105**. In general, the information and the results provided in this study report are deemed to be acceptable. The comments provided below are revisions to the sponsor's proposed labeling (version May 9, 2002) and have been incorporated into the labeling revisions that will be sent to the sponsor (see **Appendix 1, page 21 of this review**).

III. CLINICAL PHARMACOLOGY/BIPHARMACEUTICS LABELING COMMENTS for GLUCOSE EFFECTS (version: May 9, 2002; Appendix 1, page 21 of this review)

Clin Pharm/Biopharm Revisions **CLINICAL PHARMACOLOGY**

Glucose Homeostasis

Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with TEQUIN [redacted] usually in diabetic patients. Therefore, careful monitoring of blood glucose is recommended when TEQUIN is administered to patients with diabetes (see **WARNINGS, PRECAUTIONS: Information for Patients, and Drug Interactions, and ANIMAL PHARMACOLOGY**).

In a post-marketing study conducted in non-infected patients with Type 2 diabetes mellitus controlled primarily with either the combination of glyburide and metformin or metformin alone, daily administration of gatifloxacin 400 mg orally for 14 days was associated with initial hypoglycemia followed by hyperglycemia. Upon initiation of gatifloxacin dosing (i.e., first two days of treatment), there were increases in serum insulin concentrations and resulting decreases in serum glucose, as compared to baseline glucose values. [redacted]

[redacted] In some patients, the reductions in glucose produced signs and symptoms of hypoglycemia (asthenia, sweating, dizziness) and necessitated administration of additional food. With continued gatifloxacin dosing (i.e., [redacted] the third day of treatment, [redacted] serum glucose concentrations were increased from baseline [redacted]

at 28 days after the cessation of gatifloxacin treatment. Single doses of insulin were administered to 3 patients in this study to correct the hyperglycemia during continued gatifloxacin administration.

In two pre-marketing studies, no clinically significant changes in glucose tolerance (via measurement of oral glucose challenge) and glucose homeostasis (via measurement of serum glucose, serum insulin and c-peptide) were observed following single or multiple intravenous infusion doses of 200 to 800 mg TEQUIN in healthy volunteers, or 400-mg oral doses of TEQUIN for 10 days in patients with Type 2 (non-insulin-dependent) diabetes mellitus controlled on diet and exercise. Compared to placebo, transient modest increases in serum insulin of approximately 20 — % and decreases in glucose

concentrations of approximately 30% were noted with the first dose of intravenous or oral gatifloxacin.

[NOTE NEW PARAGRAPH]

In another pre-marketing study, following administration of single oral 400-mg doses of TEQUIN for 10 days in patients with Type 2 diabetes mellitus controlled with glyburide, decreases in serum insulin concentrations of approximately 30-40%, as compared to placebo, were noted following oral glucose challenge; however, these decreases were not accompanied by statistically significant changes in serum glucose levels. In this study, modest increases in fasting glucose (average increases of 40 mg/dL) were also noted by day 4 of continued gatifloxacin administration, although these changes did not reach statistical significance.

Clin Pharm/Biopharm Revisions
CLINICAL PHARMACOLOGY

Drug-Drug Interactions



Glyburide: Pharmacodynamic changes in glucose homeostasis were seen with concomitant administration of TEQUIN (once daily oral doses of 400 mg for 10 days) and glyburide (steady-state once daily regimen) in patients with type 2 diabetes mellitus. This was not associated with significant effects on the pharmacokinetic disposition of either drug. These latter results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP3A4 isoenzyme. (see **CLINICAL PHARMACOLOGY: Glucose Homeostasis and WARNINGS**).

Clin Pharm/Biopharm Revisions
WARNINGS

Disturbances in Blood Glucose

Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with TEQUIN, usually in diabetic patients. Therefore, careful monitoring of blood glucose is recommended when TEQUIN is administered to patients with diabetes (See **CLINICAL PHARMACOLOGY, PRECAUTIONS: Information for Patients and Drug Interactions, and ANIMAL PHARMACOLOGY**).

Studies conducted in patients with Type 2 diabetes mellitus controlled on oral hypoglycemic agents have demonstrated that TEQUIN is associated with disturbances in glucose homeostasis including an increase in serum insulin and decrease in serum glucose usually following administration of initial doses (i.e., first two days of treatment), and sometimes associated with symptomatic hypoglycemia. Increases in fasting serum

glucose were also observed, usually after the third day of TEQUIN administration, continuing throughout the duration of treatment.

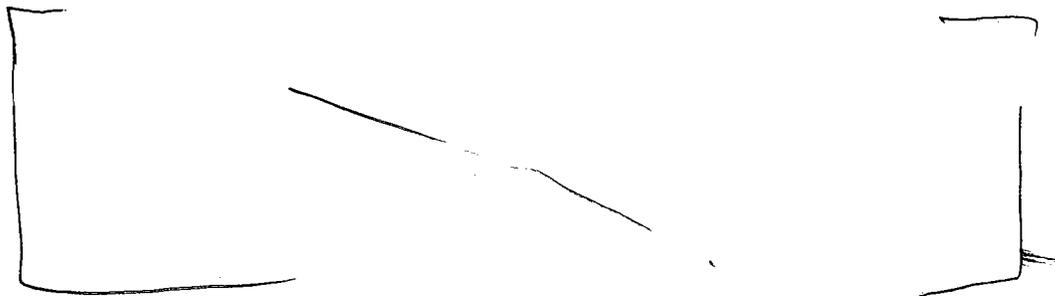
During the postmarketing period, there have been reports of serious disturbances of glucose homeostasis in patients being treated with TEQUIN. Hypoglycemic episodes, in some cases severe, have been reported in patients with diabetes mellitus treated with either sulfonylurea or non-sulfonylurea oral hypoglycemic medications. These events frequently occurred on the first day of therapy and usually within 3 days following the initiation of TEQUIN. Hyperglycemic episodes, in some cases severe and associated with hyperosmolar non-ketotic hyperglycemic coma, were reported in diabetic patients, mostly between 4 and 10 days following the initiation of TEQUIN therapy. Some of the hyperglycemic and hypoglycemic events were life-threatening and many required hospitalization, although these events were reversible when appropriately managed. Many of these patients had other underlying medical problems and were receiving concomitant medications that may have contributed to the glucose abnormality. Episodes of hyperglycemia, including hyperosmolar non-ketotic hyperglycemic coma, also occurred in patients not previously diagnosed with diabetes mellitus. Elderly patients and patients who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems and/or are taking concomitant medications associated with hyperglycemia may be at particular risk of serious hyperglycemia.

The dose of TEQUIN should be adjusted based on underlying renal function (see DOSING AND ADMINISTRATION). When TEQUIN is used in diabetic patients, blood glucose should be closely monitored. Signs and symptom of hypoglycemia should be monitored, especially during the first three days of therapy, and signs and symptoms of hyperglycemia should be monitored in diabetics and patients who may be at risk for hyperglycemia, especially with continued treatment with TEQUIN beyond three days. If signs and symptoms of either hypoglycemia or hyperglycemia occur in any patient being treated with TEQUIN, appropriate therapy must be initiated immediately.

Clin Pharm/Biopharm Revisions

PRECAUTIONS

Drug Interactions



Antidiabetic agents: Pharmacodynamic changes in glucose homeostasis have been seen with concomitant glyburide use. However, no significant pharmacokinetic interactions have been observed when glyburide was administered concomitantly with TEQUIN. (see CLINICAL PHARMACOLOGY: Glucose Homeostasis and WARNINGS).

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

RD/FT signed by Barbara Davit, Ph.D. (Team Leader) _____

IV. SUMMARY OF STUDY AI420-105

(see Appendix 2, page 71 for Detailed Study Review)

OPEN-LABEL STUDY OF THE REVERSIBILITY OF THE EFFECT OF GATIFLOXACIN ON INSULIN SECRETION FOLLOWING ORAL GLUCOSE CHALLENGE IN TYPE 2 DIABETICS

Study Rationale:

The impetus for this study has been post-marketing reports of symptomatic hypo- and hyperglycemia associated with gatifloxacin therapy for treatment of infections, particularly in Type 2 diabetics controlled with oral antidiabetic agents, with or without insulin. While the mechanism for these occurrences is currently not known, these reports have raised the possibility of a pharmacodynamic interaction between gatifloxacin and the currently prescribed oral antidiabetic agents. There is no pharmacokinetic interaction between gatifloxacin and the oral antidiabetic drug, glyburide (CYP450 substrate), in Type 2 diabetic subjects. This latter finding is consistent with the fact that gatifloxacin elimination is primarily via the kidneys and is not metabolized by hepatic CYP450.

Overall Objective:

This study was conducted to investigate the effects of gatifloxacin on glucose homeostasis and insulin and c-peptide secretion in Type 2 diabetic patients in whom their diabetes is controlled with either a glyburide containing oral antidiabetic drug regimen or a non-glyburide containing oral antidiabetic drug regimen.

Study Design and Methods:

An open-label, non-randomized study designed to examine the effects of 14 days of dosing with gatifloxacin 400 mg QD on insulin secretion and glucose tolerance following an oral glucose tolerance test (OGTT) and glucose homeostasis in Type 2 diabetics controlled with oral antidiabetic agents.

Two groups of 35 evaluable subjects who were on glyburide containing oral antidiabetic regimens or on non-glyburide containing oral antidiabetic regimens were enrolled. The enrollment was stratified with respect to the subject's other diabetic medication [metformin, a thiazolidinedione (TZD), or both metformin and a TZD]. For each subject enrolled on glyburide, a corresponding subject not on glyburide was enrolled on the same concomitant medication (metformin, a TZD, or both metformin and a TZD).

Gatifloxacin 400-mg oral tablet was administered QD along with the subject's antidiabetic medication during breakfast (~8:00 am) on Study Days 1 through 14. Therapy that was medically indicated but not specifically excluded, i.e., anti-hypertensives, were continued throughout the study and given on a consistent dose and schedule. All subjects were maintained on a standard weight maintaining diet from the time of admission to the study center until the time of discharge.

There were no pharmacokinetic evaluations performed in this study. The following pharmacodynamic evaluations were performed on all subjects:

- **Oral Glucose Tolerance Test (OGTT):** To determine the effects of gatifloxacin on glucose tolerance and insulin secretion, an OGTT was performed on Days -1, 15, 28, and 42 following

an overnight fast for at least 10 h. Blood samples for measurement of glucose, insulin, and c-peptide were collected prior to and for up to 5 hours after each OGTT.

- **Glucose Homeostasis:** Glucose and insulin homeostasis was monitored by measuring fasting serum glucose, insulin, and c-peptide on Study Days -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 26-28, and 40-42 following an overnight fast for at least 8 h.
- **Acute Effects:** Serum samples for detailed monitoring of glucose, insulin and c-peptide were obtained on Days -2, 1, 2, and 3 at the following time points: 0 (prior to gatifloxacin dosing with breakfast) 0.5, 1.0, 2, 4 (before lunch) 6, 9 (before dinner), 11, 18, and 24 hours post-dose.
- **Markers of Glucose Control:** Fructosamine (short-term marker) was determined on two occasions at 4 hours apart on Days -1, 3, 15, 28, and 42. Glycosylated hemoglobin (HbA1c; long-term marker) was determined at screening and on Days -4, 8, 15, and 42.

Subjects and Treatments:

70 subjects with stable Type 2 diabetes were enrolled and 69 subjects completed the study. The majority of the Type 2 diabetics in this study received either glyburide + metformin or metformin alone (total of 65/69 subjects). Treatment with a thiazolidinedione (TZD) either with or without glyburide/metformin occurred in only 4 of 69 subjects (see table below).

Anti-diabetic Treatments

Glyburide Containing Treatment (N=35)	n / N (%)
Glyburide + Metformin	33 / 35 (94%)
Glyburide + TZD	1 / 35 (3%)
Glyburide + Metformin +TZD	1 / 35 (3%)
Non-Glyburide Treatment (N=34)	n / N (%)
Metformin	32 / 34 (94%)
TZD	1 / 34 (3%)
Metformin +TZD	1 / 34 (3%)

Key inclusion criteria with respect to the subjects' diabetic control were as follows:

- No requirement for treatment with insulin in the previous 3 months
- HbA1c \leq 8.5%
- Fasting serum glucose between 126 and 200 mg/dL or fasting serum glucose $<$ 126 mg/dL, but abnormal oral glucose tolerance test (two values within 2 hours after an oral 75-gram glucose dose which were $>$ 200 mg/dL)

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Selected demographics for the 70 subjects enrolled into the study are provided in the table below.

Demographic Characteristics for the Type 2 Diabetics Enrolled in Study AI420-105

	Glyburide Treated* (N = 35)	Non-Glyburide Treated** (N = 35)	All Treated (N = 70)
Age (years)			
Mean (SD)	59 (10)	54 (9)	56 (10)
Range	28 - 74	37 - 75	28 - 75
Gender, n (%)			
Male	23 (65.7)	18 (51.4)	41 (58.6)
Female	12 (34.2)	17 (48.6)	29 (41.4)
Weight (kg)			
Mean (SD)	86.6 (17.3)	81.5 (13.8)	84.0 (15.7)
Range	59.0 - 128.3	56.3 - 120.2	56.3 - 128.3
Baseline Fasting Gluc (mg/dL)			
Mean (SD)	142 (31)	160 (43)	151 (38)
Range	(88, 225)	(102, 287)	(88, 287)
Baseline HbA1c (%)			
Mean (SD)	7.3 (0.77)	7.2 (0.92)	7.3 (0.84)
Range	(5.5, 8.8)	(5.4, 9.2)	(5.4, 9.2)
Baseline			
Creatinine Clearance (mL/min)			
Mean (SD)	58 (14)	58 (12)	58 (13)
Range	(39, 89)	(31, 87)	(32, 89)

*Glyburide Treated = Glyburide + Metformin; or Glyburide + a Thiazolidinedione (TZD); or Glyburide + both Metformin and a TZD

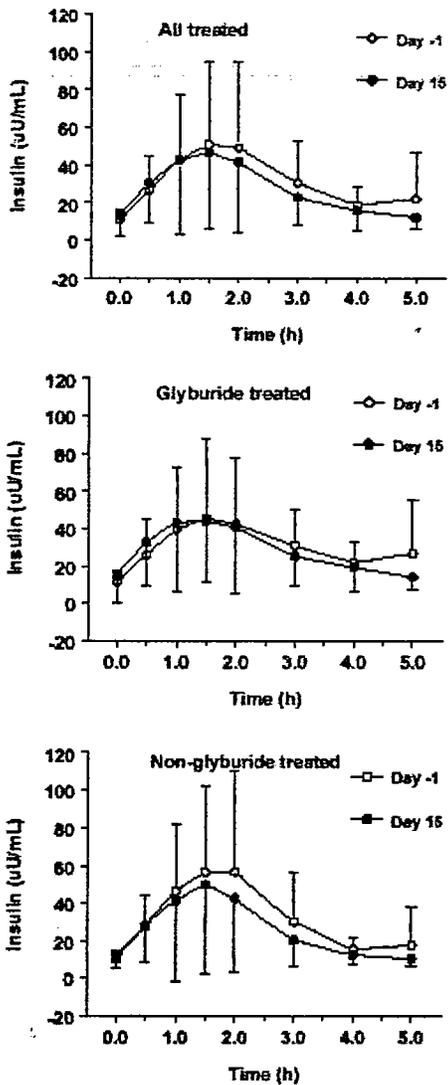
**Non-Glyburide Treated = Metformin; or a Thiazolidinedione (TZD); or Metformin and a TZD

Results and Reviewer Conclusions:

Oral Glucose Tolerance Test (OGTT) to Assess Reversibility of Gatifloxacin Effects on Glucose Tolerance and Insulin and C-Peptide Secretion:

- Following OGTT, there was no appreciable effect on serum insulin and c-peptide concentrations in the glyburide treated group at 1 day (Study Day 15), 14 days (Study Day 28), and 28 days (Study Day 42) after completion of gatifloxacin administration 400mg QD for 14 days. There were only modest reductions in insulin AUC and Cmax on Day 15 in the non-glyburide treated group of an average of 17% and 12%, respectively (see Figure 1 and Table 1 below). Only the lower limit of the 90% CI for the Day 15/Baseline Day-1 ratio for insulin AUC in the non-glyburide treated group (i.e., lower CI = 75%) fell outside of the protocol-specified equivalence/no effect 90% CI criteria of 80% to 125%.
- No statistically significant differences were detected between the glyburide and non-glyburide treatment groups for the insulin and c-peptide AUC or Cmax estimates on Day 15.

Figure 1. Mean (SD) Serum Insulin Levels on Days -1 and 15 in all Treated and in Glyburide and Non-Glyburide Treated Subjects.
 NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



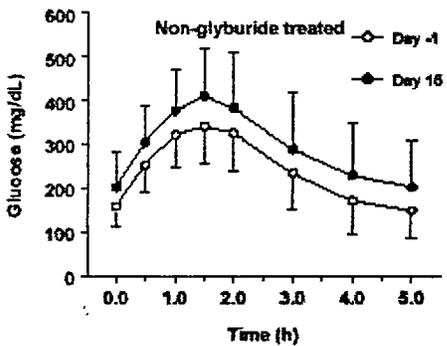
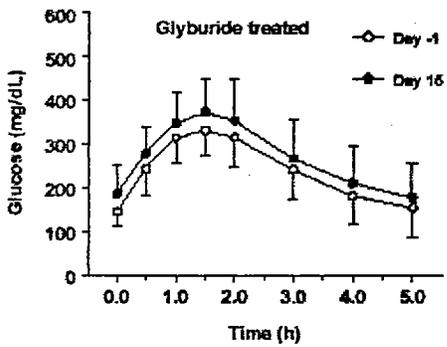
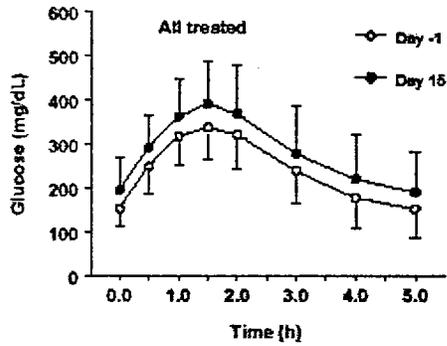
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Table 1. Ratios of AUC and Cmax of Insulin on Days 15, 28, and 42 Relative to Day -1 Following an OGTT in all Treated and in Glyburide and Non-Glyburide Treated Subjects Administered Gatifloxacin 400 mg PO QD from Days 1 to 14

Study Day	All Treated (n = 68)		Glyburide Treated (n = 35)		Non-Glyburide Treated (n = 33)	
	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)
Insulin AUC(0-5) ($\mu\text{U}\cdot\text{hr}/\text{mL}$)						
-1	129 (71%)		127 (70%)		130 (73%)	
15	114 (69%)	0.88 (0.82, 0.94)	119 (67%)	0.94 (0.85, 1.03)	108 (72%)	0.83 (0.75, 0.91)
28	129 (70%)	1.00 (0.94, 1.08)	132 (71%)	1.04 (0.94, 1.14)	126 (70%)	0.97 (0.88, 1.07)
42	133 (71%)	1.03 (0.96, 1.10)	135 (76%)	1.06 (0.96, 1.16)	130 (67%)	1.00 (0.91, 1.11)
Insulin Cmax ($\mu\text{U}/\text{mL}$)						
-1	44 (86%)		42 (83%)		46 (88%)	
15	40 (83%)	0.92 (0.84, 1.00)	40 (74%)	0.96 (0.85, 1.08)	40 (91%)	0.88 (0.78, 0.99)
28	42 (79%)	0.96 (0.88, 1.05)	42 (75%)	1.00 (0.89, 1.13)	42 (83%)	0.92 (0.82, 1.04)
42	46 (84%)	1.05 (0.97, 1.14)	43 (83%)	1.02 (0.91, 1.15)	50 (85%)	1.08 (0.95, 1.22)

- Following OGTT, gatifloxacin had no appreciable effect on serum glucose AUC and Cmax estimates on Study Days 15, 28, and 42 after completion of 400mg QD administration from Days 1 to 14 in the glyburide treated group. In the non-glyburide treated group the serum glucose AUC and Cmax were increased on Study Day 15 by an average of 18% and 16%, respectively (see Figure 2 and Table 2 below). However, the 90% CI's for the Day 15/Baseline Day-1 ratios for these parameters were within the protocol specified limits of equivalence/no-effect (i.e., 80% to 125%). There were no appreciable changes in glucose AUC or Cmax on Days 28 and 42 for the non-glyburide treated group.
- No statistically significant differences were detected between the glyburide and non-glyburide treatment groups for either glucose AUC or glucose Cmax on Day 15.

Figure 2. Mean (SD) Serum Glucose Levels on Days -1 and 15 in all Treated and in Glyburide and Non-Glyburide Treated Subjects
 NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



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Table 2. Ratios of AUC and Cmax of Glucose on Days 15, 28, and 42 Relative to Day -1 Following an OGTT in all Treated and in Glyburide and Non-Glyburide Treated Subjects Administered Gatifloxacin 400 mg PO QD from Days 1 to 14						
Study Day	All Treated (n = 68)		Glyburide Treated (n = 35)		Non-glyburide Treated (n = 33)	
	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)
Glucose AUC(0-5) (mg•hr/dL)						
-1	1187 (26%)		1194 (22%)		1179 (29%)	
15	1358 (32%)	1.15 (1.10, 1.19)	1330 (28%)	1.11 (1.05, 1.18)	1389 (36%)	1.18 (1.11, 1.25)
28	1219 (28%)	1.03 (0.99, 1.07)	1234 (23%)	1.03 (0.98, 1.09)	1204 (33%)	1.02 (0.96, 1.08)
42	1183 (27%)	1.00 (0.96, 1.04)	1209 (24%)	1.01 (0.96, 1.07)	1156 (30%)	0.98 (0.93, 1.04)
Glucose Cmax (mg/dL)						
-1	342 (20%)		340 (18%)		345 (22%)	
15	386 (23%)	1.13 (1.09, 1.16)	374 (21%)	1.10 (1.05, 1.15)	400 (25%)	1.16 (1.11, 1.21)
28	356 (20%)	1.04 (1.01, 1.07)	354 (19%)	1.04 (1.00, 1.09)	359 (22%)	1.04 (0.99, 1.09)
42	342 (20%)	1.00 (0.97, 1.03)	344 (18%)	1.01 (0.97, 1.06)	341 (22%)	0.99 (0.94, 1.03)

- Overall, these data suggested that, an OGTT on Study Day 15, one day following completion of gatifloxacin administration for 14 days, showed there were modest increases in serum glucose and modest reductions serum insulin concentrations in the non-glyburide treated diabetic subjects. With an OGTT at 14 and 28 days following completion of gatifloxacin administration, the serum glucose and insulin concentrations in the non-glyburide group were not significantly different from the baseline concentrations. There were no significant effects on glucose and insulin in the glyburide treated subjects at any time following completion of gatifloxacin administration for 14 days. Thus, it appeared that at one day following the completion of gatifloxacin treatment, gatifloxacin might have a transient effect on glucose and insulin tolerance to cause an increase in blood glucose and a reduction in insulin levels (i.e., a transient hyperglycemic effect). These perturbations in glucose and insulin tolerance were not detected at 14 and 28 and days after the completion of gatifloxacin treatment and suggest some degree of reversibility to this effect.

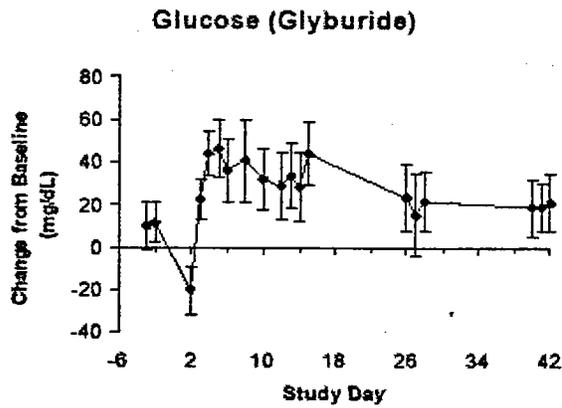
Glucose Homeostasis – Assessment of Fasting Glucose, Insulin, and C-Peptide at Pre-dose (Days -3 to -1), During Gatifloxacin Administration (days 1-14), and Following Completion of Gatifloxacin Administration (Days 15-42):

- Decreases in mean fasting glucose were apparent during the first 2 days of gatifloxacin dosing for the glyburide treated subjects, but not for the non-glyburide treated group (see **Figure 3** below). The mean decrease (from baseline) in serum glucose on Study Day 2 of gatifloxacin dosing in the glyburide group was 20 mg/dL. Following this initial decrease, the mean serum glucose from Study Days 3 to 14 of gatifloxacin administration showed persistent increases of approximately 20 to 45 mg/dL compared to the baseline measurements in both glyburide and non-glyburide treated subjects. After completion of the gatifloxacin dosing period, the mean changes in serum glucose remained increased from baseline from Study Days 15 to 42 in the range of ~15 to 44 mg/dL for the glyburide treated group and of ~5 to 42 mg/dL for the non-glyburide treated group. The mean changes in serum glucose in the glyburide group appeared to remain consistent through Study Days 26 to 42 (i.e., increases of ~20 mg/dL). However, in the non-glyburide group the mean changes in serum glucose appeared to diminish back towards baseline from Days 26 to 42 (increases of ~20 mg/dL on Study Day 26 and ~5 mg/dL on Study Day 42).

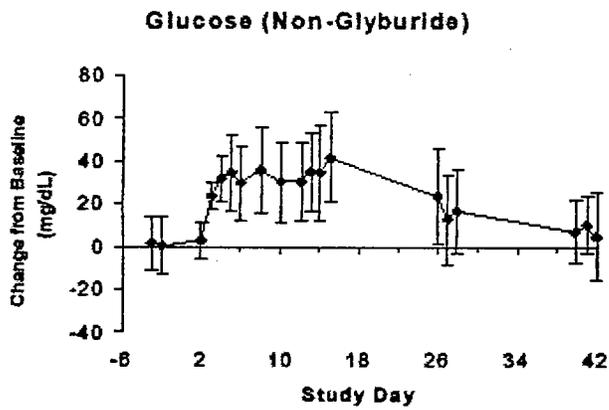
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Figure 3. Mean (95% CI) Change from Baseline in Fasting Glucose Serum Concentrations on Days -3 to 42 in Glyburide (A) and Non-Glyburide (B) Treated Type 2 Diabetics Subjects
NOTE: Gatifloxacin Administered 400mg PO QD from Days 1 - 14

A



B

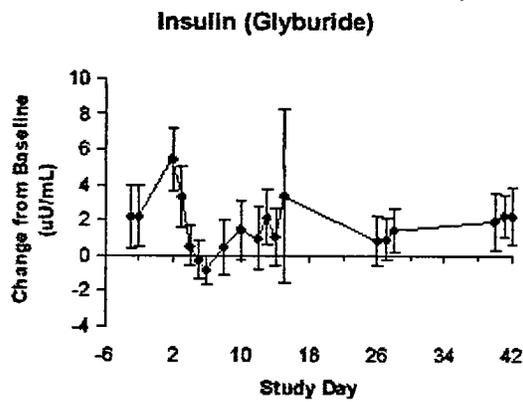


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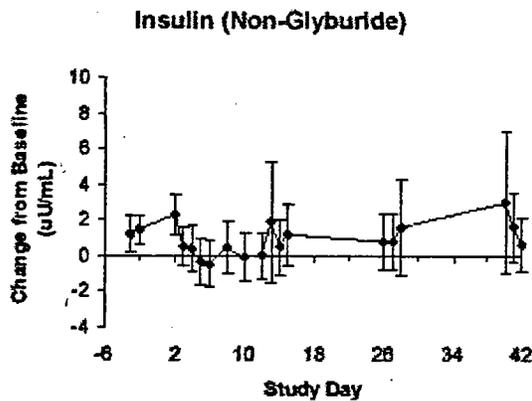
- Changes in serum insulin (see Figure 4 below) and c-peptide concentrations appeared to be more evident in the glyburide treated group than the non-glyburide group. Increases in mean fasting insulin and c-peptide were greater during the first 2 days of gatifloxacin dosing for the glyburide treated subjects compared to the non-glyburide treated group. Following these initial increases, the mean insulin and c-peptide levels in both treatment groups appeared to show no consistent pattern, decreasing below baseline values during the gatifloxacin dosing period, and then returning back to baseline levels by Study Days 28 to 42.

Figure 4. Mean (95% CI) Change from Baseline in Fasting Insulin Serum Concentrations on Days -3 to 42 in Glyburide (A) and Non-Glyburide (B) Treated Type 2 Diabetics Subjects
NOTE: Gatifloxacin Administered 400mg PO QD from Days 1 - 14

A



B



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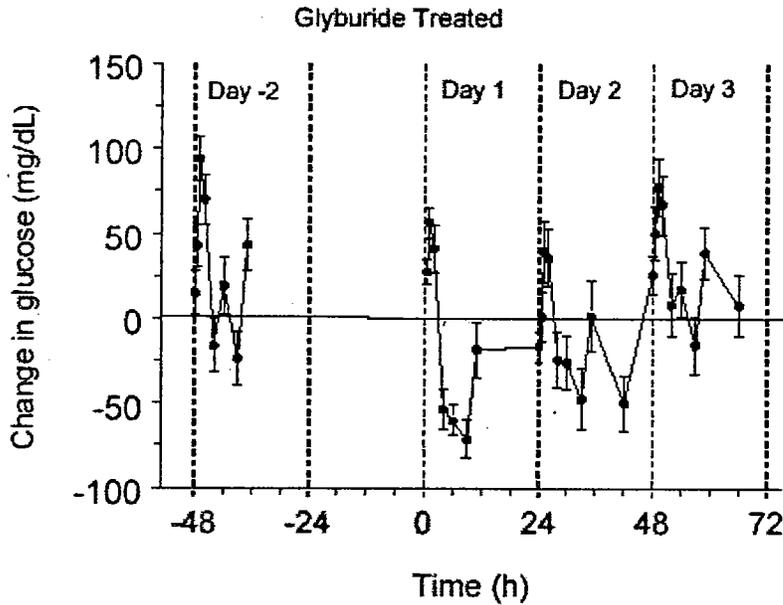
- Overall, the results suggested that initial administration of gatifloxacin within the first 2 days of repeat dose treatment had an acute effect, especially in the glyburide treated diabetic subjects, to produce a reduction in serum glucose (i.e., hypoglycemia) in concert with an increase in serum insulin and c-peptide concentrations. This acute effect was less pronounced in the non-glyburide treated diabetics. With continued repeat dose gatifloxacin administration and after the completion of a 14-day treatment regimen, there was a persistent increase in serum glucose concentrations in both the glyburide and non-glyburide treated diabetics (increases of up to ~40 mg/dL from baseline). ***This effect of increased glucose did not appear to have been completely reversed by Study Day 42 (i.e., 28 days after completion of gatifloxacin administration) particularly in the glyburide treated diabetics.***

Acute Effects – Detailed Monitoring of Serum Glucose, Insulin, and C-Peptide from 0 to 11 hr on Baseline Day-2 and With Gatifloxacin Administration on Days 1, 2, and 3:

- Decreases in glucose levels were observed in the first 2 days of gatifloxacin dosing (i.e., Study Days 1 and 2), despite lunch and dinner immediately after the 4 and 9 hour blood samples, respectively, in both the glyburide and non-glyburide treated groups (**see Figure 5 below**). The most pronounced effects were observed at 4, 6, and 9 hr postdose on Study Day 1 in both groups, where the greatest decreases in glucose levels (from baseline) were on average between ~50 and 70 mg/dL. On Study Day 2 of gatifloxacin dosing, the mean decreases in serum glucose at 4, 6, and 9 hr postdose were not as pronounced for both groups, and by Study Day 3 of dosing, there were little if any decreases in serum glucose levels at any of the postdose time points. The serum glucose AUC(0-9) estimates were reduced (from baseline) by an average of ~30% on Study Day 1 and by ~15% on Study Day 2 of gatifloxacin dosing in both treatment groups; these reductions were statistically significant.
- In concert with the decrease in serum glucose, the serum insulin (**see Figure 6 below**) and c-peptide levels were increased on Study Days 1 and 2 during gatifloxacin administration for both treatment groups. By Study Day 3, serum insulin and c-peptide levels approached those at baseline.

Figure 5. Mean (95% CI) Change from Baseline in Serum Glucose Levels Over 24 Hours in Glyburide (A) and Non-Glyburide (B) Treated Subjects on Days -2, 1, 2, and 3
NOTE: Gatifloxacin Administration 400mg PO QD from Days 1 to 14

A



B

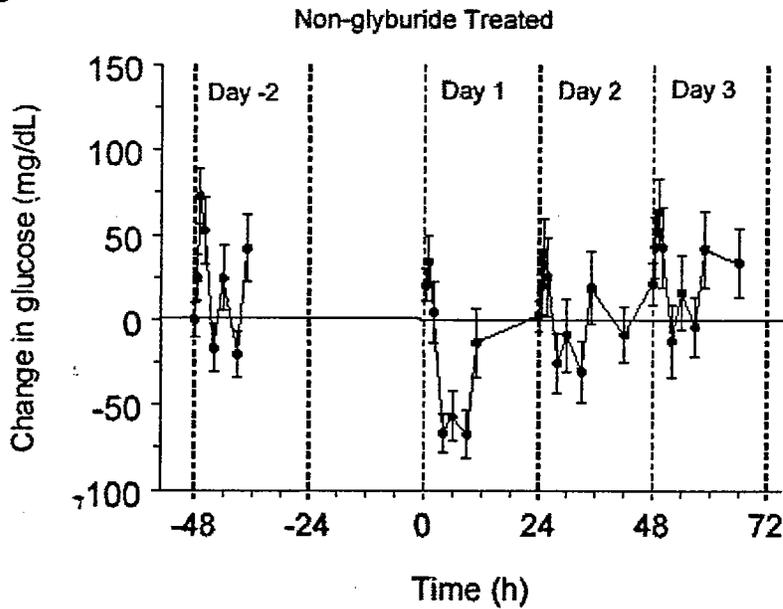
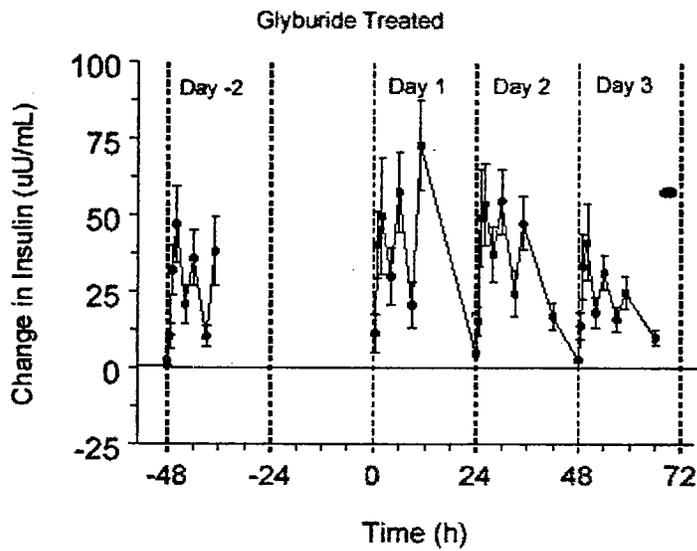
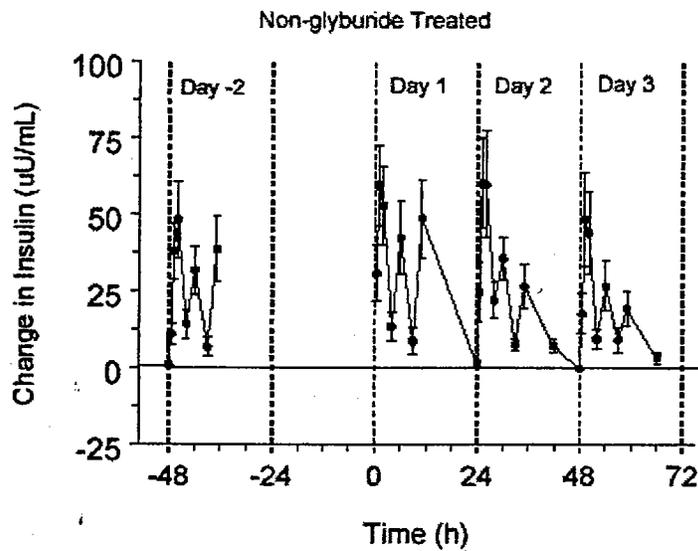


Figure 6. Mean (95% CI) Change from Baseline in Serum Insulin Levels Over 24 Hours in Glyburide (A) and Non-Glyburide (B) Treated Subjects on Days -2, 1, 2, and 3
NOTE: Gatifloxacin Administration 400mg PO QD from Days 1 to 14

A



B



Markers of Overall Glucose Control – Glycosylated Hemoglobin (HbA1c) and Fructosamine:

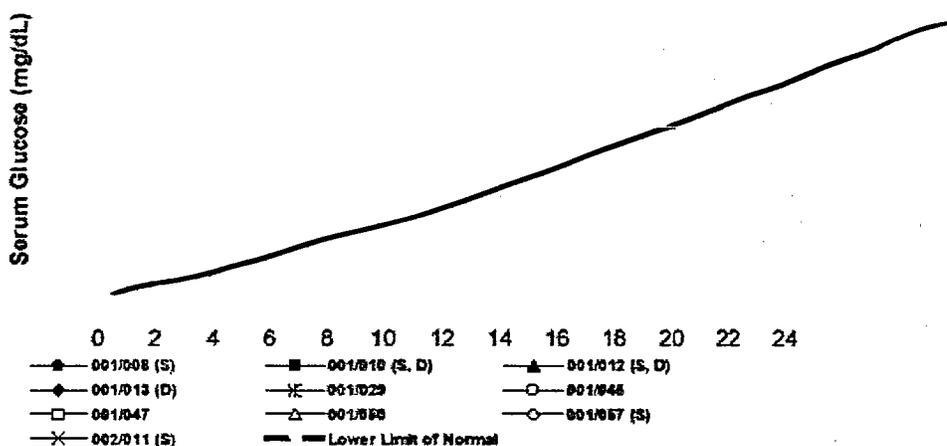
- Fructosamine serum concentrations, marker of short-term glucose control (i.e., weeks), were increased in both glyburide and non-glyburide treatment groups up to 14 days following completion of gatifloxacin treatment (Study Day 15 and 28) and then appeared to plateau at 28 days after the end of gatifloxacin therapy (Study Day 42).
- Glycosylated hemoglobin (HbA1c) values, marker of long-term glucose control (i.e., months), were not appreciably altered during or after the completion of gatifloxacin treatment in either treatment groups.

Safety/Adverse Events Related to Alterations in Blood Glucose:

- Signs and symptoms consistent with hypoglycemia were only reported by subjects in the glyburide treated group, especially at the initiation of gatifloxacin treatment (i.e., Study Days 1 and 2) over the time period from approximately 6 to 24 hours post gatifloxacin dose administration. A total of 10 of 35 (29%) glyburide treated subjects reported various symptoms associated with hypoglycemia (i.e., asthenia, sweating, dizziness, abnormal vision). These 10 subjects were shown to have blood glucose concentrations below the lower limit of normal (i.e., 65 mg/dL) from approximately 4 to 12 hours after the 1st gatifloxacin dose administration on Study Day 1 (see Figure 7 below). It is particularly noteworthy that 7 of these 10 subjects received concomitant treatment with food, in addition to the standard lunch, for weakness and/or dizziness or perspiration.
- Hyperglycemia was reported as a Grade 3 laboratory AE (i.e., 250-500 mg/dL) in 3 of the 35 (8.6%) non-glyburide treated subjects during continued dose administration of gatifloxacin (i.e., beyond Study Day 3). These 3 subjects each received a single dose of insulin (ranging from 4 to 10 units) to correct the hyperglycemia.

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Figure 7. Detailed Glucose Levels In Subjects Who had Asthenia in the Glyburide Treated Group on Day 1 after the 1st Dose of Gatifloxacin. Subjects are Identified as Site Number/Subject Number. Additional Symptoms are Identified Next to Subject Numbers as Sweating (S) and Dizziness (D). The Dotted Line Indicates the Lower Limit of Normal for Serum Glucose Concentration, 65 mg/dL)



Overall Summary of Conclusions:

- In the well-controlled Type 2 diabetics studied, repeat dose administration of gatifloxacin (400mg QD for 14 days) appears to have a dual effect on glucose and insulin control. Upon initiation of gatifloxacin treatment (within the 1st two days of dosing), there appears to be a hypoglycemic effect, with an increase in serum insulin and the resultant reduction in blood glucose by approximately 50 to 70 mg/dL of baseline glucose values. With continued gatifloxacin treatment (beyond the 3rd day of dosing) there appears to be a hyperglycemic effect, with a persistent increase in serum glucose concentrations in both the glyburide and non-glyburide treated diabetics of up to approximately 40 mg/dL, from baseline. ***This effect of increased glucose did not appear to have been completely reversed at 28 days after completion of gatifloxacin administration, particularly in the glyburide treated diabetics.***



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 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

APPENDIX 2:
CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW OF
GATIFLOXACIN STUDY AI420-105

Study AI420-105: OPEN-LABEL STUDY OF THE REVERSIBILITY OF THE EFFECT OF GATIFLOXACIN ON INSULIN SECRETION FOLLOWING ORAL GLUCOSE CHALLENGE IN TYPE 2 DIABETICS; Study Dates: 8/03/2001 – 12/16/2001

NDA Vols. 2–15; pp. 1–4122

OBJECTIVES:

Primary:

Examine the reversibility of any effects of 14 days of once-daily gatifloxacin on insulin secretion following oral glucose challenge in Type 2 diabetics controlled with oral antidiabetic agents.

Secondary:

Compare the effects of gatifloxacin on insulin secretion and glucose tolerance following oral glucose tolerance test (OGTT) in Type 2 diabetics controlled with glyburide-containing compared to Type 2 diabetics controlled with non-glyburide-containing oral antidiabetic regimens.

Examine the effects of gatifloxacin on glucose tolerance and c-peptide secretion in Type 2 diabetics controlled with glyburide-containing versus non-glyburide-containing oral antidiabetic regimens and to assess reversibility of any noted effect.

Examine the effects of gatifloxacin on glucose homeostasis in Type 2 diabetics controlled with glyburide-containing versus non-glyburide-containing oral antidiabetic regimens.

Examine the safety and tolerability of gatifloxacin administered for 14 days in Type 2 diabetics controlled with oral antidiabetic agents.

STUDY TREATMENTS / FORMULATIONS:

Gatifloxacin 400 mg film coated tablet, Batch No. 1319520C1

SUBJECTS:

70 subjects with stable Type 2 diabetes; 35 subjects (23 male, 12 female) enrolled in the glyburide group; 35 subjects (18 male, 17 female) enrolled in the non-glyburide group.

Key inclusion criteria with respect to the subjects' diabetic control were as follows:

Established diagnosis of stable Type 2 diabetes mellitus in subjects who were controlled with a glyburide containing regimen (glyburide and metformin; glyburide and a TZD; or glyburide, metformin, and a TZD) or controlled with a non-glyburide containing regimen (metformin, a TZD, or metformin and a TZD) for at least 3 months, with:

- b) no requirement for treatment with insulin in the previous 3 months
- b) HbA1c \leq 8.5%
- c) fasting serum glucose between 126 and 200 mg/dL or fasting serum glucose $<$ 126 mg/dL, but abnormal oral glucose tolerance test (two values within 2 hours after an oral 75-gram glucose dose which were $>$ 200 mg/dL [11.1 mmol/L]).

Subject demographics are provided in the table below.

Demographic Characteristics for the Type 2 Diabetics Enrolled in Study AI420-105

	Glyburide Treated* (N = 35)	Non-Glyburide Treated** (N = 35)	All Treated (N = 70)
Age (years)			
Mean (SD)	59 (10)	54 (9)	56 (10)
Range	28 - 74	37 - 75	28 - 75
Gender, n (%)			
Male	23 (65.7)	18 (51.4)	41 (58.6)
Female	12 (34.2)	17 (48.6)	29 (41.4)
Race, n (%)			
White	26 (74.3)	24 (68.6)	50 (71.4)
Black	1 (2.8)	4 (11.4)	5 (7.1)
Hispanic/Latino	8 (22.8)	7 (20)	15 (21.4)
Weight (kg)			
Mean (SD)	86.6 (17.3)	81.5 (13.8)	84.0 (15.7)
Range	59.0 - 128.3	56.3 - 120.2	56.3 - 128.3
Height (cm)			
Mean (SD)	166.9 (8.6)	163.2 (7.6)	165.1 (8.2)
Range	149.9 - 182.9	144.8 - 176.5	144.8 - 182.9
Body Mass Index (kg/m²)			
Mean (SD)	31.2 (4.6)	30.8 (4.1)	31.0 (4.4)
Range	23.0 - 40.1	23.6 - 40.3	23.0 - 40.3
Baseline Fasting Gluc (mg/dL)			
Mean (SD)	142 (31)	160 (43)	151 (38)
Range	(88, 225)	(102, 287)	(88, 287)
Baseline HbA1c (%)			
Mean (SD)	7.3 (0.77)	7.2 (0.92)	7.3 (0.84)
Range	(5.5, 8.8)	(5.4, 9.2)	(5.4, 9.2)
Baseline			
Fructosamine (μmol/L)			
Mean (SD)	298 (46)	294 (60)	296 (53)
Range	(186, 382)	(134, 460)	(134, 460)
Creatinine Clearance (mL/min)			
Mean (SD)	58 (14)	58 (12)	58 (13)
Range	(39, 89)	(31, 87)	(32, 89)

*Glyburide Treated = Glyburide + Metformin; or Glyburide + a Thiazolidinedione (TZD); or Glyburide + both Metformin and a TZD

**Non-Glyburide Treated = Metformin; or a Thiazolidinedione (TZD); or Metformin and a TZD

STUDY DESIGN AND METHODS:

An open-label, non-randomized study designed to examine the effects of 14 days of dosing with gatifloxacin 400 mg QD on insulin secretion and glucose tolerance following an oral glucose tolerance test (OGTT) and glucose homeostasis in Type 2 diabetics controlled with oral antidiabetic agents.

Seventy (70) subjects with stable Type 2 diabetes mellitus participated in this study. Two groups of 35 evaluable subjects who were on glyburide containing oral antidiabetic regimens or on non-glyburide containing oral antidiabetic regimens were enrolled. The enrollment was stratified with respect to the subject's other diabetic medication [metformin, a thiazolidinedione (TZD), or both metformin and a TZD]. For each subject enrolled on glyburide, a corresponding subject not on glyburide was enrolled on the same concomitant medication (metformin, a TZD, or both metformin and a TZD).

Gatifloxacin 400-mg oral tablet was administered QD (approximately 8 AM) along with the subject's antidiabetic medication during breakfast on Days 1 through 14. Therapy that was medically indicated but not specifically excluded, i.e., anti-hypertensives, were continued throughout the study and given on a consistent dose and schedule. No other concomitant medications, except routine anti-hypertensives, were given within 4 hours before or after gatifloxacin administration (i.e., ferrous sulfate, dietary supplements containing zinc, magnesium or iron [such as multivitamins], or aluminum/magnesium-containing antacids). All subjects were maintained on a standard weight maintaining diet from the time of admission to the study center until the time of discharge.

The following pharmacodynamic evaluations were performed on all subjects. There were no pharmacokinetic evaluations performed in this study. ●

Oral Glucose Tolerance Test (OGTT): In order to determine the effects of gatifloxacin on glucose tolerance and insulin secretion, an OGTT was performed on Days -1, 15, 28, and 42 following an overnight fast for at least 10 h. For the Day 28 and 42 OGTT, subjects were admitted to the study unit on the evening of Day 25 and Day 39, respectively, and maintained on a standard weight maintaining diet from the time of admission to the study center until the time of furlough. Subjects were discharged from the study on Day 42. Blood samples for measurement of glucose, insulin, and c-peptide were collected prior to and for up to 5 hours after each OGTT.

Glucose Homeostasis: Glucose and insulin homeostasis was monitored by measuring fasting serum glucose, insulin, and c-peptide on Study Days -3, -2, -1, 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 26-28, and 40-42 following an overnight fast for at least 8 h.

Acute Effects: Serum samples for detailed monitoring of glucose, insulin and c-peptide were obtained on Days -2, 1, 2, and 3 at the following time points: 0 (prior to gatifloxacin dosing with breakfast) 0.5, 1.0, 2, 4 (before lunch) 6, 9 (before dinner), 11, 18, and 24 hours post-dose.

Markers of Glucose Control: Fructosamine was determined on two occasions at 4 hours apart on Days -1, 3, 15, 28, and 42. Glycosylated hemoglobin (HbA1c) was determined at screening and on Days -4, 8, 15, and 42 along with the clinical laboratory measurements.

ANALYTICAL METHODS for PD MEASUREMENTS:

Glucose

Glucose was analyzed using a FDA approved kit from _____ . The lower limit of quantitation was _____. Each analytical run included sets of two QC samples manufactured by _____. The QC samples were prepared per manufacturer's specifications corresponding to low and high concentrations. Acceptance ranges (mean \pm 2 SD) for the QC's were established prior to analysis of the specimens. The measured concentrations of all QC samples were to be within the established ranges.

Insulin

Insulin was analyzed using a FDA approved kit from _____. The lower limit of quantitation was _____; the assay was _____. Each analytical run included sets of two QC samples manufactured by _____. The QC samples were prepared per manufacturer's specifications corresponding to low and high concentrations. Acceptance ranges (mean \pm 2 SD) for the QC's were established prior to analysis of the specimens. The measured concentrations of all QC samples were to be within the established ranges.

C-Peptide

C-peptide was analyzed using a FDA approved kit from _____. The lower limit of quantitation was _____. Each analytical run included sets of two quality control samples manufactured by _____. The QC samples were prepared per

manufacturer's specifications corresponding to low and high concentrations. Acceptance ranges (mean \pm 2 SD) for the QC's were established prior to analysis of the specimens. The measured concentrations of all QC samples were to be within the established ranges.

Fructosamine

Fructosamine was analyzed using a FDA approved kit from _____ The lower limit of quantitation was _____ Each analytical run included sets of two QC samples manufactured by _____ The QC samples were prepared per manufacturer's specifications corresponding to low and high concentrations. Acceptance ranges (mean \pm 2 SD) for the QC were established prior to analysis of the specimens. The measured concentrations of all QC samples were to be within the established ranges.

Glycosylated Hemoglobin

HbA1c assay was performed using a FDA approved method from _____ The lower limit of quantitation was _____ Each analytical run included sets of two QC samples manufactured by _____ The QC samples were prepared per manufacturer's specifications corresponding to low and high concentrations. Acceptance ranges (mean \pm 2 SD) for the QC's were established prior to analysis of the specimens. The measured concentrations of all QC samples were to be within the established ranges.

DATA ANALYSIS of PD MEASUREMENTS:

OGTT: PD parameters determined were AUC and Cmax of glucose, insulin, and c-peptide on Study Days -1, 15, 28 and 42.

To assess the reversibility of the effect of gatifloxacin on glucose tolerance and insulin and c-peptide secretion, an ANOVA was performed on the log-transformed ratios (over Day -1) of AUC and Cmax of insulin, glucose, and c-peptide. Reversibility of the effects of gatifloxacin on insulin secretion following an OGTT was concluded if the 90% confidence interval for the ratio of the Day 28 over Day -1 geometric means fell entirely within (0.80, 1.25) for AUC of insulin and within (0.70, 1.43) for Cmax of insulin. Similar assessments were made for the reversibility of the effects of gatifloxacin on glucose tolerance and c-peptide secretion, if such effects were seen on Day 15, based on the glucose and c-peptide AUC and Cmax parameters.

Since 66 out of the total 70 subjects had taken glyburide + metformin or metformin alone, the stratification (metformin, TZD, metformin + TZD) indicated in the study protocol was not included in the ANOVA model.

To compare the effects of gatifloxacin on glucose tolerance, and insulin and c-peptide secretion, between the glyburide treated and non-glyburide treated groups, the point estimate and confidence interval for the Day 15 (over Day -1) ratios of geometric means for AUC and Cmax of insulin, glucose, and c-peptide were obtained, and the difference of these ratios between the two treatment groups (glyburide treated and non-glyburide treated) was evaluated.

Glucose Homeostasis: PD parameters determined were change in fasting serum glucose, insulin, and c-peptide concentrations relative to baseline (average of Day -1 and Day 1 predose values) on Study Days -3, -2, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 26-28, and 40-42.

The effects of gatifloxacin on glucose and insulin homeostasis were assessed by the changes in fasting serum glucose, insulin, and c-peptide concentrations relative to baseline (average of Day -1 and Day 1 pre-dose values), using a repeated measures ANOVA model with treatment group (glyburide treated and non-glyburide treated), subjects within group, study day (Day 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 26-28, and 40-42), and group-by-day interactions.

Acute Effects: PD parameters determined on Study Days -2, 1, 2 and 3 were: (i) change in serum glucose, insulin, and c-peptide concentrations relative to baseline (pre-dose values on Day 1); (ii) AUC and Cmax of glucose (additionally, Cmin was determined for glucose only), insulin, and c-peptide; and (iii) partial AUC [i.e., AUC(0-9)] of glucose.

The distribution of AUC and Cmax of glucose (additionally, Cmin for glucose only), insulin, and c-peptide based on detailed monitoring of serum glucose, insulin, and c-peptide on Days 1, 2, and 3, and their changes from Day -2 value were summarized by group and study day. Cmin for glucose is provided for informational purpose only.

On an *ad hoc* basis, assessment of the AUC(0-9) for glucose on Days -2, 1, 2, and 3 was performed. Values on Day -2 were used as baseline. ANOVA model with group, subject within group, study day (Days 1, 2, and 3), as factors and group-by-day as interaction were used to test the effect of study day, group, and interaction.

Markers of Glucose Control: Fructosamine levels were determined on two occasions four hours apart on Study Days -1, 3, 15, 28, and 42. HbA1c levels were measured on Study Days -4, 8, 15, and 42.

The distribution of fructosamine levels, and the changes from baseline, were summarized by group, study day (Days -1, 3, 15, 28, and 42) and time point (0 and 4 h).

The distribution of HbA1c, and the changes from baseline, were summarized by group and study day (Days -4, 8, 15, and 42).

RESULTS:

A total of 69 of the 70 subjects enrolled completed the study. One subject, who was in the non-glyburide group (i.e., metformin only), discontinued due to an adverse event. Subject 010 discontinued after receiving one dose of gatifloxacin due to moderate dyspnea, hoarseness, tightness in the throat area, and mild tingling at the tip of the tongue on Day 1. All AEs resolved prior to the subject's discharge on Day 2. This subject was not replaced.

A summary of the antidiabetic treatments for all 69 subjects completing the study is provided in the table below. As can be seen from this table, the majority of the Type 2 diabetics in this study received either glyburide + metformin or metformin alone (total of 65/69 subjects). Treatment with a thiazolidinedione either with or without glyburide/metformin occurred in only 4 of 69 subjects.

Anti-diabetic Treatments

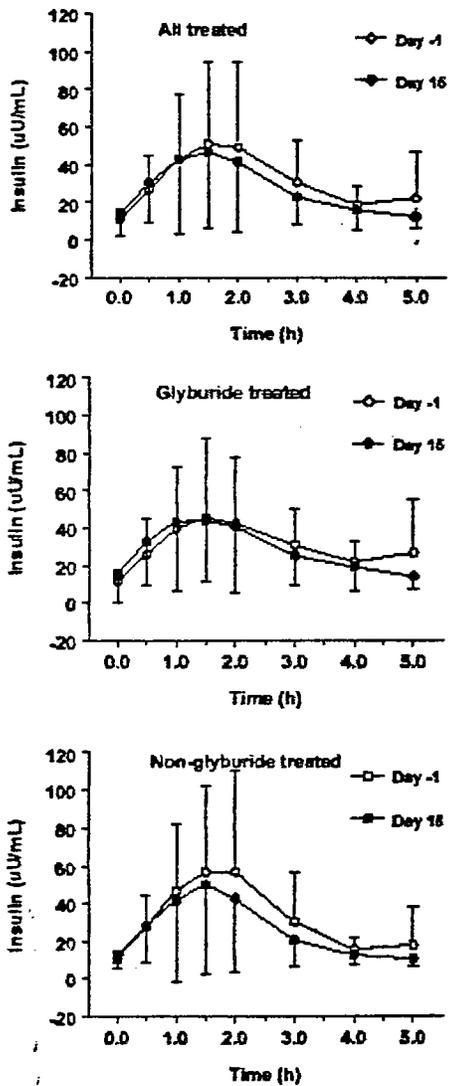
Glyburide Containing Treatment (N=35)	n / N (%)
Glyburide + Metformin	33 / 35 (94%)
Glyburide + TZD	1 / 35 (3%)
Glyburide + Metformin +TZD	1 / 35 (3%)
Non-Glyburide Treatment (N=34)	n / N (%)
Metformin	32 / 34 (94%)
TZD	1 / 34 (3%)
Metformin +TZD	1 / 34 (3%)

1.a. OGTT – Serum Insulin Concentrations Post Gatifloxacin Dosing

The mean (SD) of the serum insulin levels on Days 15, 28, and 42 versus Day -1 in all treated, glyburide treated, and non-glyburide treated groups are shown in Figures 1 through 3 below.

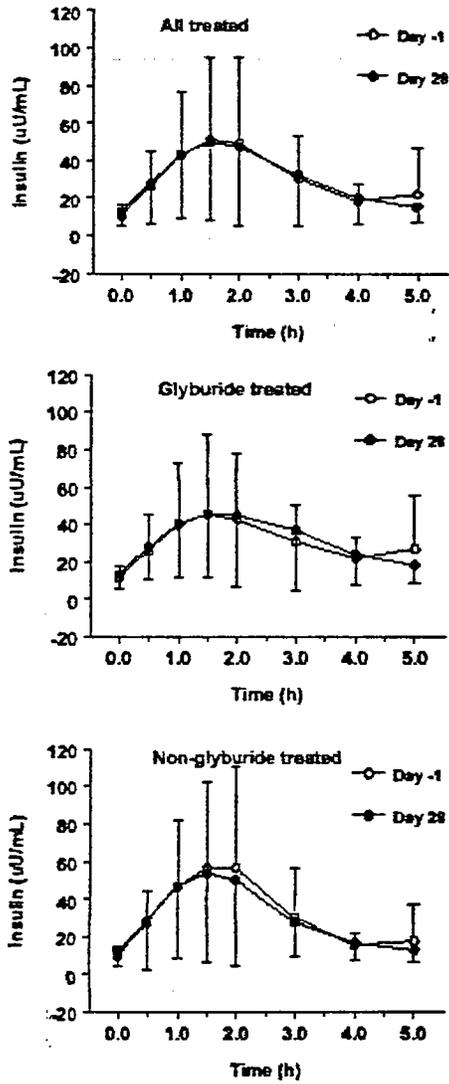
Figure 1. Mean (SD) Serum Insulin Levels on Days -1 and 15 in all Treated and in Glyburide and Non-Glyburide Treated Subjects.

NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



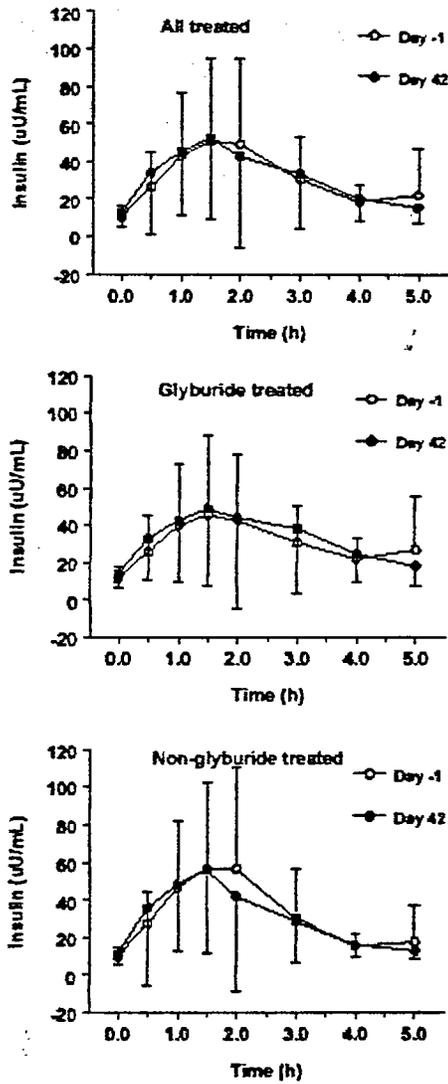
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Figure 2. Mean (SD) Serum Insulin Levels on Days -1 and 28 in all Treated and in Glyburide and Non-Glyburide Treated Subjects
 NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



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Figure 3. Mean (SD) Serum Insulin Levels on Days -1 and 42 in all Treated and in Glyburide and Non-Glyburide Treated Subjects
 NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



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Insulin concentrations measured over a 5-hour interval following an OGTT were used to compute insulin AUC and Cmax for each study day. To test the reversibility of the effect on insulin levels following an OGTT, ratios of insulin AUC and Cmax on study Days 15, 28, and 42 to baseline (Day -1) were computed and an ANOVA on the logarithms of these ratios was performed. The statistical results are briefly summarized in the table below.

Ratios of AUC and Cmax of Insulin on Days 15, 28, and 42 Relative to Day -1 Following an OGTT in all Treated and in Glyburide and Non-Glyburide Treated Subjects Administered Gatifloxacin 400 mg PO QD from Days 1 to 14

Study Day	All Treated (n = 68)		Glyburide Treated (n = 35)		Non-Glyburide Treated (n = 33)	
	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)
Insulin AUC(0-5) ($\mu\text{U}\cdot\text{hr}/\text{mL}$)						
-1	129 (71%)		127 (70%)		130 (73%)	
15	114 (69%)	0.88 (0.82, 0.94)	119 (67%)	0.94 (0.85, 1.03)	108 (72%)	0.83 (0.75, 0.91)
28	129 (70%)	1.00 (0.94, 1.08)	132 (71%)	1.04 (0.94, 1.14)	126 (70%)	0.97 (0.88, 1.07)
42	133 (71%)	1.03 (0.96, 1.10)	135 (76%)	1.06 (0.96, 1.16)	130 (67%)	1.00 (0.91, 1.11)
Insulin Cmax ($\mu\text{U}/\text{mL}$)						
-1	44 (86%)		42 (83%)		46 (88%)	
15	40 (83%)	0.92 (0.84, 1.00)	40 (74%)	0.96 (0.85, 1.08)	40 (91%)	0.88 (0.78, 0.99)
28	42 (79%)	0.96 (0.88, 1.05)	42 (75%)	1.00 (0.89, 1.13)	42 (83%)	0.92 (0.82, 1.04)
42	46 (84%)	1.05 (0.97, 1.14)	43 (83%)	1.02 (0.91, 1.15)	50 (85%)	1.08 (0.95, 1.22)

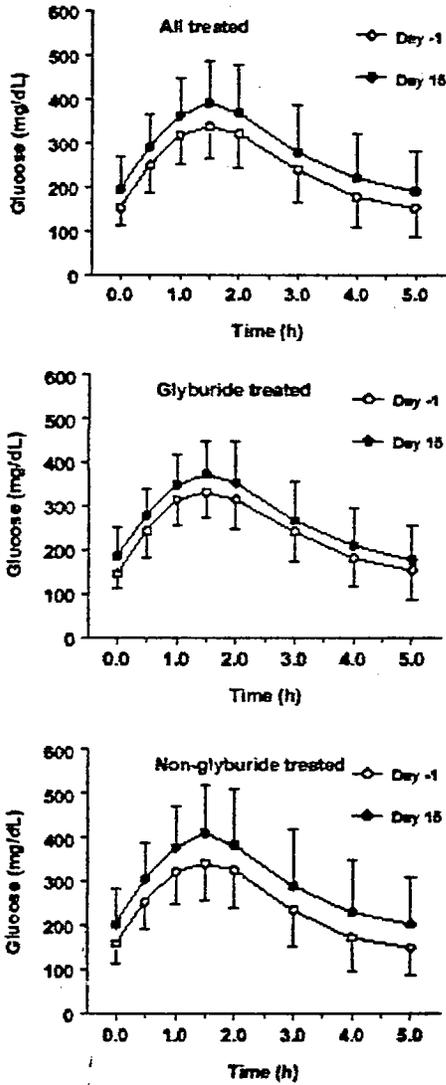
Insulin concentrations and the resultant insulin AUC(0-5) and Cmax estimates were highly variable across Study Days -1, 15, 28, and 42, as evidenced by the %CV of approximately 70% and greater for both parameters. The data in the table above showed no appreciable effect on serum insulin concentrations in the glyburide treated, non-glyburide treated, and all treated groups at 1 day (Study Day 15), 14 days (Study Day 28), and 28 days (Study Day 42) following gatifloxacin administration 400mg QD for 14 days. There were only modest reductions in insulin AUC and Cmax on Day 15 in the non-glyburide treated group of an average of 17% and 12%, respectively. Only the lower limit of the 90% CI for the Day 15/Day-1 ratio for insulin AUC in the non-glyburide treated group (i.e., 0.75) was below the protocol-specified equivalence criteria of

No statistically significant differences were detected between the glyburide and non-glyburide treatment groups for either insulin AUC(0-5) ($p = 0.14$) and insulin Cmax ($p = 0.40$) on Day 15.

1.b. OGTT – Serum Glucose Concentrations Post Gatifloxacin Dosing

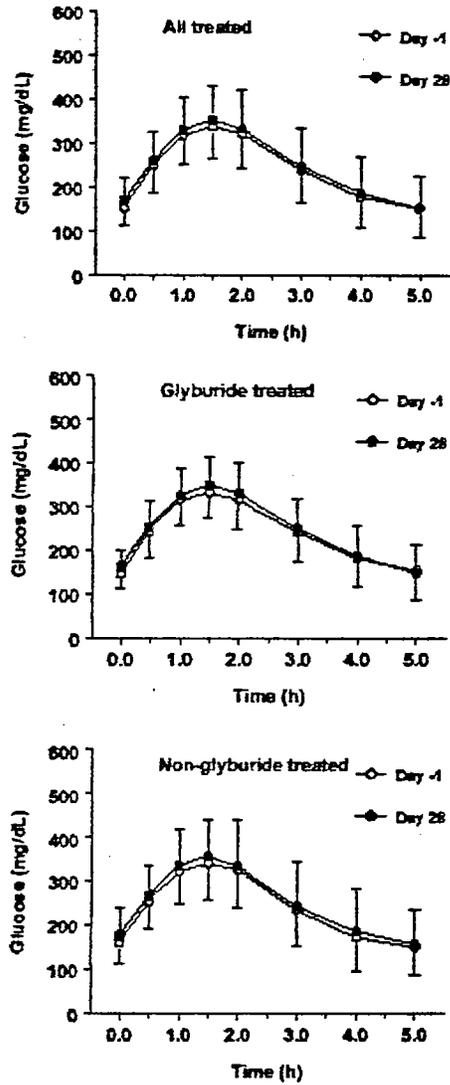
The mean (SD) of the serum glucose levels on Days 15, 28, and 42 versus Day -1 in all treated, glyburide treated, and non-glyburide treated groups are shown in Figures 4 through 6 below.

Figure 4. Mean (SD) Serum Glucose Levels on Days -1 and 15 in all Treated and in Glyburide and Non-Glyburide Treated Subjects
NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



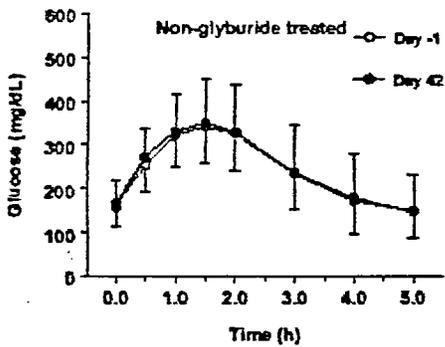
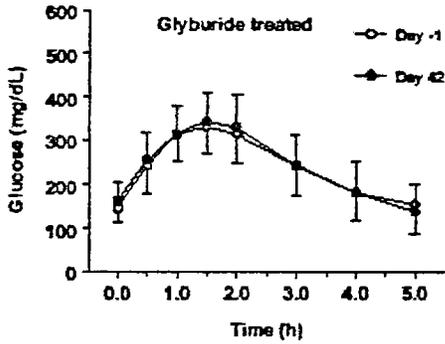
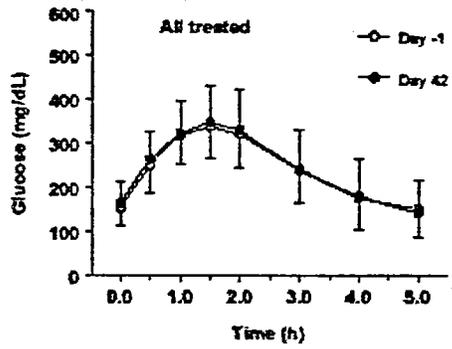
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Figure 5. Mean (SD) Serum Glucose Levels on Days -1 and 28 in all Treated and in Glyburide and Non-Glyburide Treated Subjects
 NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



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Figure 6. Mean (SD) Serum Glucose Levels on Days -1 and 42 in all Treated and in Glyburide and Non-Glyburide Treated Subjects
 NOTE: Gatifloxacin was Administered 400mg QD from Days 1 - 14



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Glucose concentrations measured over a 5-hour interval following an OGTT were used to compute AUC and Cmax for each study day. To test the reversibility of the effect on glucose levels after an OGTT, ratios of AUC and Cmax on Study Days 15, 28, and 42 to baseline (Day -1) were computed and an ANOVA on the logarithms of these ratios was performed. The statistical results are summarized in the table below.

Ratios of AUC and Cmax of Glucose on Days 15, 28, and 42 Relative to Day -1 Following an OGTT in all Treated and in Glyburide and Non-Glyburide Treated Subjects Administered Gatifloxacin 400 mg PO QD from Days 1 to 14						
	All Treated (n = 68)		Glyburide Treated (n = 35)		Non-glyburide Treated (n = 33)	
Study Day	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)
Glucose AUC(0-5) (mg•hr/dL)						
-1	1187 (26%)		1194 (22%)		1179 (29%)	
15	1358 (32%)	1.15 (1.10, 1.19)	1330 (28%)	1.11 (1.05, 1.18)	1389 (36%)	1.18 (1.11, 1.25)
28	1219 (28%)	1.03 (0.99, 1.07)	1234 (23%)	1.03 (0.98, 1.09)	1204 (33%)	1.02 (0.96, 1.08)
42	1183 (27%)	1.00 (0.96, 1.04)	1209 (24%)	1.01 (0.96, 1.07)	1156 (30%)	0.98 (0.93, 1.04)
Glucose Cmax (mg/dL)						
-1	342 (20%)		340 (18%)		345 (22%)	
15	386 (23%)	1.13 (1.09, 1.16)	374 (21%)	1.10 (1.05, 1.15)	400 (25%)	1.16 (1.11, 1.21)
28	356 (20%)	1.04 (1.01, 1.07)	354 (19%)	1.04 (1.00, 1.09)	359 (22%)	1.04 (0.99, 1.09)
42	342 (20%)	1.00 (0.97, 1.03)	344 (18%)	1.01 (0.97, 1.06)	341 (22%)	0.99 (0.94, 1.03)

These data suggested that gatifloxacin had no effect on serum glucose AUC(0-5) and Cmax estimates on either Days 15, 28, and 42 after 400mg QD administration from Days 1 to 14. Although glucose AUC and Cmax were increased on Day 15 by an average of 18% and 16%, respectively, in the non-glyburide treated group, the 90% CI for these parameters were within the protocol specified limits of equivalence or no-effect. There were no appreciable changes in glucose AUC or Cmax on Days 28 and 42 for the non-glyburide treated group.

No statistically significant differences were detected between the glyburide and non-glyburide treatment groups for either glucose AUC(0-5) ($p = 0.25$) and glucose Cmax ($p = 0.17$) on Day 15.

1.c. OGTT – Serum C-Peptide Concentrations Post Gatifloxacin Dosing

C-peptide serum concentrations measured over a 5-hour interval following an OGTT were used to compute AUC and Cmax for each study day. To test the reversibility of the effect on c-peptide levels after an OGTT, ratios of AUC and Cmax on Study Days 15, 28, and 42 to baseline (Day -1) were computed and an ANOVA on the logarithms of these ratios was performed. The statistical results are summarized in the table below.

Ratios of AUC and Cmax of C-Peptide on Days 15, 28, and 42 Relative to Day -1 Following an OGTT in all Treated and in Glyburide and Non-Glyburide Treated Subjects Administered Gatifloxacin 400 mg PO QD from Days 1 to 14

Study Day	All Treated (n = 68)		Glyburide Treated (n = 35)		Non-glyburide Treated (n = 33)	
	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)	Geometric Mean (% CV)	Point Estimate (90% CI)
C-Peptide AUC (ng•hr/mL)						
-1	38.2 (31%)		39.1 (30%)		37.2 (33%)	
15	32.7 (33%)	0.86 (0.83, 0.89)	33.9 (31%)	0.86 (0.82, 0.91)	31.5 (34%)	0.85 (0.81, 0.89)
28	32.8 (36%)	0.86 (0.83, 0.89)	34.5 (34%)	0.88 (0.84, 0.92)	31.0 (39%)	0.83 (0.80, 0.88)
42	35.5 (34%)	0.93 (0.90, 0.96)	36.2 (35%)	0.92 (0.88, 0.97)	34.7 (33%)	0.93 (0.89, 0.98)
C-Peptide Cmax (ng/mL)						
-1	9.9 (36%)		9.9 (34%)		9.8 (39%)	
15	8.7 (38%)	0.88 (0.85, 0.92)	8.8 (31%)	0.89 (0.84, 0.94)	8.6 (45%)	0.88 (0.83, 0.93)
28	8.5 (43%)	0.86 (0.83, 0.90)	8.7 (37%)	0.88 (0.83, 0.93)	8.3 (48%)	0.85 (0.80, 0.90)
42	9.3 (39%)	0.94 (0.91, 0.98)	9.1 (39%)	0.92 (0.87, 0.97)	9.5 (40%)	0.97 (0.92, 1.03)

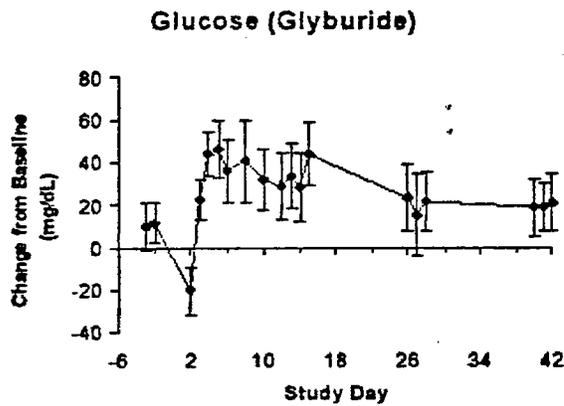
Following an OGTT, the no-effect criteria were met for all comparisons in the all treated, and in the glyburide and non-glyburide treated subjects for c-peptide Cmax and AUC. The Day 15 to Day -1 ratios of the geometric means of AUC and Cmax of c-peptide were compared between the glyburide and non-glyburide treated groups. There was no statistically significant differences detected between the groups for either AUC (p = 0.60) or Cmax (p = 0.80) of c-peptide.

2.a. Glucose Homeostasis – Serum Glucose Assessments Pre-dose (Days -3, -2, -1), During Gatifloxacin Administration (Days 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14) and Post Gatifloxacin Administration (Days 15, 26-28, and 40-42)

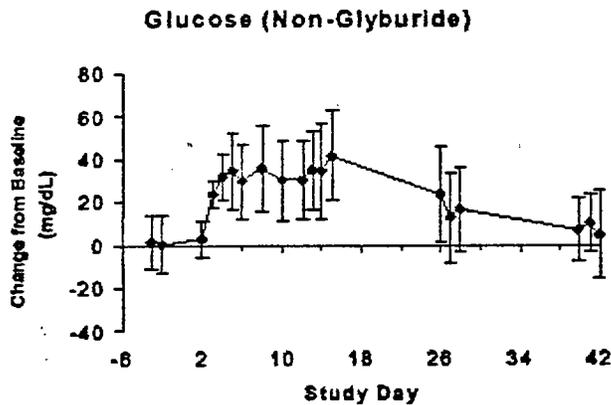
The mean (95% CI) change from baseline in fasting glucose levels on Days -3 to 42 in glyburide and non-glyburide treated groups are presented below in Figures 7A and 7B, respectively.

Figure 7. Mean (95% CI) Change from Baseline in Fasting Glucose Serum Concentrations on Days -3 to 42 in Glyburide (A) and Non-Glyburide (B) Treated Type 2 Diabetics Subjects
NOTE: Gatifloxacin Administered 400mg PO QD from Days 1 - 14

A



B



Decreases in mean fasting glucose were apparent during the first 2 days of gatifloxacin dosing for the glyburide treated subjects, but not for the non-glyburide treated group. The mean (min to max) changes (from baseline) in serum glucose on Day 2 of gatifloxacin dosing in the glyburide group was -20 (-109 to 35.5) mg/dL; the same statistics for the non-glyburide group were 2.8 (-63 to 84) mg/dL.

Following these initial changes, the changes in mean serum glucose from Days 3 to 14 showed increases ranging from approximately 20 to 45 mg/dL compared to the baseline measurements in both glyburide and non-glyburide treated subjects that persisted through the gatifloxacin dosing period. After the gatifloxacin dosing period, the mean changes in serum glucose remained increased from baseline from Days 15 to 42 in the range from ~15 to 44 mg/dL for the glyburide treated group and from ~5 to 42 mg/dL for the non-glyburide treated group. The mean changes in serum glucose in the glyburide group appeared to remain consistent through Days 26 to 42 (i.e., increases of ~20 mg/dL). However, in the non-glyburide group the mean changes in serum glucose appeared to diminish back towards baseline from Days 26 to 42 (increases of ~20 mg/dL on Day 26 and ~5 mg/dL on Day 42).

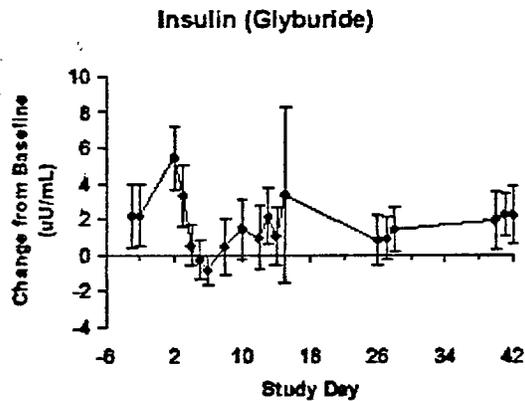
An ANOVA on the change from baseline (average of Days -1 and 1 values) on fasting glucose levels was conducted. Only study day was statistically significant ($p = 0.0001$); treatment group ($p = 0.77$) and treatment group-by-study day interaction ($p = 0.14$) were not statistically significant. These results suggested that change from baseline in fasting glucose was statistically different between study days, and that this difference was less influenced by whether subjects were in the glyburide or non-glyburide treated groups.

2.b. Glucose Homeostasis – Serum Insulin and C-Peptide Assessments Pre-dose (Days -3, -2, -1), During Gatifloxacin Administration (Days 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14) and Post Gatifloxacin Administration (Days 15, 26-28, and 40-42)

The mean (95% CI) change from baseline in fasting serum insulin and c-peptide levels on Days -3 to 42 in glyburide and non-glyburide treated groups are presented below in Figures 8A and 8B for insulin and 9A and 9B for c-peptide, respectively.

Figure 8. Mean (95% CI) Change from Baseline in Fasting Insulin Serum Concentrations on Days -3 to 42 in Glyburide (A) and Non-Glyburide (B) Treated Type 2 Diabetics Subjects
NOTE: Gatifloxacin Administered 400mg PO QD from Days 1 - 14

A



B

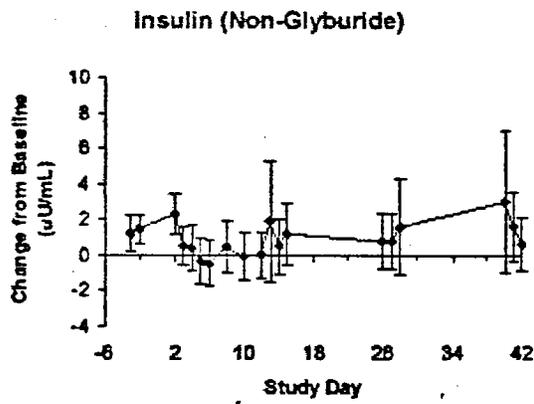
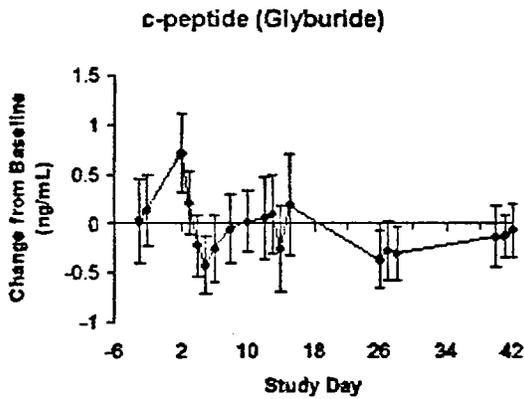


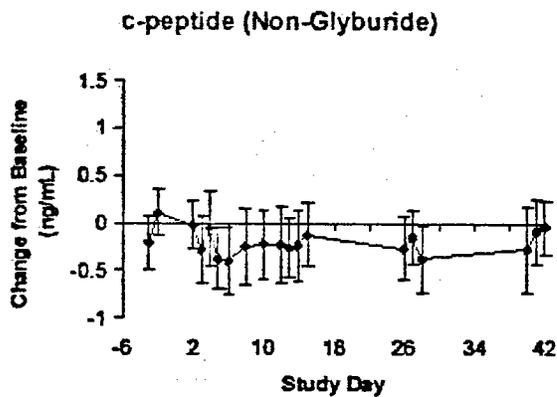
Figure 9. Mean (95% CI) Change from Baseline in Fasting C-Peptide Serum Concentrations on Days -3 to 42 in Glyburide (A) and Non-Glyburide (B) Treated Type 2 Diabetics Subjects

NOTE: Gatifloxacin Administered 400mg PO QD from Days 1 - 14

A



B



In general, changes in serum insulin and c-peptide concentrations appeared to be more evident in the glyburide treated group than the non-glyburide group. Increases in mean fasting insulin were greater during the first 2 days of gatifloxacin dosing for the glyburide treated subjects compared to the non-glyburide treated group. The mean (min to max) changes (from baseline) in serum insulin on Day 2 of gatifloxacin dosing in the glyburide group was 5.4 (-1 to 22) μ U/mL; the same statistics for the non-glyburide group were 2.3 (-2.5 to 12) μ U/mL.

Subsequently, the mean insulin levels in both treatment groups appeared to show no consistent pattern, but decreased below baseline values during the gatifloxacin dosing period, and returned back to baseline levels by Day 28 to Day 42.

An ANOVA on the change from baseline (average of Days -1 and 1 values) on fasting insulin levels was conducted. Only study day was statistically significant ($p = 0.0001$); treatment group ($p = 0.33$) and treatment group-by-study day interaction ($p = 0.32$) were not statistically significant. These results suggested that change from baseline in fasting insulin was statistically different between study days, and that this difference was less influenced by whether subjects were in the glyburide or non-glyburide treated groups.

The c-peptide levels in the glyburide treated group increased within the first 2 days of gatifloxacin treatment but subsequently did not show any consistent trend. However, the c-peptide levels were similar to baseline measurements at the end of therapy (Day 15) and slightly below baseline after gatifloxacin treatment from Days 26 to 42.

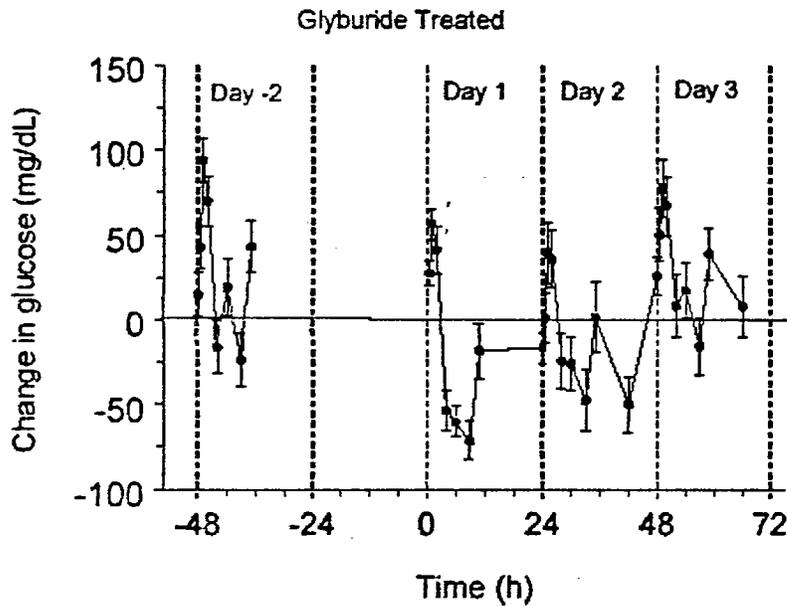
In the non-glyburide treated subjects, the mean c-peptide levels were decreased slightly lower both with gatifloxacin administration and after gatifloxacin therapy.

An ANOVA on the change from baseline (average of Days -1 and 1 values) in fasting c-peptide levels was conducted. Both study day ($p = 0.0001$) and treatment group-by-study day interaction ($p = 0.02$) were statistically significant; treatment group ($p = 0.38$) was not statistically significant. This indicated that the change from baseline in fasting c-peptide was statistically different for study days and that the time courses across study days were different for the two treatment groups.

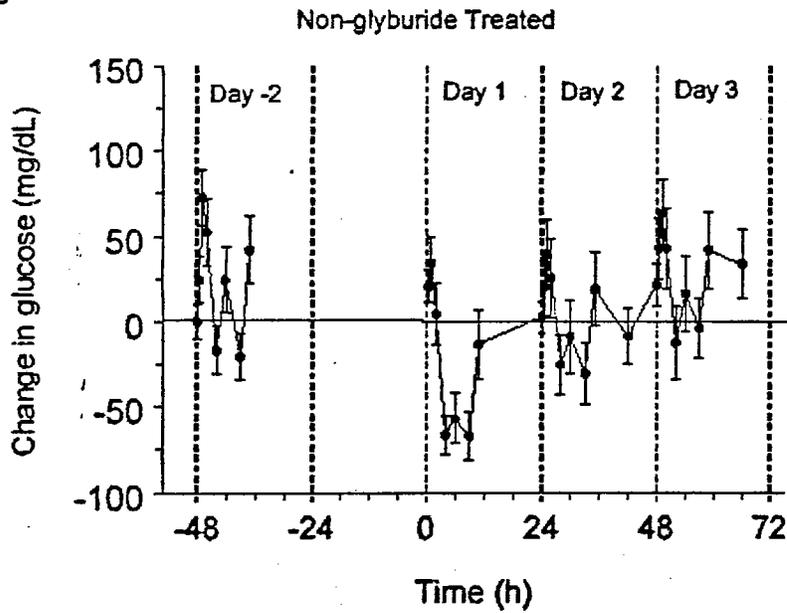
3.a. Acute Effects – Detailed Monitoring of Serum Glucose from 0 to 11 hr on Baseline Day-2 and With Gatifloxacin Administration on Days 1, 2, and 3

Figure 10. Mean (95% CI) Change from Baseline in Serum Glucose Levels Over 24 Hours in Glyburide (A) and Non-Glyburide (B) Treated Subjects on Days -2, 1, 2, and 3
NOTE: Gatifloxacin Administration 400mg PO QD from Days 1 to 14

A



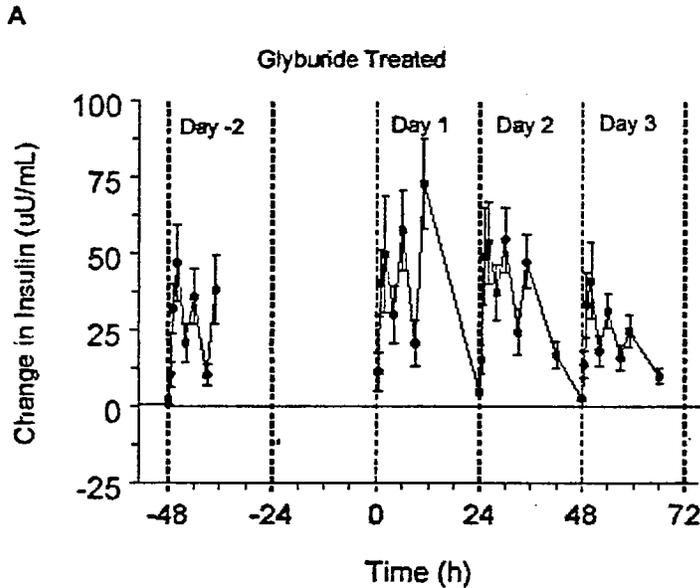
B



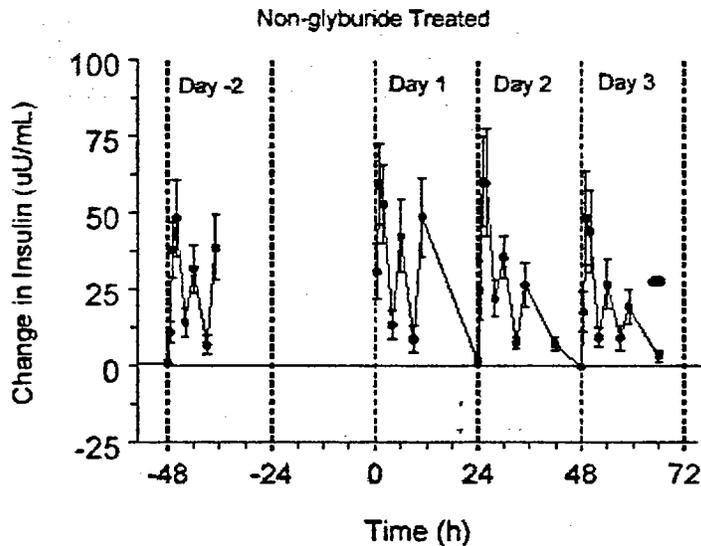
Decreases in glucose levels were observed in the first 2 days of gatifloxacin dosing (i.e., Days 1 and 2), despite lunch and dinner immediately after the 4 and 9 hour blood samples, respectively, in both the glyburide and non-glyburide treated groups. The most pronounced effects were noted in the glyburide treated group where the greatest decreases in glucose levels (from baseline Day -2) were on average between -54, 60, and 72 mg/dL at 4, 6, and 9 hr postdose, respectively, on Day 1. In the non-glyburide group, the greatest decreases in mean serum glucose on Day 1 were also at 4, 6, and 9 hr postdose and were -67, 57, and 67 mg/dL, respectively. On Day 2 of gatifloxacin dosing, the mean decreases in serum glucose at 4, 6, and 9 hr postdose were not as pronounced for both groups, and by Day 3 of dosing, there were little if any decreases in serum glucose levels at any of the postdose time points.

3.b. Acute Effects – Detailed Monitoring of Serum Insulin and C-Peptide from 0 to 11 hr on Baseline Day-2 and With Gatifloxacin Administration on Days 1, 2, and 3

Figure 11. Mean (95% CI) Change from Baseline in Serum Insulin Levels Over 24 Hours in Glyburide (A) and Non-Glyburide (B) Treated Subjects on Days -2, 1, 2, and 3
NOTE: Gatifloxacin Administration 400mg PO QD from Days 1 to 14



B



Increases in serum insulin levels were observed on Days 1 and 2 of gatifloxacin dosing in both glyburide and non-glyburide treated groups. It appeared that the magnitude of the mean increases in insulin were similar for both groups. By Day 3 of dosing, it appeared that serum insulin levels were somewhat similar to those on baseline Day -2.

Although the data is not shown here, the c-peptide levels in both groups paralleled those of serum insulin.

3.c. Partial AUC Assessment for Detailed Glucose Levels

To investigate the response to food intake on glucose levels, glucose concentrations for the first 9 hr postdose were used to compute partial areas under the glucose concentration curves, AUC(0-9).

Summary Statistics for Glucose AUC(0-9) Based on Detailed Measurements

Treatment Group	Study Days	Mean AUC(0-9) (mg•hr/mL)	S.D.	CV (%)	Min	Max
Glyburide	-2	1435	385	27	925	2472
	1	1005	258	26	591	1655
	2	1149	381	33	629	2095
	3	1472	436	30	890	2509
Non-glyburide	-2	1554	539	35	603	2893
	1	1114	363	33	464	2122
	2	1414	582	41	674	2735
	3	1603	676	42	881	3315

To test the significance of study day and treatment group on glucose levels, ratios of glucose AUC(0-9) on Study Days 1, 2, and 3 relative to baseline Day -2 were computed and an ANOVA on the logarithms of these ratios was performed. The statistical results are presented in the table below.

**Statistical Analysis - Ratio of Glucose AUC(0-9) Relative to Day -2
Based on Detailed Measurements**

Treatment Group	Study Day*	Geometric Mean AUC(0-9) (mg•hr/mL) (CV%)	AUC Ratio	p Value
Glyburide (n = 34)	-2	1392 (27%)		
	1	974 (26%)	0.70	0.0001
	2	1094 (33%)	0.79	0.0001
	3	1413 (30%)	1.02	0.7099
Non-glyburide (n = 35)	-2	1466 (35%)		
	1	1061 (33%)	0.72	0.0001
	2	1312 (41%)	0.89	0.0072
	3	1483 (42%)	1.01	0.7961
All treated (n = 69)	-2	1429 (31%)		
	1	1017 (30%)	0.71	0.0001
	2	1198 (39%)	0.84	0.0001
	3	1447 (37%)	1.01	0.6557

*Gatifloxacin Administered 400mg PO QD from Days 1 to 14

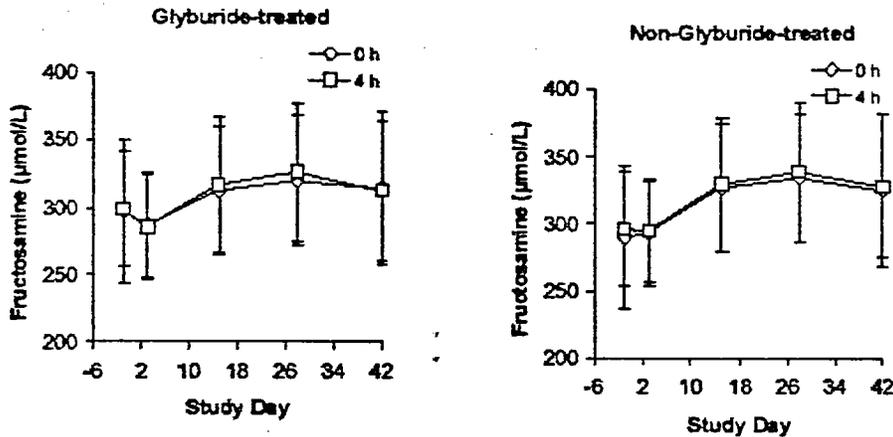
The ratios of AUC(0-9) on Days 1 and 2 of gatifloxacin dosing, relative to baseline Day -2, were significantly different from unity for all treatment groups. The ratios indicated a reduction in serum glucose by an overall average of ~30% on Day 1 and ~15% on Day 2 of gatifloxacin dosing. The ratios on Day 3 were not significantly different for all three groups. The AUC(0-9) ratios for study days were compared between the glyburide and non-glyburide treated groups. Only the Day 2 ratios were significantly different (p = 0.03) between the groups. For Days 1 (p = 0.58) and 3 (p = 0.93) there was no evidence of a significant difference between the glyburide and non-glyburide groups.

4.a. Markers of Glucose Control – Fructosamine Serum Concentrations

Fructosamine is considered a marker of short-term glucose control (i.e., weeks). Fructosamine concentrations in serum were determined on two occasions at 4 hours apart on the following study days:

- Study Day -1 (one day prior to start of gatifloxacin administration);
- Study Day 3 (3rd day of gatifloxacin administration);
- Study Day 15 (one day after end of gatifloxacin treatment);
- Study Day 28 (14 days after end of gatifloxacin treatment);
- Study Day 42 (28 days after end of gatifloxacin treatment).

Figure 12. Mean (SD) Fructosamine Serum Concentrations in Glyburide and Non-Glyburide Treated Subjects Measured 4 Hours Apart on Study Days -1, 3, 15, 28, and 42
 NOTE: Gatifloxacin Administration 400mg PO QD from Days 1 to 14



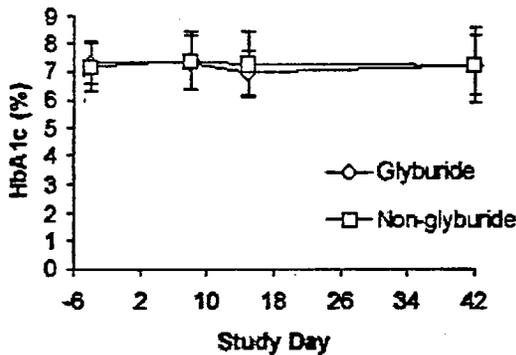
In both groups fructosamine serum concentrations were slightly reduced from baseline values (Day -1) on Study Day 3 during gatifloxacin administration. The magnitude of the reduction was greater for the glyburide treated group (mean reduction of $\sim 12 \mu\text{mol/L}$) compared with the non-glyburide group (mean reduction of $\sim 2 \mu\text{mol/L}$). After the end of gatifloxacin treatment (Study Days 15, 28, and 42) fructosamine serum concentrations had increased in both groups up to Day 28 and appeared to plateau at Day 42. The mean increases on Study Days 15, 28, and 42 were greater for the non-glyburide treatment group ($\sim 32, 41, 30 \mu\text{mol/L}$, respectively) vs. the glyburide group ($\sim 17, 25, 16 \mu\text{mol/L}$, respectively).

4.b. Markers of Glucose Control – Glycosylated Hemoglobin (HbA1c)

HbA1c is considered to be a marker of long-term glucose control (i.e., months). Glycosylated hemoglobin (HbA1c) was determined at screening and on the following study days:

- Study Day -4 (4 days prior to start of gatifloxacin administration)
- Study Day 8 (8th day of gatifloxacin administration)
- Study Day 15 (one day after end of gatifloxacin treatment);
- Study Day 42 (28 days after end of gatifloxacin treatment).

Figure 13. Mean (SD) Glycosylated Hemoglobin (HbA1c) Values in Glyburide and Non-Glyburide Treated Subjects Measured 4 Hours Apart on Study Days -4, 8, 15, and 42
 NOTE: Gatifloxacin Administration 400mg PO QD from Days 1 to 14



The mean HbA1c values were not appreciably altered prior to the start of gatifloxacin treatment, during gatifloxacin treatment, or after gatifloxacin treatment was completed for both the glyburide and non-glyburide treated groups.

SAFETY/ADVERSE EVENTS

Safety data were available for a total of 70 enrolled subjects (35 subjects each in the glyburide non-glyburide groups); 69 subjects completed the study. One subject, who was in the non-glyburide group (i.e., metformin only) discontinued after receiving one dose of gatifloxacin due to moderate dyspnea, hoarseness, tightness in the throat area, and mild tingling at the tip of the tongue on Day 1. All of these AEs resolved prior to the subject's discharge on Day 2.

Glyburide Treated Group

In the glyburide group, there were 43 treatment emergent AEs reported in 19 (54.3%) of 35 subjects. Treatment emergent AEs were either mild (40) or moderate (3) in intensity and unrelated (12), not likely (5), possibly (25), or probably (1) related to study drug. All AEs resolved prior to study discharge.

The most frequently reported treatment emergent AEs in the glyburide treated group were asthenia reported in 10 (28.6%) subjects, sweating reported in 5 (14.3%) subjects, dizziness reported in 5 (14.3%) subjects, abnormal vision reported in 3 (8.6%) subjects, dyspepsia reported in 2 (5.7%) subjects, pain reported in 2 (5.7%) subjects, and nausea reported in 2 (5.7%) subjects. It is particularly noteworthy that 7 subjects in the glyburide group received concomitant treatment, which consisted of food administration, for weakness and/or dizziness or perspiration (Subjects 012, 013, 024, 029, 045, 050, and 057). This was strongly suggestive of signs and symptoms of hypoglycemia (*see below for further details*).

Non-Glyburide Treated Group

In the non-glyburide group, there were 40 treatment emergent AEs reported in 19 (54.3%) of 35 subjects. Treatment emergent AEs were either mild (33) or moderate (7) in intensity and unrelated (10), not likely (12), possibly (12), probably (5) or certainly (1) related to study drug. *The only laboratory results reported as AEs by the Investigator was hyperglycemia reported for 3 subjects (all Grade 3; 250-500 mg/dL).* All AEs resolved prior to study discharge.

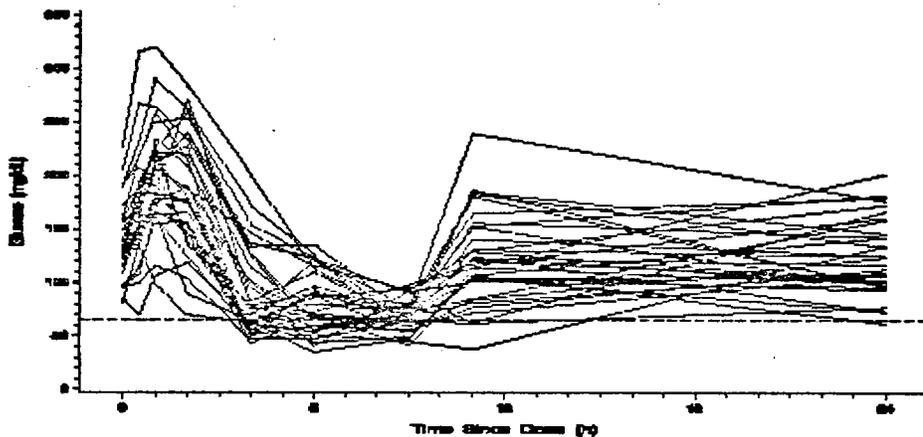
The most frequently reported treatment emergent AEs in the non-glyburide treated group were headache, vomiting, abnormal lab values, and vaginal disorder each reported in 3 (8.6%) subjects, and constipation, dyspepsia, voice alteration, and nausea each reported in 2 (5.7%) subjects. It is particularly noteworthy that 3 subjects in the non-glyburide group received concomitant treatment with insulin to treat hyperglycemia. Subject 021 received 10 units of insulin, Subject 023 received 4 units of human insulin, and Subject 052 received 7 units of insulin all for signs and symptoms of hyperglycemia.

Additional Analyses of AEs Related to Alterations of Glucose Control

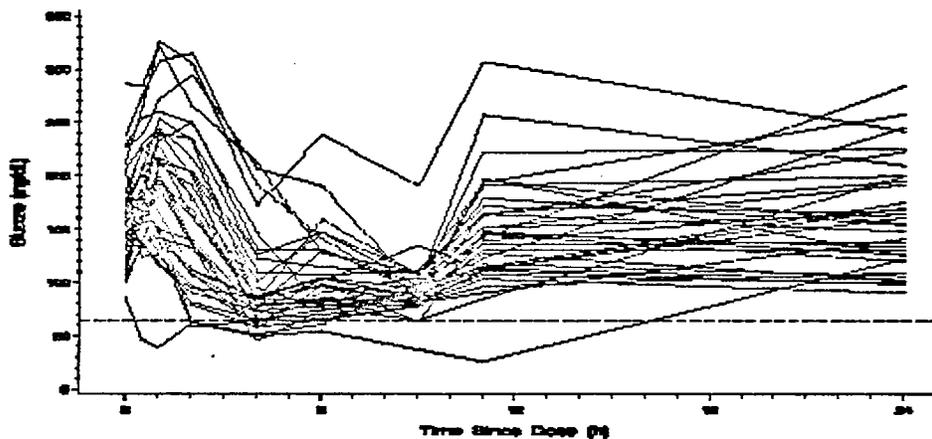
Figure 14 below shows the 24-hour serum glucose concentration profiles for all subjects in the glyburide and non-glyburide treated groups on Study Day 1, i.e., after the 1st dose of gatifloxacin.

Figure 14. Individual Subject Detailed Glucose Levels on Day 1 of Gatifloxacin Dosing in the Glyburide (A) and Non-Glyburide (B) Treated Groups. Dotted Line Indicates Lower Limit of Normal Serum Glucose Concentration, 65 mg/dL.

A. Glyburide

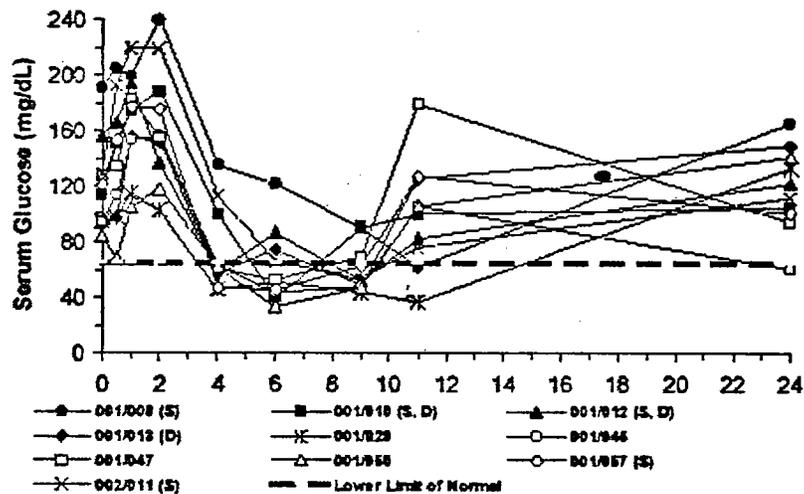


B. Non-Glyburide



Visual inspection of these figures suggested that serum glucose levels were lower in the glyburide group especially between 4 and 12 hours after the first gatifloxacin dose was given on Day 1. Symptoms consistent with hypoglycemia were only reported by subjects in the glyburide treated group. Ten (10) of 35 (29%) subjects reported asthenia; 8 subjects reported asthenia within 6 to 13 hours after the first day of dosing, 1 subject reported asthenia at about 23 hours on Day 1, and 1 subject reported asthenia within 9 hours after the second day of dosing. Of the 10 subjects that reported asthenia, 5 subjects reported sweating within 6 to 13 hours and 3 subjects reported dizziness. Figure 15 below shows the serum glucose concentrations for the 10 subjects with asthenia in the glyburide treated group.

Figure 15. Detailed Glucose Levels In Subjects Who had Asthenia in the Glyburide Treated Group on Day 1 after the 1st Dose of Gatifloxacin. Subjects are Identified as Site Number/Subject Number. Additional Symptoms are Identified Next to Subject Numbers as Sweating (S) and Dizziness (D). The Dotted Line Indicates the Lower Limit of Normal for Serum Glucose Concentration, 65 mg/dL



As can be seen from this plot, nearly all 10 subjects, including those with symptoms of hypoglycemia, had serum glucose concentrations below the lower limit of normal from 4 to 12 hours after gatifloxacin administration on Day 1.

Appears This Way
On Original

REVIEWER CONCLUSIONS

The following conclusions may be made regarding the effects of gatifloxacin, 400mg PO QD for 14 days (Study Days 1 – 14), on glucose control in the Type 2 diabetic subjects stabilized on either a glyburide-containing (N=35) or a non-glyburide-containing (N=34) antidiabetic drug regimen:

- The majority of the Type 2 diabetics in this study received either glyburide + metformin or metformin alone as their antidiabetic drug regimen (total of 65/69 subjects). Treatment with a thiazolidinedione either with or without glyburide/metformin occurred in only 4 of 69 subjects.
- Oral Glucose Tolerance Test (OGTT) to Assess Reversibility of Gatifloxacin Effects on Glucose Tolerance and Insulin and C-Peptide Secretion:
 - Following OGTT, there was no appreciable effect on serum insulin and c-peptide concentrations in the glyburide treated group at 1 day (Study Day 15), 14 days (Study Day 28), and 28 days (Study Day 42) after completion of gatifloxacin administration 400mg QD for 14 days. There were only modest reductions in insulin AUC and Cmax on Day 15 in the non-glyburide treated group of an average of 17% and 12%, respectively. Only the lower limit of the 90% CI for the Day 15/Baseline Day-1 ratio for insulin AUC in the non-glyburide treated group (i.e., lower CI = 75%) fell outside of the protocol-specified equivalence/no effect 90% CI criteria of 80% to 125%.
 - No statistically significant differences were detected between the glyburide and non-glyburide treatment groups for the insulin and c-peptide AUC or Cmax estimates on Day 15.
 - Following OGTT, gatifloxacin had no appreciable effect on serum glucose AUC and Cmax estimates on Study Days 15, 28, and 42 after completion of 400mg QD administration from Days 1 to 14 in the glyburide treated group. In the non-glyburide treated group the serum glucose AUC and Cmax were increased on Study Day 15 by an average of 18% and 16%, respectively. However, the 90% CI's for the Day 15/Baseline Day-1 ratios for these parameters were within the protocol specified limits of equivalence/no-effect (i.e., 80% to 125%). There were no appreciable changes in glucose AUC or Cmax on Days 28 and 42 for the non-glyburide treated group.
 - No statistically significant differences were detected between the glyburide and non-glyburide treatment groups for either glucose AUC or glucose Cmax on Day 15.
 - Overall, these data suggested that, an OGTT on Study Day 15, one day following completion of gatifloxacin administration for 14 days, showed there were modest increases in serum glucose and modest reductions serum insulin concentrations in the non-glyburide treated diabetic subjects. With an OGTT at 14 and 28 days following completion of gatifloxacin administration, the serum glucose and insulin concentrations in the non-glyburide group were not significantly different from the baseline concentrations. There were no significant effects on glucose and insulin in the glyburide treated subjects at any time following completion of gatifloxacin administration for 14 days. Thus, it appeared that at one day following the completion of gatifloxacin treatment, gatifloxacin might have a transient effect on glucose and insulin tolerance to cause an increase in blood glucose and a reduction in insulin levels (i.e., a transient hyperglycemic effect). These perturbations in glucose and insulin tolerance were not detected at 14 and 28 and days after the completion of gatifloxacin treatment and suggest some degree of reversibility to this effect.

- Glucose Homeostasis – Assessment of Fasting Glucose, Insulin, and C-Peptide at Pre-dose (Days -3 to -1), During Gatifloxacin Administration (days 1-14), and Following Completion of Gatifloxacin Administration (Days 15-42):
 - Decreases in mean fasting glucose were apparent during the first 2 days of gatifloxacin dosing for the glyburide treated subjects, but not for the non-glyburide treated group. The mean decrease (from baseline) in serum glucose on Study Day 2 of gatifloxacin dosing in the glyburide group was 20 mg/dL. Following this initial decrease, the mean serum glucose from Study Days 3 to 14 of gatifloxacin administration showed persistent increases of approximately 20 to 45 mg/dL compared to the baseline measurements in both glyburide and non-glyburide treated subjects. After completion of the gatifloxacin dosing period, the mean changes in serum glucose remained increased from baseline from Study Days 15 to 42 in the range of ~15 to 44 mg/dL for the glyburide treated group and of ~5 to 42 mg/dL for the non-glyburide treated group. The mean changes in serum glucose in the glyburide group appeared to remain consistent through Study Days 26 to 42 (i.e., increases of ~20 mg/dL). However, in the non-glyburide group the mean changes in serum glucose appeared to diminish back towards baseline from Days 26 to 42 (increases of ~20 mg/dL on Study Day 26 and ~5 mg/dL on Study Day 42).
 - Changes in serum insulin and c-peptide concentrations appeared to be more evident in the glyburide treated group than the non-glyburide group. Increases in mean fasting insulin and c-peptide were greater during the first 2 days of gatifloxacin dosing for the glyburide treated subjects compared to the non-glyburide treated group. Following these initial increases, the mean insulin and c-peptide levels in both treatment groups appeared to show no consistent pattern, decreasing below baseline values during the gatifloxacin dosing period, and then returning back to baseline levels by Study Days 28 to 42.
 - Overall, the results suggested that initial administration of gatifloxacin within the first 2 days of repeat dose treatment had an acute effect, especially in the glyburide treated diabetic subjects, to produce a reduction in serum glucose (i.e., hypoglycemia) in concert with an increase in serum insulin and c-peptide concentrations. This acute effect was less pronounced in the non-glyburide treated diabetics. With continued repeat dose gatifloxacin administration and after the completion of a 14-day treatment regimen, there was a persistent increase in serum glucose concentrations in both the glyburide and non-glyburide treated diabetics (increases of up to ~40 mg/dL from baseline). ***This effect of increased glucose did not appear to have been completely reversed by Study Day 42 (i.e., 28 days after completion of gatifloxacin administration) particularly in the glyburide treated diabetics.***

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- Acute Effects – Detailed Monitoring of Serum Glucose, Insulin, and C-Peptide from 0 to 11 hr on Baseline Day-2 and With Gatifloxacin Administration on Days 1, 2, and 3:
 - Decreases in glucose levels were observed in the first 2 days of gatifloxacin dosing (i.e., Study Days 1 and 2), despite lunch and dinner immediately after the 4 and 9 hour blood samples, respectively, in both the glyburide and non-glyburide treated groups. The most pronounced effects were observed at 4, 6, and 9 hr postdose on Study Day 1 in both groups, where the greatest decreases in glucose levels (from baseline) were on average between ~50 and 70 mg/dL. On Study Day 2 of gatifloxacin dosing, the mean decreases in serum glucose at 4, 6, and 9 hr postdose were not as pronounced for both groups, and by Study Day 3 of dosing, there were little if any decreases in serum glucose levels at any of the postdose time points. The serum glucose AUC(0-9) estimates were reduced (from baseline) by an average of ~30% on Study Day 1 and by ~15% on Study Day 2 of gatifloxacin dosing in both treatment groups; these reductions were statistically significant.
 - In concert with the decrease in serum glucose, the serum insulin and c-peptide levels were increased on Study Days 1 and 2 during gatifloxacin administration for both treatment groups. By Study Day 3, serum insulin and c-peptide levels approached those at baseline.
- Markers of Overall Glucose Control – Glycosylated Hemoglobin (HbA1c) and Fructosamine:
 - Fructosamine serum concentrations, marker of short-term glucose control (i.e., weeks), were increased in both glyburide and non-glyburide treatment groups up to 14 days following completion of gatifloxacin treatment (Study Day 15 and 28) and then appeared to plateau at 28 days after the end of gatifloxacin therapy (Study Day 42).
 - Glycosylated hemoglobin (HbA1c) values, marker of long-term glucose control (i.e., months), were not appreciably altered during or after the completion of gatifloxacin treatment in either treatment groups.
- Safety/Adverse Events Related to Alterations in Blood Glucose:
 - Signs and symptoms consistent with hypoglycemia were only reported by subjects in the glyburide treated group, especially at the initiation of gatifloxacin treatment (i.e., Study Days 1 and 2) over the time period from approximately 6 to 24 hours post gatifloxacin dose administration. A total of 10 of 35 (29%) glyburide treated subjects reported various symptoms associated with hypoglycemia (i.e., asthenia, sweating, dizziness, abnormal vision). These 10 subjects were shown to have blood glucose concentrations below the lower limit of normal (i.e., 65 mg/dL) from approximately 4 to 12 hours after the 1st gatifloxacin dose administration (Study Day 1). It is particularly noteworthy that 7 of these 10 subjects received concomitant treatment with food, in addition to the standard lunch, for weakness and/or dizziness or perspiration.
 - Hyperglycemia was reported as a Grade 3 laboratory AE (i.e., 250-500 mg/dL) in 3 of the 35 (8.6%) non-glyburide treated subjects during continued dose administration of gatifloxacin (i.e., beyond Study Day 3). These 3 subjects each received a single dose of insulin (ranging from 4 to 10 units) to correct the hyperglycemia.
- Summary of Conclusions:
 - In the well-controlled Type 2 diabetics studied, repeat dose administration of gatifloxacin (400mg QD for 14 days) appears to have a dual effect on glucose and insulin control. Upon initiation gatifloxacin treatment (within the 1st two days of dosing), there appears to

be a hypoglycemic effect, with an increase in serum insulin and the resultant reduction in blood glucose by approximately 50 to 70 mg/dL of baseline glucose values. With continued gatifloxacin treatment (beyond the 3rd day of dosing) there appears to be a hyperglycemic effect, with a persistent increase in serum glucose concentrations in both the glyburide and non-glyburide treated diabetics of up to approximately 40 mg/dL, from baseline. *This effect of increased glucose did not appear to have been completely reversed at 28 days after completion of gatifloxacin administration, particularly in the glyburide treated diabetics.*

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8/14/02 01:39:45 PM
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8/15/02 12:21:59 PM
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CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-061; SLR 010 21-062; SLR 011	Submission Dates:	July 20, 2001 May 28, 2002
NDA:	21-404 21-405	Submission Dates:	June 29, 2001 February 6, 2002
IND:	52,081; SN 213	Submission Date:	February 7, 2001
Drug Product:	Gatifloxacin Tablets (400 mg) and Injection		
Trade Name:	TEQUIN®		
Sponsor:	Bristol-Myers Squibb Wallingford, CT 06492		
Submission Type:	Labeling Supplement Regarding Studies of Effect of Gatifloxacin on the QT-Interval in Humans; New Indication – Uncomplicated Skin and Skin Structure Infections; Phase IV Studies to Evaluate Clinical Safety of Gatifloxacin and Effect on the QT-Interval in Humans		
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.		

Executive Summary

The potential for gatifloxacin to prolong the QT / QTc interval in humans was assessed by the sponsor at the request of the Division of Special Pathogen and Immunologic Drug Products (DSPIDP, HFD-590). In the action letter for the initial NDA submission, the indication of uncomplicated skin and skin structure infections (uSSSI) was deemed to be approvable by DSPIDP pending submission of additional post-marketing data confirming adequate safety of gatifloxacin in order to demonstrate an acceptable benefit/risk profile for this indication. The Division requested that the sponsor perform several Phase IV studies to address the effect of gatifloxacin on the QT / QTc interval. In fulfillment of this request, the sponsor provided to the Division six (6) completed study reports of the overall safety of gatifloxacin, including QT interval prolongation, in both healthy subjects and patients.

This Clinical Pharmacology / Biopharmaceutics review focused on 4 of the 6 study reports since these incorporated determination of plasma concentrations of gatifloxacin and ECG recordings corresponding to the time of PK blood sampling for QT-interval determination prior to and following oral gatifloxacin administration. The following general conclusions may be made regarding the effect of oral gatifloxacin on the QT / QTc interval in the healthy subjects and patients studied in these 4 trials:

- Following oral administration of a single 400mg clinical dose the average increase in the QTc interval, either from baseline or from placebo, was <10 msec in both healthy subjects and patients.
- Repeat oral dose administration of the 400mg clinical dose (i.e., at steady state) to patients with coronary artery disease resulted in a similar change in the QTc interval as that after the first dose administration. The lack of a greater effect of repeat dose gatifloxacin administration on the QT interval was consistent with the lack of plasma accumulation of the drug at steady state.
- There was an apparent weak linear relationship between the gatifloxacin dose (i.e., up to 1200mg = 3x clinical dose) or gatifloxacin plasma concentrations vs. the change in QTc, from baseline, in both healthy subjects and patients. The slope estimates of the linear relationships for the healthy subjects and patients were similar and suggested similar QT responsiveness between subjects and patients.
- Following the oral clinical dose of 400mg the majority of healthy subjects and patients had absolute post dose QTc intervals that were deemed to be of little or no clinical concern (i.e., <450 msec for males; <470 msec for females). Similarly, the majority of healthy subjects and patients had post dose QTc changes from baseline (i.e., Δ QTc) that were of little or no clinical concern (i.e., <30 msec).
- There appeared to be little difference in QT / QTc interval changes following oral gatifloxacin administration between male and female subjects or patients, but the potential for greater degree of post dose QT / QTc interval prolongation in elderly (>65 years) vs. non-elderly (\leq 65 years) subjects or patients.

Recommendation

The following 4 Phase IV study reports evaluating the effect of gatifloxacin on the QT / QTc interval in humans have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB):

- Study AI420-092: RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, SINGLE DOSE, FOUR WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN ON QTc INTERVAL IN HEALTHY ADULT VOLUNTEERS
- Study AI420-093: RANDOMIZED, OPEN LABEL, SINGLE DOSE, FOUR-WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN, CIPROFLOXACIN, SPARFLOXACIN, AND CLARITHROMYCIN ON QTc INTERVAL IN ADULT VOLUNTEERS
- Study AI420-095: AN OPEN LABEL, MULTICENTER, NONCOMPARATIVE, PHASE IV STUDY OF ORAL GATIFLOXACIN IN THE TREATMENT OF COMMUNITY ACQUIRED RESPIRATORY INFECTIONS – ANALYSIS OF EFFECTS ON THE QT INTERVAL OF THE ECG
- Study CV 123-229: PRAVASTATIN OR ATORVASTATIN EVALUATION AND INFECTION THERAPY (PROVE IT): ECG SUB-STUDY OF GATIFLOXACIN EFFECTS ON THE QTC INTERVAL



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 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

RD/FT signed by Barbara Davit, Ph.D. (TL) _____

QT Studies: Integrated Summary and Overall Conclusions

I. Introduction / Background

Gatifloxacin (TEQUIN®) is a fluoroquinolone antibiotic that was approved in 1999 by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP, HFD-590) for treatment of respiratory and urinary tract infections caused by a variety susceptible organisms (NDA 21-061 - Tablets; NDA 21-062 - Injection). In the action letter from the Division, the indication of uncomplicated skin and skin structure infections (uSSSI) was deemed to be approvable pending submission of additional post-marketing data confirming adequate safety of gatifloxacin in order to demonstrate an acceptable benefit/risk profile for this indication.

One of the primary safety concerns during the NDA review was the potential for gatifloxacin to prolong the QT interval of the ECG in humans. Thus, the Division requested that the sponsor perform several Phase IV studies to address the clinical safety of gatifloxacin. In fulfillment of this request, the sponsor has provided to the Division completed reports of the following safety information:

- (1) all spontaneously reported adverse events following treatment of the first one million adult patients with gatifloxacin;
- (2) safety of orally administered gatifloxacin via an active surveillance program that included at least 15,000 adult patients treated for respiratory tract infections (**Study AI420-088**);
- (3) evaluation of the effects of oral gatifloxacin on the QT interval in adult patients with community acquired respiratory tract infections (**Study AI420-095**);
- (4) evaluation of the effects of oral gatifloxacin on the QT interval in adult patients with coronary artery disease receiving concomitant treatment with pravastatin or atorvastatin (**Study CV 123-229 / PROVE-IT**);
- (5) evaluation of the effects of gatifloxacin on the QT interval following escalating single oral doses of 400mg, 800mg, and 1200mg to healthy adult subjects (**Study AI420-092**);
- (6) evaluation of the effects of single oral doses of gatifloxacin (800mg), ciprofloxacin (1000mg), sparfloxacin (400mg), and clarithromycin (1000mg) on the QT interval in healthy adult subjects (**Study AI420-093**).

This Clinical Pharmacology review will focus on the effects of gatifloxacin on the QT-interval from the four reports described in (3) through (6) above. These studies incorporated determination of plasma concentrations of gatifloxacin and ECG recordings corresponding to the time of PK blood sampling for QT-interval determination at protocol-specified timepoints prior to and following dose administration. Please refer to the Medical Officer review (Ekopimo Ibia, M.D.) for an assessment of the overall safety information, including effects of gatifloxacin on the QT-interval, contained in all of the reports described above.

II. Clinical Pharmacology Issues / Question Based Review

From a Clinical Pharmacology perspective, the issues (or questions) that wanted to be addressed by the Phase IV studies were the following:

- What is the magnitude of QT-interval prolongation following escalating doses of gatifloxacin to healthy male and female subjects?
- How does the effect of gatifloxacin on the QT-interval compare with other fluoroquinolone antibiotics and antibiotics outside of the fluoroquinolone class in healthy male and female subjects?
- How does the effect of gatifloxacin on the QT-interval in patients compare with that in healthy subjects?
- What is the relationship between the change in QTc and drug exposure (i.e., dose and/or plasma concentrations of gatifloxacin) in both healthy subjects and patients?
- Does the effect of gatifloxacin on the QT-interval differ between single and multiple dose (i.e., steady state) administration?
- Does the effect of gatifloxacin on the QT-interval differ between male and female subjects/patients or between young and elderly subjects/patients?

To address these issues the findings from the studies in healthy subjects will be first evaluated. The findings from patients will then be evaluated and compared with those from the healthy volunteer studies.

II.1. What is the magnitude of QT-interval prolongation following escalating doses of gatifloxacin to healthy male and female subjects?

II.2. How does the effect of gatifloxacin on the QT-interval compare with other fluoroquinolone antibiotics and antibiotics outside of the fluoroquinolone class in healthy male and female subjects?

The tables below show the combined results of the QTc and Δ QTc parameters for **Studies AI420-092 and AI420-093.**

QTc PARAMETERS FOLLOWING SINGLE ORAL DOSES to HEALTHY ADULT SUBJECTS
MEAN ± SD; Min, Max

	Gatifloxacin				
	Placebo Study -092	400mg Study -092	800mg Study -092	800mg Study -093	1200mg Study -092
N	31	34	37	40	33
Average QTc(0-12) (msec)	382 ± 14	386 ± 11	396 ± 16	396 ± 21	401 ± 17
QTc at Cmax (msec)	377 ± 20	388 ± 18	397 ± 22	399 ± 25	412 ± 21
Maximum QTc (msec)	400 ± 17	405 ± 14	413 ± 18	418 ± 23	424 ± 18

QTc PARAMETERS FOLLOWING SINGLE ORAL DOSES to HEALTHY ADULT SUBJECTS
MEAN ± SD; Min, Max

	Comparators		
	Ciprofloxacin 1000mg Study -093	Sparfloxacin 400mg Study -093	Clarithromycin 1000mg Study -093
N	39	39	40
Average QTc(0-12) (msec)	388 ± 17	398 ± 19	393 ± 16
QTc at Cmax (msec)	385 ± 23	402 ± 25	388 ± 19
Maximum QTc (msec)	407 ± 19	417 ± 19	415 ± 19

ΔQTc PARAMETERS FOLLOWING SINGLE ORAL DOSES to HEALTHY ADULT SUBJECTS
MEAN ± SD; Min, Max

	Gatifloxacin				
	Placebo Study -092	400mg Study -092	800mg Study -092	800mg Study -093	1200mg Study -092
N	31	34	37	40	33
Average ΔQTc(0-12) (msec)	-0.1 ± 6.3	4.1 ± 7.5	10.0 ± 6.9	12.7 ± 7.1	15.5 ± 8.2
ΔQTc at Cmax (msec)	-4.7 ± 13.4	5.5 ± 14.9	11.0 ± 11.0	15.3 ± 14.2	25.8 ± 20.8
Maximum ΔQTc (msec)	18.1 ± 10.1	22.6 ± 9.2	27.5 ± 9.4	34.4 ± 8.7	38.0 ± 16.6

ΔQTc PARAMETERS FOLLOWING SINGLE ORAL DOSES to HEALTHY ADULT SUBJECTS
MEAN ± SD; Min, Max

	Comparators		
	Ciprofloxacin 1000mg Study -093	Sparfloxacin 400mg Study -093	Clarithromycin 1000mg Study -093
N	39	39	40
Average ΔQTc(0-12) (msec)	4.2 ± 5.8	13.7 ± 9.1	10.3 ± 7.0
ΔQTc at Cmax (msec)	0.5 ± 12.4	18.3 ± 14.9	5.5 ± 10.5
Maximum ΔQTc (msec)	23.1 ± 10.1	32.9 ± 11.9	32.4 ± 16.6

Study -093: ΔQTc STATISTICAL COMPARISONS in HEALTHY SUBJECTS
COMPARATORS vs. GATIFLOXACIN 800mg

	Difference from Gatifloxacin (95% Confidence Interval)		
	ΔQTc at Cmax (msec)	Maximum ΔQTc (msec)	Average ΔQTc(0-12) (msec)
Ciprofloxacin 1000mg	-14.7 (-20.3, -8.9)*	-11.2 (-15.8, -6.6)*	-8.4 (-11.4, -5.3)*
Sparfloxacin 400mg	3.0 (-2.7, 8.7)	-1.4 (-6.0, 3.2)	1.1 (-1.9, 4.1)
Clarithromycin 1000mg	-10.0 (-15.6, -4.3)*	-2.6 (-7.1, 2.0)	-2.6 (-5.6, 0.4)

*p < 0.05

- A dose-response relationship was observed with all ΔQTc parameters following single oral escalating gatifloxacin doses of 400mg (clinical dose), 800mg (2 x clinical dose), and 1200mg (3 x clinical dose) to healthy young male and female subjects. Overall, the average ΔQTc was <10 msec (approximately 4 to 6 msec) following administration of the single oral clinical dose of 400 mg; 10 to 15 msec after the 800 mg single dose; and 15 to 25 msec after the 1200 mg single dose.
- There were no healthy male or female subjects with any “clinically significant” changes in QTc (i.e., QTc >500 msec or ΔQTc >60 msec) following single oral escalating doses of gatifloxacin. The majority of subjects (>90%) had QTc changes deemed to be “normal” (i.e., QTc <430 msec for males and <450msec for females; ΔQTc <30msec).
- Administration of single oral 800mg dose of gatifloxacin resulted in similar QTc changes compared to administration of single oral doses of sparfloxacin 400mg (2x clinical dose) and clarithromycin 1000mg (2x to 4x clinical dose).
- Single oral dose administration of ciprofloxacin 1000mg (1.3x to 2x clinical dose) had the least effect on QTc and the QTc changes were significantly lower compared to single oral 800mg dose of gatifloxacin.
- Overall, QTc changes appeared to be most similar following the single oral clinical dose of gatifloxacin 400mg and the single oral dose of ciprofloxacin 1000mg.

II.3. How does the effect of gatifloxacin on the QT-interval in patients (Study AI420-095 - RTI; Study CV 123-229 - PROVE-IT) compare with that in healthy subjects?

- Following oral administration of a single clinical oral dose of gatifloxacin (400mg), changes in the QTc interval determined at 2 hours post dose (i.e., at C_{max}) appeared to be similar between patients and healthy subjects. Mean increases in QTc in patients with respiratory tract infections (Study AI420-095) and patients with coronary artery disease after an acute coronary syndrome (Study CV 123-229 - PROVE-IT) were 9 msec and 6.5 msec, respectively. Similar to the results from healthy subjects, in general, the average Δ QTc was <10 msec following administration of the single oral clinical dose of 400 mg to patients. However, the range of individual QTc changes was wider for patients as compared to healthy subjects.
- Following the single oral clinical dose of 400mg, the majority of patients and healthy subjects (i.e., $\geq 90\%$) had Δ QTc <30 msec from baseline. At this dose, there were no healthy subjects with Δ QTc >60 msec and <1% of patients with Δ QTc >60 msec. Approximately 10% of patients and approximately 15% of healthy subjects had Δ QTc of "moderate clinical concern" (i.e., 30 to 60 msec) after the single oral gatifloxacin dose of 400mg.
- Following single oral administration of 400mg gatifloxacin, there were no patients or healthy subjects with a QTc interval ≥ 500 msec (as well as after single oral doses of 800mg and 1200mg to healthy subjects). The majority of patients and healthy subjects (>90%) had post dose changes in absolute QTc intervals considered to be without clinical concern for males and females (<430 msec and <450 msec, respectively). $\leq 10\%$ of patients had post dose QTc intervals that were considered to be prolonged and/or potentially significant for males and females.

II.4. What is the relationship between the change in QTc and drug exposure (i.e., dose and/or plasma concentrations of gatifloxacin) in both healthy subjects and patients?

- A weak linear relationship between Δ QTc (i.e., QTc changes from pre dose baseline) and postdose gatifloxacin plasma concentrations was observed in both healthy subjects and patients with either respiratory tract infections or patients with coronary artery disease after an acute coronary syndrome.
- The linear relationships between post dose Δ QTc and gatifloxacin plasma concentrations were similar between patients receiving single or repeated 400mg oral doses and healthy subjects receiving single oral doses of 400mg, 800mg, and 1200mg. The estimates of the slope for the respective regressions were similar for patients and subjects (i.e., approximately 2.5 – 3.0 msec/ μ g/mL) and suggested similar QT responsiveness between healthy subjects and patients.
- The range of plasma gatifloxacin concentrations at 2 hours post dose in patients receiving the clinical oral dose of 400mg (i.e., up to approximately 8 μ g/mL) were consistent with

those concentrations in the healthy subjects following single oral doses of 400mg to 800mg (i.e., approximately 3 to 10 µg/mL).

II.5. Does the effect of gatifloxacin on the QT-interval differ between single and multiple dose (i.e., steady state) administration?

- Single and multiple dose assessment of the QT prolonging effect of gatifloxacin was only evaluated in patients with coronary artery disease after an acute coronary syndrome (**Study CV 123-229 - PROVE-IT**). Overall, it appears that the effects of gatifloxacin on the QT interval are similar following single and repeated clinical doses of 400 mg.
- Mean plasma concentrations of gatifloxacin determined at approximately 2 hr following 1st and 6th dose administration of 400mg were similar at 3.0 µg/mL and 3.3-3.4 µg/mL, respectively. The majority of gatifloxacin-treated patients had plasma concentrations at approximately 2 hr post dose between 2 µg/mL and 5 µg/mL after the 1st and 6th doses. This indicated minimal accumulation of gatifloxacin in plasma (i.e., 10-13%) and is consistent with the PK characteristics of gatifloxacin observed in healthy subjects.
- Following the 6th dose of gatifloxacin 400mg (i.e., at presumed steady-state) to 36 patients with coronary artery disease after an acute coronary syndrome, the average increase in QTc (from baseline) was the same as that after the 1st dose in these same patients (i.e., mean QTc change 6.5 msec after 1st and 6th doses). This effect is consistent with the minimal plasma accumulation of gatifloxacin after repeated doses.
- Following the 6th dose of gatifloxacin 400mg to patients with coronary artery disease after an acute coronary syndrome, the QTc intervals at 2 hr postdose were <450 msec for the majority of patients (94%). In addition, the change in QTc at 2 hr postdose was <30 msec for the majority (90%) of gatifloxacin-treated patients. There was one 50 year old female gatifloxacin-treated patient with QTc >500 msec who also had a change in QTc >60 msec. No clinical signs or symptoms of any cardiac abnormalities were associated with these QTc changes in this patient.

II.6. Does the effect of gatifloxacin on the QT-interval differ between male and female subjects/patients or between young (<65 years) and elderly (≥65 years) subjects/patients?

- The number of healthy elderly males and females evaluated in the studies of healthy subjects (**Studies AI420-092 and AI420-093**) was inadequate to derive any conclusions regarding the effect of gatifloxacin on the QT / QTc interval in elderly subjects.
- In the studies of healthy young males and females (**Studies AI420-092 and AI420-093**) there were no apparent differences in the QT / QTc changes between these two subgroups of subjects. No healthy male or female subjects were reported to have any clinically significant ECG alterations following single escalating doses of gatifloxacin or following single oral doses of the comparator drugs (i.e., ciprofloxacin, sparfloxacin, clarithromycin).
- In the studies of patients with respiratory tract infections (**Study AI420-095**) and patients with coronary artery disease after an acute coronary syndrome (**Study CV 123-229 -**

PROVE-IT), there were no apparent gender-related differences in QT / QTc changes between males and females of all ages.

- In the patients with respiratory tract infections (**Study AI420-095**), there was no apparent trend for greater prolongation of QTc by gatifloxacin in those patients ≥ 65 years of age (23/262; 9%) vs. patients < 65 years (241/262; 91%) or in those patients classified as "high risk" for QTc prolongation (i.e., hypokalemia; concomitant medications known to prolong QT interval) vs. patients with "low risk".
- In the patients with coronary artery disease after an acute coronary syndrome (**Study CV 123-229 - PROVE-IT**), there appeared to be a greater prolongation of the QTc following 1st dose gatifloxacin 400mg in the elderly (n/N = 107/374) vs. non-elderly (n/N = 267/374) patients (i.e., mean QTc 8.7 msec vs. 5.6 msec).
- Overall, the results suggested little difference between male and female subjects/patients, but the potential for greater QT-interval prolongation in elderly vs. younger subjects/patients.

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- Summary of Studies

- I. Results

- I.1. Healthy Subjects

Two studies were performed to evaluate the effects of gatifloxacin on the QT interval of healthy male and female volunteers:

Study AI420-092: RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, SINGLE DOSE, FOUR WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN ON QTc INTERVAL IN HEALTHY ADULT VOLUNTEERS

Study AI420-093: RANDOMIZED, OPEN LABEL, SINGLE DOSE, FOUR-WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN, CIPROFLOXACIN, SPARFLOXACIN, AND CLARITHROMYCIN ON QTc INTERVAL IN ADULT VOLUNTEERS

Of the four studies reviewed, these two trials incorporated the greatest degree of QT-interval assessment in the study design following gatifloxacin dose administration.

- II.1.1. Study AI420-092

This study was designed to evaluate the effects of gatifloxacin on the QT-interval following single oral escalating doses of up to 3-times the clinical dose in healthy male and female subjects, i.e., 400mg = clinical dose, 800mg = 2 x clinical dose, and 1200mg = 3 x clinical dose. A placebo treatment arm was also employed and each subject received all 4 treatments in a randomized, double blind, crossover fashion.

On the day prior to dosing (i.e., Day -1), baseline QTc intervals were determined from 11 ECG's (12-lead) recorded at serial timepoints from 0 to 12 hours. On the day of study treatment administration (i.e., Day 1; gatifloxacin or placebo), QTc intervals and gatifloxacin plasma concentrations were determined at the same times from 0 to 12 hours postdose as the baseline day. All 12-lead ECG's were performed under standardized conditions. ECG intervals were determined using the _____ ECG measurement system. _____

The _____ system was calibrated for accuracy prior to each session and was found to be accurate to within ± 3 msec.

QTc values were calculated for each of 3 sets of R-R/QT measurements using Bazett's (B) and Fridericia's (F) heart rate correction formulae, i.e., $QTcB = QT/\sqrt{RR}$ and $QTcF = QT/\sqrt[3]{R-R}$. The mean QTc equaled the sum of the 3 QTc measurements divided by 3. Neither gatifloxacin nor placebo was shown to significantly alter heart rate (or R-R interval) in these subjects. Thus, the QTc results presented here are corrected using Bazett's formula.

The PK parameters determined for gatifloxacin were C_{max} , T_{max} , $AUC(0-6)$, $AUC(0-12)$, and $C_{avg}(0-6)$ and $C_{avg}(0-12)$. The sponsor determined 4 different PD parameters for QTc and 5 different baseline QTc parameters.

The PD parameters for QTc were defined as follows:

- 1) *Delta QTcAvg (0-6)* = the change from baseline (Day -1 outcome) in time-averaged QTc during the first 6 hours after dosing on Day 1, i.e., the area under the QTc curve from 0 (predose) to 6 hr after dosing, divided by 6 hr.
- 2) *Delta QTcAvg (0-12)* = the change from baseline (Day -1 outcome) in the time-averaged QTc during the first 12 hours after dosing on Day 1, i.e., the area under the QTc curve from 0 (predose) to 12 hr after dosing, divided by 12 hr.
- 3) *Delta QTcMax* = the change from baseline (Day -1 outcome) in the longest QTc recorded after dosing on Day 1.
- 4) *Delta QTc at Tmax* = the change from baseline (Day -1 outcome) in the QTc recorded at the time (*Tmax*) of peak gatifloxacin concentration (*Cmax*) on Day 1. For the placebo treatment, QTc at *Tmax* was the QTc at the median of the *Tmax* values from the other periods.

The baseline QTc parameters were defined as follows:

- 1) *Baseline QTcAvg(0-6)* = the time averaged QTc during the 6 hours on Day -1, i.e., the area under the QTc curve over 6 hours on Day -1, divided by 6 hours.
- 2) *Baseline QTcAvg(0-12)* = the time averaged QTc during the 12 hours on Day -1, i.e., the area under the QTc curve over 12 hours on Day -1, divided by 12 hours.
- 3) *Baseline QTcMax* = the QTc recorded on Day -1 at the time corresponding to the time of longest QTc recorded on Day 1.
- 4) *Baseline QTc at Tmax* = the QTc recorded on Day -1 at the time corresponding to the gatifloxacin *Tmax* on Day 1.
- 5) *QTc at 0 hr* = the mean of the QTc intervals recorded just prior to gatifloxacin dosing on Day 1 and at the corresponding time 24 hours earlier on Day -1.

Baselines (1), (4), and (5) were used in the analyses of the *QTcAvg(0-6)*. Baselines (2), (4), and (5) were used in the analyses of the *QTcAvg (0-12)*. Baselines (1), (2), (3), (4), and (5) were used in the analyses of *QTcMax*. Baselines (1), (2), (4), and (5) were used in the analyses of QTc at *Tmax*.

Scatter plots and linear regressions were used to explore the relationship between gatifloxacin exposure and the changes from baseline in each of the derived QTc outcome measures. The changes in each of the derived QTc outcome measures from the corresponding baseline values were also summarized by treatment.

For the outlier analyses, the sponsor chose to use the QTc Max since this parameter represents the worst case scenario. The QTc Max was cross tabulated against baseline for each treatment. For males, QTc Max values were grouped as QTc <430msec, 430msec ≤ QTc ≤ 450msec, or QTc >450msec. For females, QTc Max values were grouped as QTc <450msec, 450msec ≤ QTc ≤ 470msec, or QTc >470msec. Additionally, the changes in QTc Max from baseline were also tabulated as ΔQTc Max < 30 msec, 30 msec ≤ ΔQTc Max ≤ 60 msec, or ΔQTc Max > 60 msec.

The sponsor classified the QTc Max values and changes in QTc Max from baseline by clinical risk according to the following criteria.

Categories for Absolute QTc Values

Classification	QTc Interval for Males (msec)	QTc Interval for Females (msec)
Normal	<430	<450
Borderline	430 to 450	450 to 470
Prolonged	>450	>470

Risk Categories for Changes in QTc from Baseline

Risk Classification for Drug to Induce Arrhythmia, Including <i>Torsades de Pointes</i>	Δ QTc (msec)
Unlikely – Non-Significant/Minimal Clinical Concern	<30
Likely – Moderate Clinical Concern	30 to 60
Highly Likely – Significant/High Clinical Concern	>60

Reviewer Comments: The cross tabulations and risk classifications were consistent with the previously published 1997 CPMP/EMA Points to Consider document entitled, "The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products".

The cross tabulations were to be presented by gender and age group, but due to the small numbers of subjects in the older age group, they were only presented by gender.

A total of 40 subjects entered the study and 33 subjects completed all 4 treatment periods. The table below provides a summary of subject demographics, by treatment, for which PK and QTc data was obtained.

Study AI420-092: Subject Demographics

Treatment	PK DATA			QTc DATA		
	N	M / F	≥65 Years	N	M / F	≥65 Years
Placebo	—	—	—	31	18 M 13 F	2 M 3 F
400 mg Gatifloxacin	33	18 M 15 F	2 M 1 F	34	18 M 16 F	2 M 3 F
800 mg Gatifloxacin	34	19 M 15 F	2 M 2 F	37	18 M 19 F	2 M 3 F
1200 mg Gatifloxacin	31	19 M 12 F	2 M 3 F	30	18 M 12 F	2 M 3 F

Reviewer Comment: Note that there were very few elderly male and female subjects evaluated for both PK and QTc. Because of the small numbers, no conclusions can be made regarding the effects of gatifloxacin on the QT / QTc interval in elderly subjects.

Pharmacokinetics

The table below provides a summary of the PK parameters determined for gatifloxacin.

Study AI420-092: Gatifloxacin PK Parameters Following Single Oral Doses to Healthy Subjects

Dose	Cmax* (µg/mL)	Tmax** (h)	AUC(0-T)*** (µg.h/mL)	Cav(0-6)* (µg/mL)	Cav(0-12)* (µg/mL)
400 mg N=33	3.52 (31.7)	1.5	21.3 (25.5)	2.30 (23.5)	1.77 (25.5)
800 mg N=34	6.25 (20.6)	1.5	44.6 (19.7)	4.49 (21.2)	3.71 (19.7)
1200 mg N=31	9.00 (22.2)	2.0	68.9 (22.0)	6.69 (19.8)	5.74 (22.0)

*Geometric Mean (%CV); Min, Max

**Median Tmax (Min, Max)

***AUC(0-T) = area under the curve to time of last quantifiable concentration

The table shows that mean PK parameters for gatifloxacin were approximately dose proportional. The between subject variability in all PK parameters, as % CV, was reasonable - ranging approximately from 20% to 30% - and was consistent with what has been previously reported for these gatifloxacin doses.

Pharmacodynamics / Exposure-QT Response

Summaries of the statistical and regression results are presented below for each derived QTc parameter and the change in each QTc parameter from the respective baselines. The regression plots for each QTc parameter vs. the relevant gatifloxacin plasma exposure variable are provided in the individual study report for **Study AI420-092** in **Appendix 2** as **Figures 1 through 4**, pages 104-107.

Reviewer Comment: The sponsor focused on the QTcAvg(0-6) as the primary QTc parameter. While this was acceptable, it is the opinion of the reviewer that the QTcAvg(0-12) is equally important, since although both are time-averaged parameters, the QTcAvg(0-12) may represent a more robust time-averaged parameter, especially if the QTc exhibits diurnal variability greater than over a 6-hour time period. Thus, the reviewer will place greater emphasis on the QTcAvg(0-12) than the QTcAvg(0-6).

QTcAvg(0-6)

Study AI420-092: Summary Statistics for QTcAvg(0-6) and Changes in QTcAvg(0-6)

Treatment	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800 mg	Gatifloxacin 1200 mg
QTcAvg(0-6) (msec) Mean (SD) Min, Max	381 (14)	386 (12)	396 (16)	403 (16)
Baseline QTc	Change in QTcAvg(0-6) from Baseline (msec) Mean (SD); Min, Max			
Day-1 QTcAvg(0-6)	-2.3 (7.1)	4.0 (7.9)	10.8 (6.6)	16.9 (7.7)

Study AI420-092: Regression Summary of Δ QTcAvg(0-6) on Cav(0-6)

Dependent Variable	QTc Baseline (msec)	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/ μ g/mL)
Δ QTcAvg(0-6)	QTcAvg(0-6)	Cav(0-6) (μ g/mL)	-1.8	2.7 (2.1, 3.2)

QTcAvg(0-12)

Study AI420-092: Summary Statistics for QTcAvg(0-12) and Changes in QTcAvg(0-12)

Treatment	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800 mg	Gatifloxacin 1200 mg
QTcAvg(0-12) (msec) Mean(SD) Min,Max	382 (14)	386 (11)	396 (16)	401 (17)
Baseline QTc	Change in QTcAvg(0-12) from Baseline (msec) Mean (SD) Min, Max			
Day-1 QTcAvg(0-12)	-0.1 (6.3)	4.1 (7.5)	10.0 (6.9)	15.5 (8.2)

Study AI420-092: Regression Summary of Δ QTcAvg(0-12) on Cav(0-12)

Dependent Variable	QTc Baseline (msec)	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/ μ g/mL)
Δ QTcAvg(0-12)	QTcAvg(0-12)	Cav(0-12) (μ g/mL)	0.1	2.5 (1.9, 3.1)

QTc Max

Study AI420-092: Summary Statistics for QTcMax and Changes in QTcMax

Treatment	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800mg	Gatifloxacin 1200 mg
QTcMax (msec) Mean (SD) Min, Max	400 (17)	405 (14)	413 (18)	424 (18)
Baseline QTc	Change in QTcMax from Baseline (msec) Mean (SD) Min, Max			
Day -1 QTc Avg(0-12)	18.1 (10.1)	22.6 (9.2)	27.5 (9.4)	38.0 (16.6)
Day -1 QTcMax	15.1 (15.7)	22.4 (13.8)	29.2 (15.7)	38.6 (18.6)

Study AI420-092: Regression Summary of Δ QTc Max

Dependent Variable	QTc Baseline (msec)	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/ μ g/mL)
Δ QTc Max	QTc Avg(0-12) QTcMax	Cavg(0-12) (μ g /mL)	17.3	3.1 (2.2, 4.1)
			15.4	3.7 (2.4, 5.1)

QTc at Tmax

Study AI420-092: Summary Statistics for QTc at Tmax and Changes in QTc at Tmax

	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800 mg	Gatifloxacin 1200 mg
QTc at Tmax (msec) Mean (SD) Min, Max	377 (20) _____	388 (18) _____	397 (22) _____	412 (21) _____
Baseline QTc	Delta QTc at Tmax from Baseline (msec) Mean (SD) Min, Max			
Day -1 QTc at Tmax	-2 (20.4) _____	7.2 (17.6) _____	12.6 (17.5) _____	24.5 (24.3) _____
Day -1 QTc Avg(0-12)	-4.7 (13.4) _____	5.5 (14.9) _____	11.0 (11.0) _____	25.8 (20.8) _____

Study AI420-092: Regression Summaries of Δ QTc at Tmax

Dependent Variable	QTc Baseline	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/ μ g /mL)
Δ QTc at Tmax	QTc Avg(0-12) QTc at Tmax	Cmax (μ g /mL)	-5.4	3.0 (2.2, 3.8)
			-2.8	2.7 (1.6, 3.7)
Δ QTc at Tmax	QTcAvg(0-12) QTc at Tmax	Cav(0-12) (μ g /mL)	-4.8	4.7 (3.5, 6.0)
			-2.9	4.5 (2.9, 6.0)

Reviewer Assessment of Time to Maximum QTc (QTc Max) vs. Time to Gatifloxacin Cmax (i.e., Tmax)

This assessment was performed to evaluate whether the time of occurrence of the maximum QTc interval and the change in QTc Max from baseline coincided with the Tmax of gatifloxacin. It has generally been assumed that the greatest change in the QTc would occur at time of Cmax (i.e., Tmax) for the fluoroquinolones and other non-cardiovascular drugs that prolong the QT interval. The table below summarizes the results.

Study AI420-092: Gatifloxacin Plasma Tmax vs. Time to QTc Max and Time to ΔQTc Max

	Median Tmax (hr) (Min, Max)	Median Time to QTc Max (hr) (Min, Max)	Median Time to ΔQTc Max (hr) (Min, Max)
Placebo	NA	3.5	3.0
400mg Gatifloxacin	1.5	3.0	2.0
800mg Gatifloxacin	1.5	2.0	3.0
1200mg Gatifloxacin	2.0	2.0	2.0

Reviewer Conclusions Regarding Exposure-QT Response

- A dose-response relationship was observed with all ΔQTc parameters following single oral gatifloxacin doses of 400mg (clinical dose), 800mg (2xclinical dose), and 1200mg (3xclinical dose) to healthy male and female subjects.
 - **ΔQTcAvg(0-12) and ΔQTc at Tmax values (mean (overall range)):**
 Placebo → -2 to -0.1 (-50, +40) msec
 400mg → 4 to 6 (-29, +33) msec
 800mg → 10 to 12 (-17, +29) msec
 1200mg → 16 to 26 (-4, +81) msec
 - **ΔQTc Max values (mean (range)):**
 Placebo → 15 (-14, +48) msec
 400mg → 23 (6, 53) msec
 800mg → 28 (12, 48) msec
 1200mg → 38 (14, 81) msec
 - Note that for the ΔQTc Max values, if one takes into account the changes in placebo, then the mean changes in QTc Max become relatively similar to those observed for QTc at Tmax and QTcAvg(0-12).
- A concentration-response relationship was also observed with all ΔQTc parameters following single oral gatifloxacin doses of 400mg, 800mg, and 1200mg.
 - Linear regression analyses of ΔQTc parameters vs. plasma gatifloxacin concentration resulted in slope estimates from 2.5 to 3.1 msec/μg/mL.
- The median times to QTc Max and to ΔQTc Max were relatively similar to the median Tmax values determined for gatifloxacin in plasma. Similar median times for the QTc Max parameters were also observed between placebo and the 3 gatifloxacin doses. A notable difference, however, between the plasma Tmax and QTc Max parameters is that the ranges for the QTc Max parameters were appreciably wider than those for plasma Tmax, which lends support to the greater degree of temporal variability that is observed in QTc.
- Overall, similar results were obtained across all of the various baseline corrections employed by the sponsor to determine the ΔQTc parameters (see **Appendix 1: Study AI420-092**).

Outlier Analyses of QTc Max

The results for absolute QTc Max values and for ΔQTc Max in male and female subjects are shown in the tables below.

Study AI420-092: QTc MAX FOR MALES

Single Dose	Pre-Dose	Post-Dose QTc MAX		
		≤430 msec	>430 - 450 msec	>450 msec
Placebo	≤430 msec	18	0	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0
Gatifloxacin 400 mg	≤ 430 msec	18	0	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0
Gatifloxacin 800 mg	≤ 430 msec	17	1 ^a	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0
Gatifloxacin 1200 mg	≤430 msec	13	5 ^b	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0

^a < 65 years old

^b 4 subjects < 65 years old; 1 subject > 65 years old

Study AI420-092: QTc MAX FOR FEMALES

Single Dose	Pre-Dose	Post-Dose QTc MAX		
		≤450 msec	>450 - 470 msec	>470 msec
Placebo	≤450 msec	13	0	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0
Gatifloxacin 400 mg	≤ 450 msec	16	0	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0
Gatifloxacin 800 mg	≤450 msec	19	0	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0
Gatifloxacin 1200 mg	≤ 450 msec	10	2 ^a	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0

^a < 65 years of age for both subjects

**Study AI420-092: FREQUENCY DISTRIBUTION for Δ QTc MAX
(USING DAY -1 Cavg(0-12) as BASELINE)**

Single Dose	N	Males			N	Females		
		<30 msec	30-60 msec	>60 msec		<30 msec	30-60 msec	>60 msec
Placebo	18	17	1	0	13	10	3	0
Gatifloxacin 400 mg	18	17	1	0	16	11	5	0
Gatifloxacin 800 mg	19	14	5	0	19	13	6	0
Gatifloxacin 1200 mg	19	8	10	1 ^a	14	3	9	2 ^b

^aMale subject < 65 years old

^bFemale subject < 65 years old

Reviewer Conclusions Regarding Outlier Analyses

- The majority of subjects had Δ QTc Max <30 msec after a single oral dose of 400mg. There were no subjects with Δ QTc Max >60 msec at single oral doses of 400mg and 800mg, and 1/19 males and 2/14 females with Δ QTc Max >60 msec at 1200mg. There were a greater number of subjects with Δ QTc Max between 30 to 60 msec at 800mg and 1200mg vs. 400mg, with approximately the same number of males and females at each of these two higher gatifloxacin doses.
- There were no male or female subjects with QTc Max values >450 or >470 msec, respectively, and no subjects with QTc \geq 500 msec.
- QTc data from the elderly male and female subjects was limited (N = 5 subjects \geq 65 years), and therefore, no conclusions can be made regarding the effects of gatifloxacin on the QT / QTc interval in elderly subjects.

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1.1.2. Study AI420-093

This study was designed to evaluate and compare the effects of gatifloxacin, two other fluoroquinolone antibiotics: ciprofloxacin and sparfloxacin, and a non-fluoroquinolone: clarithromycin, on the QT-interval following single oral doses to healthy male and female subjects. Each of the following four single oral dose treatments were administered to all subjects in an open label, crossover fashion:

Gatifloxacin 800mg = 2X Clinical Dose (400mg)

Ciprofloxacin 1000mg = 1.3X to 2X Clinical Dose (500mg to 750mg)

Sparfloxacin 400mg = Loading Dose; 2X Maintenance Dose (200mg)

Clarithromycin 1000mg = 2X to 4X Clinical Dose (250mg to 500mg)

The determination, timing, and analyses of all ECG recordings and QTc parameters were exactly the same as in **Study AI420-092**; please refer to the description of these methods under **Section II.1.1** above. The one difference in methods with **Study AI420-093** is that PK samples for determination of plasma drug concentrations were obtained on the day of drug administration (i.e., Day 1) only at pre-dose and at the average T_{max} following administration of gatifloxacin, ciprofloxacin, and clarithromycin (i.e., at 2 hr postdose), and sparfloxacin (i.e., at 4 hr postdose).

A total of 40 subjects entered the study and 39 subjects completed all 4 treatment periods. The table below provides a summary of subject demographics, by treatment, for which PK and QTc data was obtained.

Study AI420-093: Subject Demographics by Treatment for PK and QTc Data

Single Dose	N	M / F	≥65 Years
800mg Gatifloxacin	40	20 M 20 F	1 M (70 yr.) 0 F
1000mg Ciprofloxacin	39	20 M 19 F	1 M (70 yr.) 0 F
400mg Sparfloxacin	39	20 M 19 F	1 M (70 yr.) 0 F
1000mg Clarithromycin	40	20 M 20 F	1 M (70 yr.) 0 F

Reviewer Comment: Note that in the table above, there was only 1 elderly male subject and no female subjects evaluated for PK and QTc. Because of the small numbers, no conclusions can be made regarding the effects of gatifloxacin or the comparators on the QT / QTc interval in elderly subjects.

Pharmacokinetics

The plasma concentrations of gatifloxacin and the comparators at the expected T_{max} following single dose administration of each drug are presented in the table below.

Study AI420-093: Plasma Drug Concentrations at Expected Tmax following Single Dose Oral Administration to Healthy Subjects; Data Expressed as Mean (%CV); [Min - Max]

Gatifloxacin 800mg at 2 hr (µg/mL)	Ciprofloxacin 1000mg at 2 hr (µg/mL)	Sparfloxacin 400mg at 4 hr (µg/mL)	Clarithromycin 1000mg at 2 hr (µg/mL)
6.5 (25%) [3.4-9.5]	4.1 (24%) [2.4-6.7]	1.1 (36%) [0.03-2.0]	3.4 (36%) [1.5-7.1]

The mean and range of gatifloxacin plasma concentrations at 2 hrs following 800mg were similar to that observed in the previously reviewed **Study AI420-092** (see above). It is noteworthy to mention that the mean and range of plasma concentrations for sparfloxacin at the expected Tmax are much lower than for the other antibiotics.

Pharmacodynamics – QTc Response

Summaries of the statistical results are presented in the tables below for the change in each QTc parameter from the respective baselines.

Reviewer Comment: *The sponsor focused on the QTc Avg(0-6) as the primary QTc parameter. While this was acceptable, it is the opinion of the reviewer that the QTc Avg(0-12) is equally important, since although both are time-averaged parameters, the QTc Avg(0-12) may represent a more robust time-averaged parameter, especially if the QTc exhibits diurnal variability greater than over a 6-hour time period. Thus, the reviewer will place greater emphasis on the QTc Avg(0-12) than the QTc Avg(0-6).*

Study AI420—093: Summary Statistics for ΔQTc Parameters following Single Oral Dose Administration to Healthy Subjects

	Gatifloxacin 800 mg	Ciprofloxacin 1000 mg	Sparfloxacin 400 mg	Clarithromycin 1000 mg
ΔQTc Avg(0-12) from Day -1 QTc Avg(0-12)				
Mean (Min, Max)	12.7 (-1.2, 28.9)	4.2 (-7.2, 18.3)	13.7 (-14.9, 31.6)	10.3 (-5.0, 30.0)
Difference (95% CI) from Gatifloxacin	—	-8.4 (-11.4, -5.3)	1.1 (-1.95, 4.1)	-2.6 (-5.6, 0.38)
p-Value	—	<0.001	0.48	0.09
ΔQTc at Tmax from Day -1 QTc at Tmax				
Mean (Min, Max)	14.7 (-35.0, 42.0)	0.15 (-30.0, 42.0)	14.3 (-21.0, 47.0)	4.2 (-30.0, 28.0)
Difference (95% CI) from Gatifloxacin	—	-14.2 (-20.3, -8.1)	1.1 (-5.0, 7.2)	-10.8 (-16.8, -4.7)
p-Value	—	<0.001	0.73	0.001
ΔQTc Max from Day -1 QTc Max				
Mean (Min, Max)	34.2 (6.0, 71.0)	23.7 (-13.0, 74.0)	27.7 (-21.0, 60.0)	33.2 (-12.0, 75.0)
Difference (95% CI) from Gatifloxacin	—	-10.5 (-15.7, -5.4)	-3.0 (-8.2, 2.3)	-3.1 (-8.2, 2.0)
p-Value	—	<0.001	0.26	0.23

Reviewer Comments: The values for the Δ QTc parameters derived in this study for gatifloxacin at 800mg were similar to those reported for the same dose from the previously reviewed Study AI420-092 (see II.1.1 above).

The Δ QTc Avg(0-12) and Δ QTc at Tmax values for sparfloxacin from this study are generally similar to Δ QTc values that have been previously reported in the literature at the same sparfloxacin dose. These relatively substantial changes in QTc occur despite the achievement of relatively low plasma sparfloxacin concentrations following a single 400mg oral dose, which suggests greater potency of sparfloxacin to prolong the QTc interval.

In general, there were no discernable relationships between any of the Δ QTc parameters and plasma concentrations for any of the drug treatments, including gatifloxacin. Because of this, the plots of these relationships are not shown in this review.

Reviewer Assessment of Time to Maximum QTc (QTc Max) vs. Time to Drug Cmax (i.e., Tmax)

This assessment was performed by the reviewer to evaluate whether the time of occurrence of the maximum QTc interval and the change in QTc Max from baseline coincided with the median plasma Tmax of gatifloxacin and the comparators. The table below summarizes the results.

Study AI420-093: Drug Plasma Tmax vs. Time to QTc Max and Time to Δ QTc Max

	Median Tmax (hr)* (Range)	Median Time to QTc Max (hr) (Min, Max)	Median Time to Δ QTc Max (hr) (Min, Max)
800mg Gatifloxacin	2.0	3.5 (0, 12)	3.0 (0, 12)
1000mg Ciprofloxacin	1.0 to 2.0	5.0 (0, 12)	5.0 (0.5, 12)
400mg Sparfloxacin	4.0 (3.0 to 6.0)	4.0 (0, 12)	3.0 (1.5, 12)
1000mg Clarithromycin	2.0	4.0 (0, 12)	4.0 (1.0, 12)

*Values as reported in approved labeling

This data shows that the median times to QTc Max and to Δ QTc Max were relatively similar to the median plasma Tmax values determined for gatifloxacin and sparfloxacin. There appeared to be a greater difference between the occurrence of the QTc Max parameters and the plasma Cmax for ciprofloxacin and clarithromycin. The ranges for the QTc Max parameters were wide, which lends support to the high degree of variability that is observed in QTc.

Reviewer Comments: This analysis is very limited and the results should be interpreted with caution.

Reviewer Conclusions Regarding QT Response

- The following multiples of the recommended clinical unit dose (oral) were employed in this study:
 - Gatifloxacin 800mg Single Dose = 2X (Clinical Dose 400mg)
 - Ciprofloxacin 1000mg Single Dose = 1.3X to 2X (Clinical Dose 500mg to 750mg)
 - Sparfloxacin 400mg Single Dose = Recommended Loading Dose; 2X Clinical Maintenance Dose
 - Clarithromycin 1000mg Single Dose = 2X to 4X (Clinical Dose 250mg to 500mg)
- For the Δ QTc parameters - Δ QTc at Cmax, Maximum Δ QTc, and Average Δ QTc(0-12) - administration of a single oral 800mg dose of gatifloxacin resulted in similar changes compared to administration of single oral doses of sparfloxacin 400mg and clarithromycin 1000mg.

- **Average Δ QTc(0-12) and Δ QTc at Cmax values (mean (overall range)):**
 Gatifloxacin 800mg → 12 to 15 (-18, 40) msec
 Sparfloxacin 400mg → 14 to 18 (-18, 51) msec
 Clarithromycin 1000mg → 5 to 10 (-16, 30) msec

- **Maximum Δ QTc values (mean (range)):**
 Gatifloxacin 800mg → 34 (23, 60) msec
 Sparfloxacin 400mg → 33 (-1, 67) msec
 Clarithromycin 1000mg → 32 (6, 88) msec

- Single oral dose administration of ciprofloxacin 1000mg had the least effect on Δ QTc parameters and the changes were significantly lower compared to single oral 800mg dose of gatifloxacin:
 - **Δ QTc at Cmax and Average Δ QTc(0-12) values (mean (overall range)):**
 Gatifloxacin 800mg → 12 to 15 (-18, 40) msec
 Ciprofloxacin 1000mg → 0.5 to 4 (-26, 29) msec

 - **Maximum Δ QTc values (mean (range)):**
 Gatifloxacin 800mg → 34 (23, 60) msec
 Ciprofloxacin 1000mg → 23 (6, 62) msec

- Overall, Δ QTc and QTc parameters appeared to be most similar following a single oral clinical dose of gatifloxacin 400mg (**Study AI420-092**) and a single oral dose of ciprofloxacin 1000mg (**Study AI420-093**).

Outlier Analyses

Outlier analyses for **Study AI420-093** were the same as that for the previously reviewed **Study AI420-092**. The sponsor chose to use the QTc Max for the outlier analyses since this parameter represents the worst case scenario. The results for absolute QTc Max values and for Δ QTc Max in male and female subjects are shown in the tables below.

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Study AI420-093: QTc MAX FOR MALES

Treatment	Pre-Dose	Post-Dose QTc MAX		
		<430 (msec)	>430 - <450 (msec)	>450 (msec)
Gatifloxacin 800 mg	<430 msec	16	4	0
	430-450 msec	0	0	0
	>450 msec	0	0	0
Ciprofloxacin 1000 mg	<430 msec	19	0	1
	430-450 msec	0	0	0
	>450 msec	0	0	0
Sparfloxacin 400 mg	<430 msec	16	3	0
	430-450 msec	0	1	0
	>450 msec	0	0	0
Clarithromycin 1000 mg	<430 msec	17	2	0
	430-450 msec	1	0	0
	>450 msec	0	0	0

Study AI420-093: QTc MAX FOR FEMALES

Treatment	Pre-Dose	Post-Dose QTc MAX		
		<450 (msec)	>450 - <470 (msec)	>470 (msec)
Gatifloxacin 800 mg	<450 msec	16	4	0
	450-470 msec	0	0	0
	>470 msec	0	0	0
Ciprofloxacin 1000 mg	<450 msec	18	1	0
	450-470 msec	0	0	0
	>470 msec	0	0	0
Sparfloxacin 400 mg	<450 msec	18	1	0
	450-470 msec	0	0	0
	>470 msec	0	0	0
Clarithromycin 1000 mg	<450 msec	20	0	0
	450-470 msec	0	0	0
	>470 msec	0	0	0

**Study AI420-093: FREQUENCY DISTRIBUTION for Δ QTc MAX
(USING DAY -1 QTc Avg(0-12) as BASELINE)**

Treatment	Males			Females		
	< 30 (msec)	30-60 (msec)	> 60 (msec)	< 30 (msec)	30-60 (msec)	> 60 (msec)
Gatifloxacin, 800 mg	11	9	0	5	15	0
Ciprofloxacin 1000 mg	17	3	0	18	1	0
Sparfloxacin 400 mg	6	14 ^a	0	9	9	1
Clarithromycin 1000 mg	14	5	1	9	8	3

^a one subject was \geq 65 years old

Reviewer Conclusions Regarding Outlier Analyses:

- The majority of subjects had Δ QTc Max <30 msec after single oral doses of gatifloxacin, ciprofloxacin, and clarithromycin. No subjects with Δ QTc Max >60 msec at single oral doses of gatifloxacin and ciprofloxacin; 1/19 and 3/20 females with sparfloxacin and clarithromycin, respectively; 1/19 males with sparfloxacin had Δ QTc Max >60 msec. There were a greater number of subjects with Δ QTc Max between 30 to 60 msec with gatifloxacin, sparfloxacin, and clarithromycin vs. ciprofloxacin.
- The majority of subjects had QTc Max values <430 msec (males) or <450 msec (females) for all drugs; 1/20 males with QTc Max value >450 msec after single dose ciprofloxacin 1000mg. There were no subjects with QTc Max \geq 500 msec.
- There was limited QTc data from elderly subjects (N = 1 male \geq 65 years), and therefore, no conclusions can be made regarding the effects of gatifloxacin, ciprofloxacin, sparfloxacin, and clarithromycin on the QT / QTc interval in elderly subjects.

I. Results (cont.)

I.2. Patients

Two studies in patients evaluated the effects of gatifloxacin on the QT-interval:

Study AI420-095: AN OPEN LABEL, MULTICENTER, NONCOMPARATIVE, PHASE IV STUDY OF ORAL GATIFLOXACIN IN THE TREATMENT OF COMMUNITY ACQUIRED RESPIRATORY INFECTIONS – ANALYSIS OF EFFECTS ON THE QT INTERVAL OF THE ECG

Study CV 123-229: PRAVASTATIN OR ATORVASTATIN EVALUATION AND INFECTION THERAPY (PROVE IT): ECG SUB-STUDY OF GATIFLOXACIN EFFECTS ON THE QTC INTERVAL

I.2.1. Study AI420-095

This study evaluated the effects of a single oral clinical dose of 400mg gatifloxacin on the QT-interval in male and female patients with community acquired respiratory tract infections (RTI). The dosage regimen was 400mg gatifloxacin QD for 7 to 14 days, depending on the indication. The following ECG and PK procedures were followed:

Day 1 (1st Day of Dosing):

Baseline 12-lead ECG @ 30 minutes prior to 1st dose

12-lead ECG @ 2 hours following 1st TEQUIN® dose

PK sample for determination of gatifloxacin plasma concentration @ 2 hours post-dose, immediately after the 2nd 12-lead ECG

The QT-intervals were determined in the same manner as described in the previously reviewed Study AI420-092 (see II.1.1 above). The QT was corrected using Bazett's formula.

264 adult male and female patients with community acquired RTI were enrolled and PK and QTc data were obtained from 262 patients. The table below provides the demographic details.

Study AI420-095: PATIENT DEMOGRAPHICS

	Total Enrolled = 264 Total Evaluated = 262*
	N (%)
Male	92 (35)
Female	172 (65)
Mean Age (Range)	42 years (18 to 90)
≤ 65 years	241 (91)
> 65 years	23 (9)
Sinusitis (ABS)	240 (91)
AECB	16 (6)
CAP	8 (3)

***NOTE: 10 patients stratified into "High Risk" group** – 1 with hypokalemia (not defined); 9 receiving concomitant medications recognized to prolong QT interval, i.e., tricyclic antidepressants (N=3), antihistamines (N=5), azole antifungal (N=1).

Pharmacodynamics – QTc Response

Study AI420-095: QTc SUMMARY

Statistic	QTc Interval (msec) N = 262		
	Pre-Dose	Post-Dose	Change
Mean	396.7	405.8	9.1
Std Deviation	23.4	26.8	18.6
95% CI			(6.9, 11.4)
Minimum	313	305	-47
25th Percentile	380	389	-3
Median	399	406	10
75th Percentile	414	425	22
Maximum	456	471	63

Study AI420-095: QTc SUMMARY BY GENDER, AGE AND RISK

		N	Mean QTc (msec)		
			Pre-Dose	Post-Dose	Change
Gender	Male	91	384.3	391.0	6.7
	Female	171	403.2	413.7	10.4
Age (yr.)	≤ 65	241	395.0	404.4	9.4
	> 65	21	415.4	422.0	6.5
Risk	Low	252	396.4	405.5	9.1
	High	10	402.9	412.5	9.6

Study AI420-095: POST DOSE QTc DISTRIBUTION BY GENDER, AGE, AND RISK

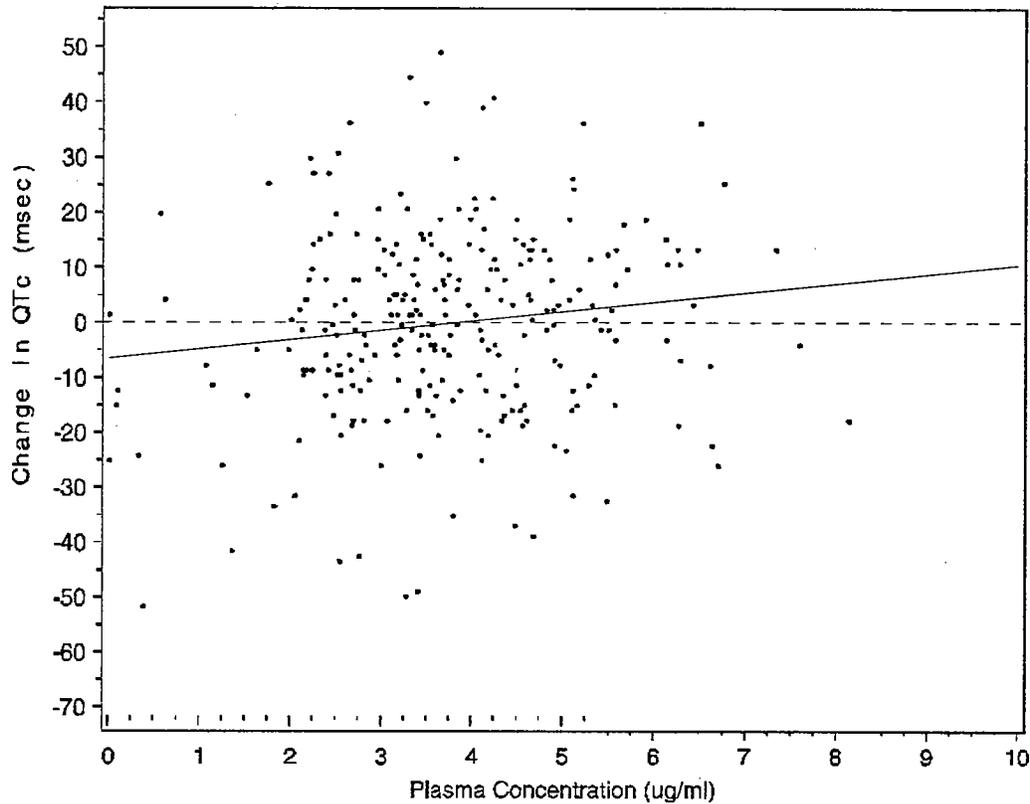
		N	N (%)		
			Normal <430 males <450 females	Borderline 430-450 msec males 450-470 msec females	Prolonged >450 msec males >470 msec females
Gender	Male	91	82 (90)	6 (7)	3 (3)
	Female	171	162 (95)	9 (5)	0
Age (yrs)	≤ 65	241	229 (95)	11 (5)	1 (<1)
	> 65	21	15 (71)	4 (19)	2 (10)
Risk	Low	252	234 (93)	15 (6)	3 (1)
	High	10	10 (100)	0	0

Study AI420-095: ΔQTc FREQUENCIES BY AGE, GENDER, AND RISK

		N	ΔQTc (msec)* N (%)			
			< 0	0 to 30	31 to 60	> 60
Gender	Male	91	31 (34)	48 (53)	12 (13)	0
	Female	171	44 (26)	113 (66)	13 (8)	1 (<1)
Age (yr.)	≤ 65	241	67 (28)	152 (63)	21 (9)	1 (<1)
	> 65	21	8 (38)	9 (43)	4 (19)	0
Risk	Low	252	72 (29)	154 (61)	25 (10)	1 (<1)
	High	10	3 (30)	7 (70)	0	0

*ΔQTc = Pre Dose QTc – Post Dose QTc

Assessment of Δ QTc vs. Plasma Gatifloxacin Concentration at 2 hr Postdose – Linear Regression Analysis



Solid Line = Estimated Regression Line with Slope 2.6 msec/ μ g/mL (95% CI: 1.0, 4.2)

Reviewer Conclusions Regarding Gatifloxacin Effects on QTc Interval in Patients with Respiratory Tract Infections

- Overall, the mean change between pre-dose and post dose QTc at 2 hours after the first oral gatifloxacin dose of 400mg to 262 patients with respiratory tract infections (RTI) was 9 msec (95% CI: 6.9, 11.4). The median increase in QTc at 2 hours post gatifloxacin was similar at 10 msec, with 25% of the patients experiencing a QTc increase of 22 msec or greater.
- There was no apparent trend for greater prolongation of QTc by gatifloxacin in those patients >65 years of age vs. patients \leq 65 years, in those patients classified as "high risk" for QTc prolongation (i.e., hypokalemia; concomitant medications known to prolong QT interval) vs. patients with "low risk", nor in females vs. males.
- No patients had a pre- or post dose QTc interval \geq 500msec. The majority of patients had post dose QTc changes considered to be without clinical concern for males (<430 msec) and females (<450 msec). Few patients (\leq 10%) had post dose QTc changes that were considered to be prolonged and/or potentially significant for males (>450 msec, N=3) and females (>470 msec, N=0).

- The majority of patients also had post dose Δ QTc of 30 msec or less. Approximately 10% of patients had Δ QTc of 30 to 60 msec and very few (<1%) of patients had changes >60 msec.
- There was an apparent linear relationship between Δ QTc (i.e., QTc at 30 minutes pre dose – QTc at 2 hours post dose) and plasma concentrations of gatifloxacin at 2 hours post dose, with the slope estimated at 2.6 msec/ μ g/mL (95% CI: 1.0, 4.2).
 - This relationship and slope in patients with RTI were similar to that determined from the single dose escalation study of healthy volunteers (**Study AI420-092**) and suggested similar QT responsiveness between healthy subjects and patients with RTI.
 - The upper range of plasma gatifloxacin concentrations at 2 hours post dose from this study, i.e., up to approximately 8 μ g/mL, was consistent with the range of concentrations in healthy subjects following single oral doses of 400mg to 800mg (i.e., approximately 3 to 10 μ g/mL, **Study AI420-092**).
 - A statistically significant (pre-dose QTc x plasma concentration) interaction was detected in the regression model ($p = 0.02$). The impact of this interaction was demonstrated as the effect of plasma concentrations tended to be *strongest* at low pre-dose QTc values (i.e., at ≤ 385 msec, slope = 5.1 msec/ μ g/mL) and *weakest* at high pre dose QTc values (i.e., at >405 msec, slope = 0.3 msec/ μ g/mL). This regression to the mean effect suggested that patients with low baseline QTc intervals would experience the greatest prolongation, whereas those patients with high baseline QTc intervals may be at lower risk of further QTc prolongation by gatifloxacin.
- It should be noted that there were several limitations with this study and included the following:
 - There was no control group (active or placebo) employed
 - Only a single pre-dose QTc (“baseline”) and a single post dose QTc were determined
 - The time of day for dosing was not strictly controlled
 - There was a relatively small number of elderly patients evaluated (n/N=21/262; 8%)

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I.2.2. Study CV 123-229 (PROVE-IT)

The **PROVE-IT** trial is an international, multicenter, randomized, double-blind, 2x2 factorial, parallel group design trial comparing pravastatin vs. atorvastatin, and comparing gatifloxacin vs. placebo in patients with coronary artery disease (CAD) following an acute coronary syndrome (i.e., post-ACS). A total of 175 sites participated in the study under a uniform protocol: 6 in Australia, 13 in Canada, 1 in France, 1 in Germany, 1 in United Kingdom, and 153 in the United States. The primary objective is to address all-cause death or major cardiovascular events after a minimum treatment period of 18 months with pravastatin + gatifloxacin or placebo vs. atorvastatin + gatifloxacin or placebo.

An **ECG substudy** was designed to assess the effects of gatifloxacin on the QTc interval in the CAD patients post-ACS. The duration for the **ECG substudy** was 20 days. The first 500 randomized subjects in the **PROVE IT** trial were targeted for enrollment into the **ECG substudy**. Within 10 days of the onset of the qualifying ACS, subjects were randomized to the following treatments:

Day 1 – Treatment A:

Pravastatin 40 mg PO QD or Atorvastatin 80 mg PO QD (1:1 ratio)

Days 15 to 28 – Treatment B:

Statin QD + Gatifloxacin 400 mg QD x 14 Days or

Statin QD + Placebo QD x 14 Days

(1:1 ratio Gatifloxacin:Placebo)

The following procedures were employed for the **ECG substudy** (duration of 20 days):

Day 15 – 1st dose of Treatment B:

- Baseline 12-lead ECG prior to 1st dose of study drug (pre-dose)
- 12-lead ECG at 2 hr postdose (median Tmax for Gatifloxacin)
- Plasma sample for measurement of gatifloxacin plasma concentration at 2 hr postdose (i.e., gatifloxacin Cmax)

Day 20 – 6th dose of Treatment B:

- First 100 ECG substudy participants were to have 12-lead ECG's at pre-dose (baseline) and at 2 hr postdose; plasma sample for measurement of gatifloxacin plasma concentration at 2 hr postdose

QTc interval was determined using Bazett's correction. Changes from baseline were analyzed using an ANCOVA (analysis of covariance) model to compare gatifloxacin to placebo at 2 hours post-dose. The analysis model consisted of treatment as the main factor and baseline QTc (**Day 15 or Day 20**) as the covariate. A 90% two-sided confidence interval was constructed for the estimated mean difference between gatifloxacin and placebo from the ANCOVA model. *To demonstrate clinical equivalence of the effect of gatifloxacin and placebo on QTc, the upper bound of the 90% two-sided confidence interval of the estimated mean difference (gatifloxacin - placebo) adjusted for baseline was expected to be less than 6 msec. This sponsor-imposed definition of clinical equivalence was based in part on studies in subjects treated with terfenadine. Compared to baseline, terfenadine was associated with a QTc increase of 6 msec in normal healthy subjects and an increase of 12 msec in subjects with cardiovascular disease.*

Reviewer Comment: This appeared to be reasonable since the QTc change with gatifloxacin at the clinical dose of 400 mg has been shown to be <10 msec in healthy subjects (mean Δ QTc range from 4 to 9 msec).

The table below provides an overview of the ECG analyses and number of patients evaluated in each.

Study CV 123-229 (PROVE-IT): Overview of ECG Dataset Analyses		
Variable	Analysis Method	Sample Dataset / N
Primary Safety Variable		
Δ QTc at 2 hr post-dose on Day 15 from baseline QTc on Day 15	ANCOVA on QTc, mean, 90% two-sided CI; median, 25th & 75th percentile (raw data)	Primary safety dataset N _{Gatifloxacin} = 372 N _{Placebo} = 384 N _{Total} = 756
Secondary Safety Variable		
Δ QTc at 2 hr post-dose on Day 20 from baseline QTc on Day 15	ANCOVA on QTc, mean, 90% two-sided CI; median, 25th & 75th percentile (raw data)	Secondary safety dataset N _{Gatifloxacin} = 36 N _{Placebo} = 37 N _{Total} = 73
Tertiary Safety Variable		
Δ QTc at 2 hr post-dose on Day 20 from baseline QTc on Day 20	ANCOVA on QTc, mean, 90% two-sided CI; median, 25th & 75th percentile (raw data)	Tertiary safety dataset N _{Gatifloxacin} = 38 N _{Placebo} = 39 N _{Total} = 77

The table below summarizes the demographic characteristics of the patients enrolled into the **ECG substudy**.

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Study CV 123-229: Demographic Characteristics of Randomized ECG Substudy Patients			
Characteristics	Treatment		
	Gatifloxacin N = 374	Placebo N = 386	Total N = 760
Age (years) Mean (SD) (Min, Max)	58 (11.3) (33, 84)	58 (11.1) (30, 89)	58 (11.2) (30, 89)
Age (years), n(%) Elderly (≥ 65) Non-Elderly (< 65)	107 (28.6%) 267 (71.4%)	112 (29.0%) 274 (71.0%)	219 (28.8%) 541 (71.2%)
Gender, ^a n (%) Male Female	295 (78.9%) 79 (21.1%)	288 (74.6%) 97 (25.1%)	583 (76.7%) 176 (23.2%)
Diabetes Mellitus, n (%)	85 (22.7%)	57 (14.8%)	142 (18.7%)
Qualifying Coronary Syndrome, n (%) Unstable angina pectoris (UAP) Acute myocardial infarction (AMI)	140 (37.4%) 233 (62.3%)	121 (31.3%) 264 (68.4%)	261 (34.3%) 497 (65.4%)
Antiarrhythmics, ^b n (%)	14 (3.7%)	11 (2.8%)	25 (3.3%)
Antihistamines, n (%)	93 (24.9%)	97 (25.1%)	190 (25.0%)
Antibiotics, ^c n (%)	17 (4.5%)	13 (3.4%)	30 (3.9%)
CNS Agents, ^d n (%)	27 (7.2%)	30 (7.8%)	57 (7.5%)

^e Reflects missing gender data in one subject

^f Class IA and Class III antiarrhythmics taken during the 2 weeks prior to the qualifying event

^g Fluoroquinolone and macrolide antibiotics taken during the 2 weeks prior to the qualifying event

^h Selective serotonin re-uptake inhibitor (SSRI) and tricyclic antidepressants taken during the 2 weeks prior to the qualifying event

The following **exclusion criteria** were pertinent to participation in the **ECG substudy**:

- QTc interval (Lead II) >450 msec or QTc >500 msec for subjects with intraventricular conduction delay (e.g., LBBB) using Bazett's formula for heart rate correction
- History of prolonged QT interval
- Current or anticipated need for treatment with Class IA or III antiarrhythmic agents (e.g., quinidine, procainamide, sotalol, amiodarone) or history of prior episode of *torsade de pointes*
- Uncorrected hypokalemia
- Renal insufficiency, defined as calculated creatinine clearance < 40 mL/min
- Treatment with any of the following agents (some of which are known to prolong the QTc interval) within the last month, or likelihood of requiring such treatment during the study period:
 - Oral or parenteral Corticosteroids

- Immunosuppressive agents (e.g., Cyclosporine)
- Estrogens, Progestogens and Androgens (except hormone replacement therapy)
- Erythromycin or Clarithromycin
- Probenecid
- Orlistat
- Terfenadine
- Cisapride
- Antipsychotics
- Tricyclic Antidepressants
- Protease Inhibitors

- Atrial fibrillation

Primary Safety Variable: Day 15 QTc Following Single Dose Gatifloxacin or Placebo

The table below provides an overall summary of the results for the **Day 15** changes in QTc at 2 hr postdose from pre-dose baseline on **Day 15**.

Study CV 123-229: Changes in QTc from Baseline on Day 15 to 2 hr Postdose on Day 15

	QTc (msec) Gatifloxacin 400mg x 1 Dose	QTc (msec) Placebo x 1 Dose
Overall		
Number of subjects:	372	384
Baseline mean (sd):	395.2 (25.9)	393.2 (26.2)
2 hours post-dose (sd):	401.4 (26.3)	395.8 (26.8)
Adjusted mean (se):	6.5 (0.94)	2.4 (0.92)
Median (25 th , 75 th percentile)	8.0 (-6.0, 19.0)	2.0 (-8.0, 14.0)
Adjusted mean difference from placebo (90% two-sided CI):	4.2 (2.00, 6.34)	
Non-elderly (< 65 years)		
Number of subjects:	265	273
Baseline mean (sd):	393.9 (26.3)	391.6 (25.6)
2 hours post-dose mean (sd):	399.2 (26.7)	394.8 (26.3)
Adjusted mean (se):	5.6 (1.09)	2.9 (1.07)
Adjusted mean difference from placebo (90% two-sided CI):	2.7 (0.19, 5.21)	
Elderly (≥ 65 years)		
Number of subjects:	107	111
Baseline mean (sd):	398.3 (24.7)	397.1 (27.2)
2 hours post-dose mean (sd):	406.8 (24.7)	398.2 (27.8)
Adjusted mean (se):	8.7 (1.85)	0.9 (1.81)
Adjusted mean difference from placebo (90% two-sided CI):	7.8 (3.49, 12.04)	
Male		
Number of subjects:	293	288
Baseline mean (sd):	392.2 (25.0)	390.2 (25.6)
2 hours post-dose mean (sd):	398.5 (25.8)	392.6 (26.2)
Adjusted mean (se):	6.5 (1.06)	2.1 (1.07)
Adjusted mean difference from placebo (90% two-sided CI):	4.4 (1.94, 6.89)	

	QTc (msec) Gatifloxacin 400mg x 1 Dose	QTc (msec) Placebo x 1 Dose
Female		
Number of subjects:	79	95
Baseline mean (sd):	406.1 (26.4)	402.3 (26.2)
2 hours post-dose mean (sd):	412.4 (25.5)	405.6 (26.2)
Adjusted mean (se):	6.9 (2.04)	2.8 (1.86)
Adjusted mean difference from placebo (90% two-sided CI):	4.1 (-0.48, 8.65)	

Summaries of cross tabulations of the **Day 15** QTc interval at baseline and 2 hours post and of the change in the QTc interval from baseline to 2 hours post dose on **Day 15** are presented below.

Study CV 123-229: Cross-tabulation of Baseline QTc on Day 15 and 2 Hours Post-Dose QTc on Day 15

	Baseline QTc (msec) (Day 15)	2 Hours Post-Dose (Day 15)	Treatment		Total N = 756 n (%)
			Gatifloxacin N = 372 n (%)	Placebo N = 384 n (%)	
< 450	< 450	< 450	360 (96.8%)	373 (97.1%)	733 (97.0%)
450-480	450-480	450-480	12 (3.2%)	9 (2.3%)	21 (2.8%)
> 480-500	> 480-500	> 480-500	0 (0.0%)	2 (0.5%)	2 (0.3%)
> 500	> 500	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)

Study CV 123-229: Change in QTc from Baseline on Day 15 to 2 Hours Post-dose on Day 15 by Treatment

Change in QTc (msec) from Baseline at 2 hours Post Dose (Day 15)	N	< 30 msec	30 - 60 msec	> 60 msec
Placebo	384	356 (92.7%)	28 (7.3%)	0 (0.0%)
Gatifloxacin	372	333 (89.5%)	39 (10.5%)	0 (0.0%)

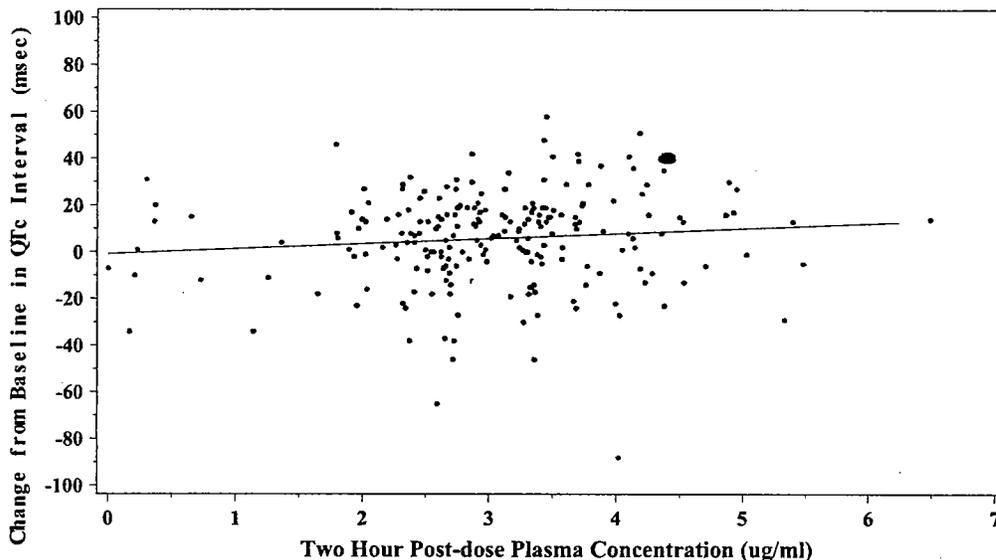
226 gatifloxacin-treated patients had paired ECG's and a blood sample collected for the measurement of gatifloxacin plasma concentration on **Day 15**. The table below provides a summary of the plasma gatifloxacin concentration data.

Study CV 123-229: Gatifloxacin Plasma Concentrations at Approximately 2 Hours Following a Single 400 mg Oral Dose on Day 15

	N (%)
N	226
MEAN (SD) CONC. (µg/mL)	3.00 (1.03)
MEDIAN CONC. (µg/mL)	2.98
QUARTILES (µg/mL)	2.5 - 3.5
CONC. RANGE (µg/mL)	0.0 - 6.5

The relationship between QTc change and gatifloxacin concentrations at 2 hr postdose on **Day 15** is shown in the figure below; the regression parameters are summarized in the table that follows after the figure.

Study CV 123-229: Change in QTc Interval from Baseline on Day 15 to 2 Hours Post-Dose on Day 15 and Drug Plasma Concentration (Solid Line = Best Fit Regression Line)



Study CV 123-229: Linear Regression Parameters for Change in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 15

Factor	Estimate	95% CI	p-value
Concentration slope ^a	2.189	(-0.3720 , 4.7510)	0.0935

^a Mean msec in QTc per µg/mL of plasma concentration

Secondary Safety Variable: Day 20 QTc Following Repeat Dose Gatifloxacin or Placebo Compared to Day 15 Baseline QTc

Day 20 represented the 6th day of gatifloxacin dosing (400 mg QD) and plasma concentrations were presumed to be at steady state. The table below provides an overall summary of change in QTc from baseline on **Day 15** to 2 hours post-dose on **Day 20** in these 73 patients.

Study CV 123-229: Changes in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 20		
	QTc (msec) Gatifloxacin 400mg QD x 6 Days	QTc (msec) Placebo QD x 6 Days
Number of subjects:	36	37
Day 15 baseline mean (sd) QTc:	398.2 (25.7)	399.6 (22.3)
Day 20 2 hr post-dose mean (sd) QTc:	404.8 (32.8)	393.4 (25.2)
Adjusted mean (se) QTc:	6.5 (3.51)	-6.0 (3.46)
Median (25 th , 75 th percentile) QTc:	4.5 (-8.0, 20.0)	-1.0 (-15.0, 5.0)
Adjusted mean QTc difference from placebo (90% two-sided CI):	12.5 (4.31, 27.73)	

Summaries of the cross-tabulations and changes in QTc from baseline on Day 15 and 2 hr postdose on Day 20 are summarized in the table below.

Study CV 123-229: Cross-tabulation of Baseline QTc on Day 15 and 2 Hours Post-Dose QTc on Day 20

Baseline QTc (msec) (Day 15)	2 Hours Post-Dose (Day 15)	Treatment		
		Gatifloxacin N = 372 n (%)	Placebo N = 384 n (%)	Total N = 756 n (%)
< 450	< 450	34 (94.4%)	37 (100%)	71 (97.3%)
450-480	450-480	1 (2.8%)	0 (0%)	1 (1.4%)
> 480-500	> 480-500	0 (0.0%)	0 (0%)	0 (0%)
> 500	> 500	1 (2.8%)	0 (0%)	1 (1.4%)

Study CV 123-229: Summary of Absolute Change in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 20

Change from Baseline at 2 hours Post Dose (Day 15)	N	< 30 msec	30 - 60 msec	> 60 msec
Placebo	37	36 (97.3%)	1 (2.7%)	0 (0.0%)
Gatifloxacin	36	32 (88.9%)	3 (8.3%)	1 (2.8%)

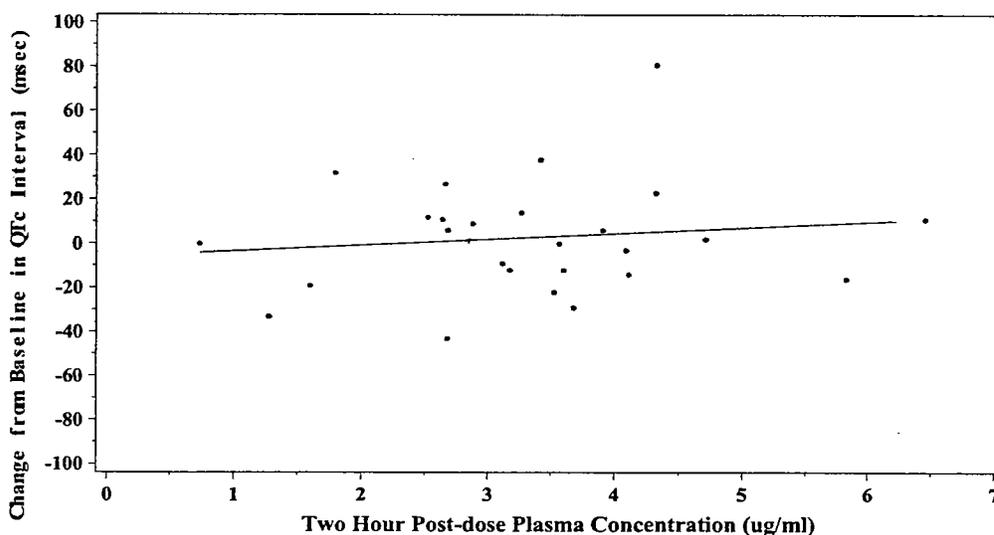
24 gatifloxacin-treated patients had paired ECG's (baseline Day 15 and 2 hr postdose Day 20) and a blood sample collected for the measurement of gatifloxacin plasma concentration on Day 20. The table below provides a summary of the plasma gatifloxacin concentration data.

Study CV 123-229: Gatifloxacin Plasma Concentrations at Approximately 2 Hours Following 400 mg QD on Day 20 (6th Dose)

N	24
MEAN (SD) CONC. (µg/mL)	3.43 (1.27)
MEDIAN CONC. (µg/mL)	3.47
QUARTILES (µg/mL)	2.7 - 4.1
CONC. RANGE (µg/mL)	0.7 - 6.5

The relationship between QTc change (2 hr postdose **Day 20** – baseline **Day 15**) and gatifloxacin concentrations at 2 hr postdose on **Day 20** is shown in the figure below; the regression parameters are summarized in the table that follows after the figure.

Study CV 123-229: Change in QTc Interval from Baseline on Day 15 to 2 Hours Post-Dose on Day 20 and Gatifloxacin Plasma Concentration at 2 Hours Postdose on Day 20 (Solid Line = Best Fit Regression Line; N=24)



Study CV 123-229: Linear Regression Analysis for Change in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 20

Factor	Estimate	95% CI	p-value
Plasma Concentration slope ^a	2.866	(-6.6290, 12.3620)	0.5390

^a Mean msec in QTc per $\mu\text{g}/\text{mL}$ of plasma concentration

Tertiary Safety Variable: Day 20 QTc Following Repeat Dose Gatifloxacin or Placebo Compared to Day 20 Baseline QTc

The results for this analysis were, in general, similar to those derived for the secondary analysis. Thus, these results will not be presented here. Please refer to the review of **Study CV 123-229** in **Appendix 1** for details of the tertiary analysis.

Reviewer Conclusions for the ECG Substudy of the PROVE-IT Protocol

- No clinically significant changes in heart rate were observed following either the 1st dose (**Day 15**) or the 6th dose (**Day 20**) of gatifloxacin or placebo. Thus, the use of Bazett's formula to correct the QT appeared to be appropriate for these patients.
- Mean plasma concentrations of gatifloxacin determined at approximately 2 hr following 1st dose (**Day 15**) and 6th dose (**Day 20**) administration of 400mg were similar at 3.0 µg/mL and 3.3-3.4 µg/mL, respectively. The majority of gatifloxacin-treated patients had plasma concentrations at approximately 2 hr postdose between 2 µg/mL and 5 µg/mL after the 1st and 6th doses. This indicated minimal accumulation of gatifloxacin in plasma (i.e., 10-13%) and is consistent with the PK characteristics of gatifloxacin observed in healthy subjects.
- Following 1st dose administration of 400mg gatifloxacin on **Day 15** (at 2 hr postdose) the mean (SD) increase in the QTc from **Day 15** baseline was 6.5 (18.1) msec in all patients (N=374). Following the 1st dose of placebo on **Day 15** (at 2 hr postdose) the mean (SD) increase in the QTc from **Day 15** baseline was 2.4 (18.0) msec in all patients (N=386). The mean (90% CI) placebo-adjusted increase in QTc following 1st dose administration of 400mg gatifloxacin on **Day 15** was 4.2 (2.0, 6.3) msec.
- There appeared to be a greater prolongation of the QTc interval, from **Day 15** baseline, following 1st dose gatifloxacin on **Day 15** in the elderly CAD post-ACS patients (N=107 ≥65 yr.) - mean (SD) QTc 8.7 (19.1) msec vs. non-elderly CAD post-ACS patients (N=265 <65 yr.) - mean (SD) QTc 5.6 (17.7) msec. The mean (90% CI) placebo-adjusted increases in QTc following 1st dose administration of 400mg gatifloxacin on **Day 15** in the elderly patients vs. non-elderly were 7.8 (3.5, 12.0) msec vs. 2.7 (0.2, 5.2) msec, respectively.
- There were no apparent gender-related differences in the change in QTc following 1st dose gatifloxacin administration on **Day 15**. Similar mean (SD) QTc increases from **Day 15** baseline were determined for males (i.e., 6.5 (18.1) msec; N=293) and females (i.e., 6.9 (18.1) msec; N=79). The mean (90% CI) placebo-adjusted increases in QTc following 1st dose administration of 400mg gatifloxacin on **Day 15** in the male patients vs. female patients were 4.4 (1.9, 6.9) msec vs. 4.1 (-0.5, 8.7) msec, respectively.
- Following 1st dose administration of either gatifloxacin 400mg or placebo on **Day 15** there were no patients who had prolongation of the QTc interval >500msec nor experienced an increase in QTc from baseline >60msec with either gatifloxacin or placebo treatment at 2 hr post dose. The majority of patients had QTc intervals <450 msec at 2 hr following 1st dose administration of either gatifloxacin (97%) or placebo (97%). In addition, the majority of patients had changes in QTc at 2 hr post dose <30 msec (~93% for placebo; ~90% for gatifloxacin).
- Following the 6th dose of gatifloxacin 400mg (i.e., at presumed steady-state) to 36 CAD post-ACS patients on **Day 20** the average increase in QTc (from **Day 15** baseline) was the same as that after the 1st dose, i.e., mean (SD) QTc change on **Day 20** = 6.5 (21.1) msec. The mean (90% CI) placebo-adjusted increase in QTc following 6th dose administration of 400mg gatifloxacin on **Day 20** was 12.5 (4.3, 27.7) msec.

*This latter placebo-adjusted change in QTc after the 6th gatifloxacin dose on **Day 20** was greater than after 1st dose administration on **Day 15** because the mean QTc in the placebo group at 2 hr post-dose on **Day 20** (compared to baseline on **Day 15**)*

decreased by nearly equal magnitude (i.e., -6.0 msec) as the increase in the gatifloxacin-treated QTc.

- On **Day 20** the QTc intervals at 2 hr postdose were <450msec for the majority of patients receiving repeat dose gatifloxacin 400mg QD x 6 days (94.4%; n/N = 34/36) or placebo QD x 6 days (100%; n/N = 37/37). In addition, the change in QTc at 2 hr postdose was <30msec for the majority of patients in both treatment groups (gatifloxacin 89%; placebo 97%). There were no placebo-treated patients with QTc >500msec or with change in QTc >60msec. However, there was one 50 year old female gatifloxacin-treated patient with QTc >500msec who also had a change in QTc >60msec. No clinical signs or symptoms of any cardiac abnormalities were associated with these QTc changes in this patient.
- The overall results of the assessment of QTc interval prolongation and changes in QTc after the 6th dose of gatifloxacin were similar when employing the baseline QTc on either **Day 15** (i.e., at the initiation of gatifloxacin or placebo treatment) or on **Day 20** (i.e., after the 6th day of QD dosing with either treatment).
- Linear regression analysis of the change in QTc (from baseline) vs. plasma gatifloxacin at 2 hr postdose on **Day 15** (i.e., 1st dose administration) and on **Day 20** (i.e., 6th dose administration) showed a relatively weak relationship, with the slopes for the regression lines not significantly different from zero (range of slope estimates 2.2-2.9 msec/μg/mL. These slope estimates are consistent with those determined from the single dose escalation study in healthy subjects (see **Section II.1.1. Study AI420-092 above**).
- There are some limitations to this study that are noteworthy and may make interpretation of the findings difficult/ambiguous:
 - Baseline QTc was determined using only a single ECG recording performed pre-dose on **Day 15** after 1st dose administration of gatifloxacin or placebo and pre-dose on **Day 20** after the 6th dose of each treatment. It is generally preferable to determine baseline QTc from several ECG recordings taken over a range of times during the day.
 - Postdose QTc was determined at only a single timepoint, i.e., 2 hr postdose on **Days 15** and **20**. This assumes that the greatest change in QTc would occur around the time of maximum plasma gatifloxacin concentration (i.e., median Tmax for gatifloxacin is 2 hr). However, in the single dose escalation study evaluating QTc changes with gatifloxacin in healthy subjects, the greatest QTc changes occurred from 0 to 12 hr postdose (see **Section II.1.1. Study AI420-092 above**).
 - There were a relatively limited number of patients evaluated in the repeat dose phase of this ECG substudy (i.e., N <100).



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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ _____ § 552(b)(5) Draft Labeling

APPENDIX 2

CLINICAL PHARMACOLOGY REVIEWS OF PHASE IV STUDIES EVALUATING EFFECTS OF GATIFLOXACIN ON THE QT INTERVAL

INDEX of STUDIES:

- 1) Study AI420-092: RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, SINGLE DOSE, FOUR WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN ON QT_c INTERVAL IN HEALTHY ADULT VOLUNTEERS
Review pages: 91-107
- 2) Study AI420-093: RANDOMIZED, OPEN LABEL, SINGLE DOSE, FOUR-WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN, CIPROFLOXACIN, SPARFLOXACIN, AND CLARITHROMYCIN ON QT_c INTERVAL IN ADULT VOLUNTEERS
Review pages: 108-118
- 3) Study AI420-095: AN OPEN LABEL, MULTICENTER, NONCOMPARATIVE, PHASE IV STUDY OF ORAL GATIFLOXACIN IN THE TREATMENT OF COMMUNITY ACQUIRED RESPIRATORY INFECTIONS – ANALYSIS OF EFFECTS ON THE QT INTERVAL OF THE ECG
Review pages: 119-126
- 4) Study CV 123-229: PRAVASTATIN OR ATORVASTATIN EVALUATION AND INFECTION THERAPY (PROVE IT): ECG SUB-STUDY OF GATIFLOXACIN EFFECTS ON THE QTC INTERVAL
Review pages: 127-148

1. **Study AI420-092: RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, SINGLE DOSE, FOUR WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN ON QTc INTERVAL IN HEALTHY ADULT VOLUNTEERS**

Study Dates: May 2000 – August 2000

Vol. 1-4, pp. 37-380

OBJECTIVES:

To examine the relationship between the change from baseline in the QTc interval and gatifloxacin plasma concentrations in healthy adult volunteers. To assess safety and tolerability of gatifloxacin following single oral doses of 400, 800 and 1200 mg and placebo. To assess pharmacokinetics of gatifloxacin following single oral doses of 400, 800 and 1200 mg.

FORMULATIONS/TREATMENTS:

Gatifloxacin 400 mg white, capsule-shaped, film-coated tablets (Batch 1319520C1)

Placebo white, capsule-shaped, film-coated tablets (Batch N97116)

SUBJECTS:

40 healthy male (N=20) and female (N=20) subjects. Males: mean (range) age 42 (22-78) yr., mean (range) weight 77 (49-99) kg. Females: mean (range) age 33 (18-71) yr., mean (range) weight 70 (55-96) kg.

NOTE: N=2/20 males aged 72 and 78 yr.; N=3/20 females aged 66, 68, and 71 yr.

STUDY DESIGN AND METHODS:

Randomized, double blind, 4-way crossover, single dose study design. All subjects received each of the following single dose treatments:

Placebo (3 placebo tablets)

Gatifloxacin 400 mg (1 x 400 mg tablets + 2 placebo tablets)

Gatifloxacin 800 mg (2 x 400 mg tablets + 1 placebo tablet)

Gatifloxacin 1200 mg (3 x 400 mg tablets)

Each treatment was separated by at least a 7-day washout period. During each of the 4 treatment periods, subjects were confined to the clinical facility for a total of 3 nights and 2 days. Subjects entered the clinical unit on Day -2. On **Day -1**, each subject had 10 ECG's (12-lead) at 0 hr and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs to provide a baseline prior to each treatment. On **Day 1** each subject was administered one treatment in the sequence assigned according to the randomization schedule. Plasma specimens and ECG's (12-lead) were obtained immediately pre-dose (0 hr) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs after dosing. The clock timing on **Day -1** and **Day 1** for ECG measurements was approximately the same. Subjects were discharged from the clinical unit on **Day 2**. Following a 7-day outpatient washout period, subjects returned to the clinical unit for the next dosing period. This process was repeated 3 more times until each subject had received all 4 treatments. All treatments were administered under fasting conditions and subjects remained fasting for at least 2 hrs post-treatment.

All 12-lead ECG's were performed under standardized conditions. Each subject was at rest for 5 minutes prior to each ECG recording (supine or 30° angle). The electrodes were placed on the subjects according to a diagram and instructions provided by an independent contract research organization, _____, and remained in place for 2 days. Prior to discharge from the clinical unit at the end of Treatment Periods 1, 2, and 3, the position of each electrode was marked with permanent marker and instructions were given to the subject not to excessively scrub the area during the 7-day washout period. Upon returning to the clinical unit for the next Treatment Period the electrode was placed at the site of the

permanent marker and remained on for the 2 days in the clinical unit. The ECG recordings were monitored by the investigator during the conduct of the study to insure the safety of all participants. The ECG readings were forwarded to _____ for formal digital analysis and reporting as outlined in the study protocol.

Relevant criteria for exclusion from this study included the following:

- Use of any drugs known to affect any part of the electrocardiogram that will impact on measurement or interpretation of QTc interval.
- QTc interval > 450 msec for males or > 470 msec for females.
- Subjects receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents.
- Personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, or recent myocardial ischemia.

ANALYTICAL METHODS:

Gatifloxacin concentrations in plasma samples were determined by an HPLC-UV method. The assay was validated over a linear range from _____ (LLOQ _____)

The validation and performance of the plasma assay for gatifloxacin was acceptable.

DATA ANALYSIS AND STATISTICAL METHODS:

Pharmacokinetics (PK)

Pharmacokinetic (PK) parameters for gatifloxacin were determined using standard noncompartmental methods. In addition to C_{max}, T_{max}, AUC(0-6) and AUC(0-12), average plasma gatifloxacin concentrations over the first 6 and 12 hours after dosing were determined as Cav(0-6) = AUC(0-6) ÷ 6 hr and Cav(0-12) = AUC(0-12) ÷ 12 hr, respectively.

Pharmacodynamics (PD)

ECG intervals were determined by trained technicians at _____ using the _____TM _____ ECG measurement system. This system utilizes a _____

_____, is translated into milliseconds and is automatically entered into a database. The _____ was calibrated for accuracy prior to each session by measuring a series of 200msec blocks from the background ECG paper grid and was found to be accurate to within ±3 msec.

The onset of the QRS complex and the end of the T wave were identified to define the QT interval. R-R duration was similarly determined selecting the peak of 2 consecutive R waves. The presence of abnormal T or U waves in each ECG recording was determined by a single, board-certified cardiologist. Manual digitization of up to 3 beats, usually from Lead II, was performed using the _____

Measurements of the following intervals were reported for each ECG tracing:

Three (3) PR → mean PR Interval

Three (3) QRS → mean QRS Width

Three (3) R-R → mean R-R Interval

Three (3) QT → mean QT Interval

Three (3) QTc → mean QTc Interval

QTc values were calculated for each of 3 sets of R-R/QT measurements using Bazett's (B) and Fridericia's (F) heart rate correction formulae, i.e., $QTcB = QT/\sqrt{RR}$ and $QTcF = QT/\sqrt[3]{R-R}$. The mean QTc equaled the sum of the 3 QTc measurements divided by 3.

A routine quality control program for the ECG interval measurement data was implemented by

PK/PD Analyses

The PD parameters for this study were defined as follows:

- *Delta QTcAvg (0-6)* = the change from baseline (Day -1 outcome) in time-averaged QTc during the first 6 hours after dosing on Day 1, i.e., the area under the QTc curve from 0 (predose) to 6 hr after dosing, divided by 6 hr.
- *Delta QTcAvg (0-12)* = the change from baseline (Day -1 outcome) in the time-averaged QTc during the first 12 hours after dosing on Day 1, i.e., the area under the QTc curve from 0 (predose) to 12 hr after dosing, divided by 12 hr.
- *Delta QTcMax* = the change from baseline (Day -1 outcome) in the longest QTc recorded after dosing on Day 1.
- *Delta QTc at Tmax* = the change from baseline (Day -1 outcome) in the QTc recorded at the time (Tmax) of peak gatifloxacin concentration (Cmax) on Day 1. For the placebo treatment, QTc at Tmax was the QTc at the median of the Tmax values from the other periods.

Five different baseline values were determined in each treatment period:

- 6) *Baseline QTcAvg(0-6)* = the time averaged QTc during the 6 hours on Day -1, i.e., the area under the QTc curve over 6 hours on Day -1, divided by 6 hours.
- 7) *Baseline QTcAvg(0-12)* = the time averaged QTc during the 12 hours on Day -1, i.e., the area under the QTc curve over 12 hours on Day -1, divided by 12 hours.
- 8) *Baseline QTcMax* = the QTc recorded on Day -1 at the time corresponding to the time of longest QTc recorded on Day 1.
- 9) *Baseline QTc at Tmax* = the QTc recorded on Day -1 at the time corresponding to the gatifloxacin Tmax on Day 1.
- 10) *QTc at 0 hr* = the mean of the QTc intervals recorded just prior to gatifloxacin dosing on Day 1 and at the corresponding time 24 hours earlier on Day -1.

Baselines (1), (4), and (5) were used in the analyses of the QTcAvg(0-6). Baselines (2), (4), and (5) were used in the analyses of the QTcAvg (0-12). Baselines (1), (2), (3), (4), and (5) were used in the analyses of QTcMax. Baselines (1), (2), (4), and (5) were used in the analyses of QTc at Tmax.

Scatter plots and linear regressions were used to explore the relationship between gatifloxacin exposure and the changes from baseline in each of the derived QTc outcome measures. The regression models include factors for gender and subject within gender. Subjects were considered as random effects.

The changes in each of the derived QTc outcome measures from the corresponding baseline values were summarized by treatment. Additionally, each of the derived QTc outcome measures was cross-tabulated against baseline, for each treatment. For males, QTc values were grouped as QTc <430msec, 430msec ≤ QTc ≤ 450msec, or QTc >450msec. For females, QTc outcome values were grouped as QTc <450msec, 450msec ≤ QTc ≤ 470msec, or QTc >470msec.

Reviewer Comments:

These cross-tabulations were consistent with the previously published 1997 CPMP/EMEA Points to Consider document entitled, "The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products".

The cross-tabulations were to be presented by gender and age group, but due to the small numbers of subjects in the older age group, they are only presented by gender.

All subjects who received study drug were included in the safety data sets, and the pharmacodynamic data listings. Only subjects who had QTc and PK data available in at least two Treatment Periods were included in the statistical analysis. All available data from subjects who received gatifloxacin were included in the PK data listings. Only subjects who had data available from at least two Treatment Periods in which they received gatifloxacin were included in the summary statistics of the PK data.

RESULTS:

A total of 40 subjects entered the study and 33 subjects completed all 4 treatment Periods. Seven (7) subjects were discontinued for various reasons and are discussed below (see SAFETY/ADVERSE EVENTS). The table below provides a summary of subject demographics, by treatment, for which PK and QTc data was obtained.

Treatment	PK DATA			QTc DATA		
	N	M / F	≥65 Years)	N	M / F	≥65 Years
Placebo	—	—	—	31	18 M 13 F	2 M 3 F
400 mg Gatifloxacin	33	18 M 15 F	2 M 1 F	34	18 M 16 F	2 M 3 F
800 mg Gatifloxacin	34	19 M 15 F	2 M 2 F	37	18 M 19 F	2 M 3 F
1200 mg Gatifloxacin	31	19 M 12 F	2 M 3 F	30	18 M 12 F	2 M 3 F

Reviewer Comment: Note that in the table above, there were very few elderly male and female subjects evaluated for both PK and QTc. Because of the small numbers, no conclusions can be made regarding the effects of gatifloxacin on the QT / QTc interval in elderly subjects.

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Pharmacokinetics

The table below provides a summary of the PK parameters determined for gatifloxacin.

Gatifloxacin PK Parameters Following Single Oral Doses to Healthy Subjects

Dose	Cmax* (µg/mL)	Tmax** (h)	AUC(0-T)*** (µg.h/mL)	Cav(0-6)* (µg/mL)	Cav(0-12)* (µg/mL)
400 mg N=33	3.52 (31.7) 2.7, 7.3	1.5 (0.5, 3.0)	21.3 (25.5) 8.2, 33.3	2.30 (23.5) 1.4, 3.6	1.77 (25.5) 0.7, 2.8
800 mg N=34	6.25 (20.6) 3.4, 9.8	1.5 (0.5, 6.0)	44.6 (19.7) 31.1, 68.6	4.49 (21.2) 2.9, 7.3	3.71 (19.7) 2.6, 5.7
1200 mg N=31	9.00 (22.2) 5.5, 14.2	2.0 (0.5, 4.0)	68.9 (22.0) 43.5, 102.4	6.69 (19.8) 4.2, 9.8	5.74 (22.0) 3.6, 8.5

*Geometric Mean (%CV); Min, Max

**Median Tmax (Min, Max)

***AUC(0-T) = area under the curve to time of last quantifiable concentration

The table shows that mean Cmax and AUC(0-T) for gatifloxacin were both approximately dose proportional. The between subject variability in all PK parameters, as % CV, was reasonable - ranging approximately from 20% to 30% - and was consistent with what has been previously reported for these gatifloxacin doses.

Exposure-QT Response

Summaries of the statistical and regression results are presented below for each derived QTc parameter and the change in each QTc parameter from the respective baselines. The regression plots for each QTc parameter vs. the relevant gatifloxacin plasma exposure variable are shown at the end of this review in Figures 1 through 4.

Reviewer Comment: *The sponsor focused on the QTcAvg(0-6) as the primary QTc parameter. While this was acceptable, it is the opinion of the reviewer that the QTcAvg(0-12) is equally important, since although both are time-averaged parameters, the QTcAvg(0-12) may represent a more robust time-averaged parameter, especially if the QTc exhibits diurnal variability greater than over a 6-hour time period. Thus, the reviewer will place greater emphasis on the QTcAvg(0-12) than the QTcAvg(0-6).*

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1. QTcAvg(0-6)

Summary Statistics for QTcAvg(0-6) and Changes in QTcAvg(0-6)

Treatment	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800 mg	Gatifloxacin 1200 mg
QTcAvg(0-6) (msec)				
Mean (SD)	381 (14)	386 (12)	396 (16)	403 (16)
Min, Max	350, 409	366, 411	367, 434	372, 444
Baseline QTc	Change in QTcAvg(0-6) from Baseline (msec) Mean (SD); Min, Max			
Day-1 QTcAvg(0-6)	-2.3 (7.1) -13.4, 12.0	4.0 (7.9) -13.7, 18.5	10.8 (6.6) -2.3, 24.5	16.9 (7.7) 0.5, 32.0
Day-1 QTc at Tmax	1.4 (14.3) -28.2, 31.3	5.6 (13.1) -26.5, 29.9	11.7 (12.7) -11.1, 39.8	15.4 (17.2) -24.3, 44.0
QTc at hr 0	-3.8 (11.9) -27.0, 29.5	2.7 (12.6) -31.0, 30.0	5.1 (12.1) -15.9, 37.3	14.1 (8.5) -0.1, 32.9

Summary of Regression Analyses of Δ QTcAvg(0-6) on Cav(0-6)

Dependent Variable	QTc Baseline (msec)	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/ μ g/mL)
Δ QTcAvg(0-6) (msec)	QTcAvg(0-6)	Cav(0-6) (μ g/mL)	-1.8	2.7 (2.1, 3.2)
	QTc at Tmax		0.7	2.2 (1.3, 3.2)
	QTc at 0 hr		-3.5	2.3 (1.5, 3.1)

No subject had a QTcAvg(0-6) greater than 450 msec at any of the 3 gatifloxacin doses or with placebo.

Dose related increases in mean change in QTcAvg(0-6) were observed regardless of the choice of baseline. The changes in mean QTcAvg(0-6) at all three gatifloxacin dose levels were greater than those of placebo. Within each gatifloxacin dose the mean and range of changes in QTcAvg(0-6) were relatively consistent regardless of the choice of baseline. At the clinical dose of 400mg, the mean change in QTcAvg(0-6) was approximately +4 msec. At higher doses of 800mg and 1200mg, the mean changes in QTcAvg(0-6) were approximately +11 and +17 msec, respectively. With placebo, the mean change in QTcAvg(0-6) was approximately -2 msec.

The regression analyses showed a positive association between Δ QTcAvg(0-6) and gatifloxacin plasma exposure / concentrations (i.e., Cav(0-6); see **Figure 1**). Similar slopes were obtained with all three baselines for the regression of Δ QTcAvg(0-6) vs. Cav(0-6). In each case, the regression slopes were statistically different from zero, as indicated by the 95% CI.

2. QTcAvg(0-12)

Summary Statistics for QTcAvg(0-12) and Changes in QTcAvg(0-12)

Treatment	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800 mg	Gatifloxacin 1200 mg
QTcAvg(0-12) (msec)				
Mean(SD)	382 (14)	386 (11)	396 (16)	401 (17)
Min,Max	351, 410	364, 410	362, 431	369, 445
Baseline QTc	Change in QTcAvg(0-12) from Baseline (msec)			
	Mean (SD)			
	Min, Max			
Day-1 QTcAvg(0-12)	-0.1 (6.3) -11.1, 14.4	4.1 (7.5) -12.7, 20.3	10.0 (6.9) -4.6, 22.6	15.5 (8.2) -1.5, 32.1
Day -1 QTc at Tmax	2.7 (14.7) -27.5, 33.6	5.8 (13.4) -23.1, 29.2	11.1 (13.6) -14.1, 41.7	14.2 (17.4) -29.3, 45.0
QTc at hr 0	-2.7 (11.2) -18.8, 29.8	3.0 (12.7) -27.7, 29.7	4.5 (12.3) -16.3, 35.2	12.9 (8.8) -2.8, 35.9

Summary of Regression Analyses of Δ QTcAvg(0-12) on Cav(0-12)

Dependent Variable	QTc Baseline (msec)	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/ μ g/mL)
Δ QTcAvg(0-12) (msec)	QTcAvg(0-12)	Cav(0-12) (μ g/mL)	0.1	2.5 (1.9, 3.1)
	QTc at Tmax		1.8	2.3 (1.1, 3.4)
	QTc at hr 0		-2.2	2.3 (1.4, 3.2)

The results from the analyses of QTcAvg(0-12) were similar to those for QTcAvg(0-6). No subject had a QTcAvg(0-12) greater than 450 msec at any of the 3 gatifloxacin doses or with placebo.

Dose related increases in mean change in QTcAvg(0-12) were observed regardless of the choice of baseline. The changes in mean QTcAvg(0-12) at all three gatifloxacin dose levels were greater than those of placebo. Within each gatifloxacin dose the mean and range of changes in QTcAvg(0-6) were relatively consistent regardless of the choice of baseline. At the clinical dose of 400mg, the mean change in QTcAvg(0-12) was approximately +4 msec. At higher doses of 800mg and 1200mg, the mean changes in QTcAvg(0-12) were approximately +10 and +15 msec, respectively. With placebo, the mean change in QTcAvg(0-12) was negligible (-0.1 msec).

The regression analyses showed a positive association between Δ QTcAvg(0-12) and gatifloxacin plasma exposure / concentrations (i.e., Cav(0-12); see **Figure 2**). Similar slopes were obtained with all three baselines for the regression of Δ QTcAvg(0-12) vs. Cav(0-12). In each case, the regression slopes were statistically different from zero, as indicated by the 95% CI.

3. QTc Max

Summary Statistics for QTcMax and Changes in QTcMax

Treatment	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800mg	Gatifloxacin 1200 mg
QTcMax (msec)				
Mean (SD)	400 (17)	405 (14)	413 (18)	424 (18)
Min, Max	363, 435	376, 440	376, 449	384, 463
Baseline QTc	Change in QTcMax from Baseline (msec)			
	Mean (SD)			
	Min, Max			
Day -1 QTc Avg(0-6)	17.1 (12.0) -0.3, 49.3	22.7 (8.5) 4.8, 48	27.6 (9.9) 6.8, 52.5	38.2 (15.5) 14.3, 77.8
Day -1 QTc Avg(0-12)	18.1 (10.1) 1.6, 40.9	22.6 (9.2) 6.4, 53	27.5 (9.4) 11.6, 47.8	38.0 (16.6) 14.0, 81.2
Day -1 QTc at Tmax	20.8 (19.3) -15.0, 63.0	24.3 (14.7) 3, 66	28.7 (16.2) -4.0, 61.0	36.6 (21.5) -13.0, 79.0
Day -1 QTcMax	15.1 (15.7) -14, 48.0	22.4 (13.8) -1.0, 62.0	29.2 (15.7) 4.0, 60.0	38.6 (18.6) 9.0, 81.0
QTc at hr 0	15.5 (14.5) -6.0, 55.0	21.4 (13.8) -3.0, 64.5	22.1 (14.7) -2.0, 55.0	35.3 (16.9) 15.5, 84.0

Regression Summary of Δ QTc Max

Dependent Variable	QTc Baseline (msec)	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/ μ g/mL)
Δ QTc Max (msec)	QTc Avg(0-6)	Cavg(0-12) (μ g /mL)	16.6	3.3 (2.4, 4.3)
	QTc Avg(0-12)		17.3	3.1 (2.2, 4.1)
	QTcMax		15.4	3.7 (2.4, 5.1)
	QTc at Tmax		19.1	2.8 (1.4, 4.3)
	QTc at hr 0		15.0	2.9 (1.7, 4.2)

The results for this PD parameter showed that 2 young females (ages 23 and 36 yr.) had QTc Max values between 450 and 470 msec (i.e., 463 msec for the 23 yr. old and 455 msec for the 36 yr. old) following the highest gatifloxacin dose of 1200mg. No other male or female subjects had QTc Max values greater than 450 msec at either 800mg or 400mg.

Although dose related increases in mean change in QTcMax were observed, regardless of the choice of baseline, the mean changes in QTcMax between the 400mg clinical dose and the next higher 800mg dose were not as pronounced as between the 800mg and 1200mg doses. The changes in mean QTcMax at all three gatifloxacin dose levels were greater than those of placebo. Within each gatifloxacin dose the mean and range of changes in QTcMax were relatively consistent regardless of the choice of baseline. At the clinical dose of 400mg, the mean change in QTcMax was approximately +22 msec. At higher doses of 800mg and 1200mg, the mean changes in QTcMax were approximately +28 and +38 msec, respectively. With placebo, the mean change in QTcMax ranged between 15 to 20 msec. If one takes into account the changes in placebo, then the mean increases in QTcMax become relatively similar to those observed for both QTcAvg(0-6) and QTcAvg(0-12).

The regression analyses showed a positive association between Δ QTcMax and gatifloxacin plasma exposure / concentrations (i.e., Cav(0-12); see Figure 3). Similar slopes were obtained with all baselines for the regression of Δ QTcMax vs. Cav(0-12). In each case, the regression slopes were statistically different from zero, as indicated by the 95% CI.

4. QTc at Tmax

Summary Statistics for QTc at Tmax and Changes in QTc at Tmax

	Placebo	Gatifloxacin 400 mg	Gatifloxacin 800 mg	Gatifloxacin 1200 mg
QTc at Tmax (msec)				
Mean (SD)	377 (20)	388 (18)	397 (22)	412 (21)
Min, Max	339, 415	350, 417	334, 442	374, 463
Baseline QTc	Delta QTc at Tmax from Baseline (msec)			
	Mean (SD)			
	Min, Max			
Day -1	-2 (20.4)	7.2 (17.6)	12.6 (17.5)	24.5 (24.3)
QTc at Tmax	-50.0, 40.0	-24.0, 43.0	-23.0, 49.0	-23.0, 79.0
Day -1	-5.7 (14.5)	5.6 (15.5)	11.1 (12.4)	26.1 (19.3)
QTc Avg(0-6)	-49.4, 29.3	-29.2, 39.0	-25.3, 30.2	-3.4, 77.8
Day -1	-4.7 (13.4)	5.5 (14.9)	11.0 (11.0)	25.8 (20.8)
QTc Avg(0-12)	-51.8, 15.8	-29.0, 33.3	-16.6, 28.6	-4.0, 81.2
QTc at hr 0	-7.3 (18.1)	4.3 (18.4)	6.1 (16.3)	23.2 (20.9)
	-63.0, 34.5	-45.0, 50.0	-33.5, 41.5	-7.5, 84.0

Regression Summaries of ΔQTc at Tmax

Dependent Variable	QTc Baseline	Independent Variable	Point Estimate of Regression Parameter	
			Intercept (msec)	Slope (95% C.I.) (msec/μg /mL)
ΔQTc at Tmax	QTc Avg(0-6)	Cmax (μg /mL)	-6.1	3.1 (2.3, 3.9)
	QTc Avg(0-12)		-5.4	3.0 (2.2, 3.8)
	QTc at Tmax		-2.8	2.7 (1.6, 3.7)
	QTc at hr 0		-7.8	2.9 (1.9, 3.8)
ΔQTc at Tmax	QTcAvg(0-6)	Cav(0-12) (μg /mL)	-5.5	5.0 (3.7, 6.2)
	QTcAvg(0-12)		-4.8	4.7 (3.5, 6.0)
	QTc at Tmax		-2.9	4.5 (2.9, 6.0)
	QTc at hr 0		-7.0	4.5 (3.1, 6.1)

No subjects receiving 400mg or 800mg gatifloxacin, or placebo had QTc at Tmax greater than 450 msec. One female subject (age 23 years) had QTc at Tmax of 463 msec after 1200mg gatifloxacin.

In general, the mean changes in QTc at Tmax increased with the increase in gatifloxacin dose for all baselines and tended to be smaller than those observed for QTc Max. The changes in mean QTc at Tmax at all three gatifloxacin dose levels were greater than those of placebo. Within each gatifloxacin dose the mean and range of changes in QTc at Tmax were relatively consistent regardless of the choice of baseline. At the clinical dose of 400mg, the mean change in QTc at Tmax was approximately +5 to +7 msec. At higher doses of 800mg and 1200mg, the mean changes in QTc at Tmax were approximately +12 and +25 msec, respectively. With placebo, the mean change in QTc at Tmax ranged between -2 to -7 msec. The changes in QTc at Tmax after 400mg and 800mg of gatifloxacin were similar to those observed for QTcAvg(0-6) and QTcAvg(0-12) at these same doses, but were higher for QTc at Tmax at 1200mg gatifloxacin.

The regression analyses showed positive associations between ΔQTc at Tmax and gatifloxacin plasma exposure / concentrations (i.e., either Cmax or Cav(0-12); see Figure 4). Similar slopes were obtained with all baselines for the respective regressions of ΔQTc at Tmax vs. Cmax and for ΔQTc at Tmax vs.

Cav(0-12). However, the values for the slopes for the latter regression (Δ QTc at Tmax vs. Cav(0-12)) were slightly higher/steeper than those for the former (Δ QTc at Tmax vs. Cmax). In each case, the regression slopes were statistically different from zero, as indicated by the 95% CI.

Outlier Analyses

QTc values and changes in QTc from baseline were categorized by the sponsor according to criteria published by the EMEA/CPMP Points to Consider document. These criteria are summarized below.

Categories for Absolute QTc Values

Classification	QTc Interval for Males (msec)	QTc Interval for Females (msec)
Normal	<430	<450
Borderline	430 to 450	450 to 470
Prolonged	>450	>470

Risk Categories for Changes in QTc from Baseline

Risk Classification for Drug to Induce Arrhythmia, Including <i>Torsades de Pointes</i>	Δ QTc (msec)
Unlikely – Non-Significant/Minimal Clinical Concern	<30
Likely – Moderate Clinical Concern	30 to 60
Highly Likely – Significant/High Clinical Concern	>60

The sponsor chose to use the QTc Max for the outlier analyses since this parameter represents the worst case scenario. The results for absolute QTc Max values and for Δ QTc Max in male and female subjects are shown in the tables below.

QTc MAX FOR MALES

Single Dose	Pre-Dose	Post-Dose QTc MAX		
		≤430 msec	>430 - 450 msec	>450 msec
Placebo	≤430 msec	18	0	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0
Gatifloxacin 400 mg	≤ 430 msec	18	0	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0
Gatifloxacin 800 mg	≤ 430 msec	17	1 ^a	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0
Gatifloxacin 1200 mg	≤430 msec	13	5 ^b	0
	>430 - 450 msec	0	0	0
	> 450 msec	0	0	0

^a< 65 years old

^b4 subjects < 65 years old; 1 subject > 65 years old

QTc MAX FOR FEMALES

Single Dose	Pre-Dose	Post-Dose QTc MAX		
		≤450 msec	>450 - 470 msec	>470 msec
Placebo	≤450 msec	13	0	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0
Gatifloxacin 400 mg	≤ 450 msec	16	0	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0
Gatifloxacin 800 mg	≤450 msec	19	0	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0
Gatifloxacin 1200 mg	≤ 450 msec	10	2 ^a	0
	> 450 - 470 msec	0	0	0
	> 470 msec	0	0	0

^a < 65 years of age for both subjects

FREQUENCY DISTRIBUTION for ΔQTc MAX (USING DAY -1 Cavg(0-12) as BASELINE)

Single Dose	N	Males			N	Females		
		<30 msec	30-60 msec	>60 msec		<30 msec	30-60 msec	>60 msec
Placebo	18	17	1	0	13	10	3	0
Gatifloxacin 400 mg	18	17	1	0	16	11	5	0
Gatifloxacin 800 mg	19	14	5	0	19	13	6	0
Gatifloxacin 1200 mg	19	8	10	1 ^a	14	3	9	2 ^b

^a Male subject < 65 years old

^b Female subject < 65 years old

The table of QTc Max values showed that at all three gatifloxacin doses no subject had a "prolonged" maximum QTc interval of >450 msec for males or >470 msec for females. Five (5) males and 2 females had "borderline" prolongation in QTc Max at the highest gatifloxacin dose of 1200mg, with only one of the 6 total subjects at >65 years of age.

For the frequency distribution of ΔQTc Max, the majority of subjects had changes of <30 msec after the single oral clinical dose of 400mg. There were no subjects with ΔQTc Max of >60 msec at single oral doses of 400mg and 800mg, and 1/19 males and 2/14 females with changes >60 msec at 1200mg. There were a greater number of subjects with ΔQTc Max between 30 to 60 msec at 800mg and 1200mg vs. 400mg, with approximately the same number of males and females at each of these two higher gatifloxacin doses.

Reviewer Assessment of Time to Maximum QTc (QTc Max) vs. Time to Gatifloxacin Cmax (i.e., Tmax)

This assessment was performed by the reviewer to evaluate whether the time of occurrence of the maximum QTc interval and the change in QTc Max from baseline coincided with the Tmax of gatifloxacin. It has generally been assumed that the greatest change in the QTc would occur at time of Cmax (i.e., Tmax) for the fluoroquinolones and other non-cardiovascular drugs that prolong the QT interval. The table below summarizes the results.

Gatifloxacin Plasma Tmax vs. Time to QTc Max and Time to ΔQTc Max

	Median Tmax (hr) (Min, Max)	Median Time to QTc Max (hr) (Min, Max)	Median Time to ΔQTc Max (hr) (Min, Max)
Placebo	NA	3.5 (0, 12)	3.0 (0, 12)
400mg Gatifloxacin	1.5 (0.5, 3.0)	3.0 (0, 12)	2.0 (0, 12)
800mg Gatifloxacin	1.5 (0.5, 6.0)	2.0 (1, 12)	3.0 (1, 12)
1200mg Gatifloxacin	2.0 (0.5, 4.0)	2.0 (1, 12)	2.0 (0.5, 12)

This data shows that the median times to QTc Max and to ΔQTc Max were relatively similar to the median Tmax values determined for gatifloxacin in plasma. Similar median times for the QTc Max parameters were also observed between placebo and the 3 gatifloxacin doses. A notable difference, however, between the plasma Tmax and QTc Max parameters is that the ranges for the QTc Max parameters were appreciably wider than those for plasma Tmax, which lends support to the greater degree of time variability that is observed in QTc.

SAFETY:

With respect to the ECG, there were no clinically significant ECG abnormalities observed during the entire duration of the study.

REVIEWER CONCLUSIONS:

The following conclusions may be made regarding the effects of single oral escalating doses of gatifloxacin at 400mg (clinical dose), 800mg (2X clinical dose), and 1200mg (3x clinical dose) on the QTc interval in healthy male and female subjects:

- A **dose** relationship was observed with all ΔQTc parameters following single oral gatifloxacin doses of 400mg, 800mg, and 1200mg.
 - **ΔQTc at Tmax and ΔQTcAvg(0-12) values (mean (overall range)):**
 Placebo → -2 to -0.1 (-50, +40) msec
 400mg → 4 to 6 (-29, +33) msec
 800mg → 10 to 12 (-17, +29) msec
 1200mg → 16 to 26 (-4, +81) msec
 - **ΔQTc Max values (mean (range)):**
 Placebo → 15 (-14, +48) msec
 400mg → 23 (6, 53) msec
 800mg → 28 (12, 48) msec
 1200mg → 38 (14, 81) msec
 - Note that for the ΔQTc Max values, if one takes into account the changes in placebo, then the mean changes in QTc Max become relatively similar to those observed for QTc at Tmax and QTcAvg(0-12).
- A **concentration** relationship was also observed with all ΔQTc parameters following single oral gatifloxacin doses of 400mg, 800mg, and 1200mg.
 - Linear regression analyses of ΔQTc parameters vs. plasma gatifloxacin concentration resulted in slope estimates from 2.5 to 3.1 msec/μg/mL.
- The median times to QTc Max and to ΔQTc Max were relatively similar to the median Tmax values determined for gatifloxacin in plasma. Similar median times for the QTc Max parameters were also observed between placebo and the 3 gatifloxacin doses. A notable difference, however, between the

plasma Tmax and QTc Max parameters is that the ranges for the QTc Max parameters were appreciably wider than those for plasma Tmax, which lends support to the greater degree of temporal variability that is observed in QTc.

- Overall, similar results were obtained across all of the various baseline corrections employed to determine the Δ QTc parameters.
- In the outlier analyses, the majority of subjects had Δ QTc Max <30 msec after a single oral dose of 400mg. There were no subjects with Δ QTc Max >60 msec at single oral doses of 400mg and 800mg, and 1/19 males and 2/14 females with Δ QTc Max >60 msec at 1200mg. There were a greater number of subjects with Δ QTc Max between 30 to 60 msec at 800mg and 1200mg vs. 400mg, with approximately the same number of males and females at each of these two higher gatifloxacin doses.
- There were no male or female subjects with QTc Max values >450 or >470 msec, respectively, and no subjects with QTc \geq 500 msec.
- QTc data from the elderly male and female subjects was limited (N = 5 subjects \geq 65 years), and therefore, no conclusions can be made regarding the effects of gatifloxacin on the QT / QTc interval in elderly subjects.

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Figure 1. Change from Baseline (Day -1 without Gatifloxacin) in QTcAvg(0-6) vs. Average Plasma Concentrations of Gatifloxacin from 0 to 6 hr (Cav(0-6)) following Single Oral Doses of 400mg, 800mg and 1200mg to Healthy Male and Female Subjects

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Linear Regression Parameters for Δ QTc Avg(0-6) vs. Cav(0-6):
Slope (95% CI): 2.7 (2.1, 3.2) msec/ μ g/mL
Intercept: -1.8 msec

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Figure 2. Change from Baseline (Day -1 without Gatifloxacin) in QTcAvg(0-12) vs. Average Plasma Concentrations of Gatifloxacin from 0 to 12 hr (Cav(0-12)) following Single Oral Doses of 400mg, 800mg and 1200mg to Healthy Male and Female Subjects

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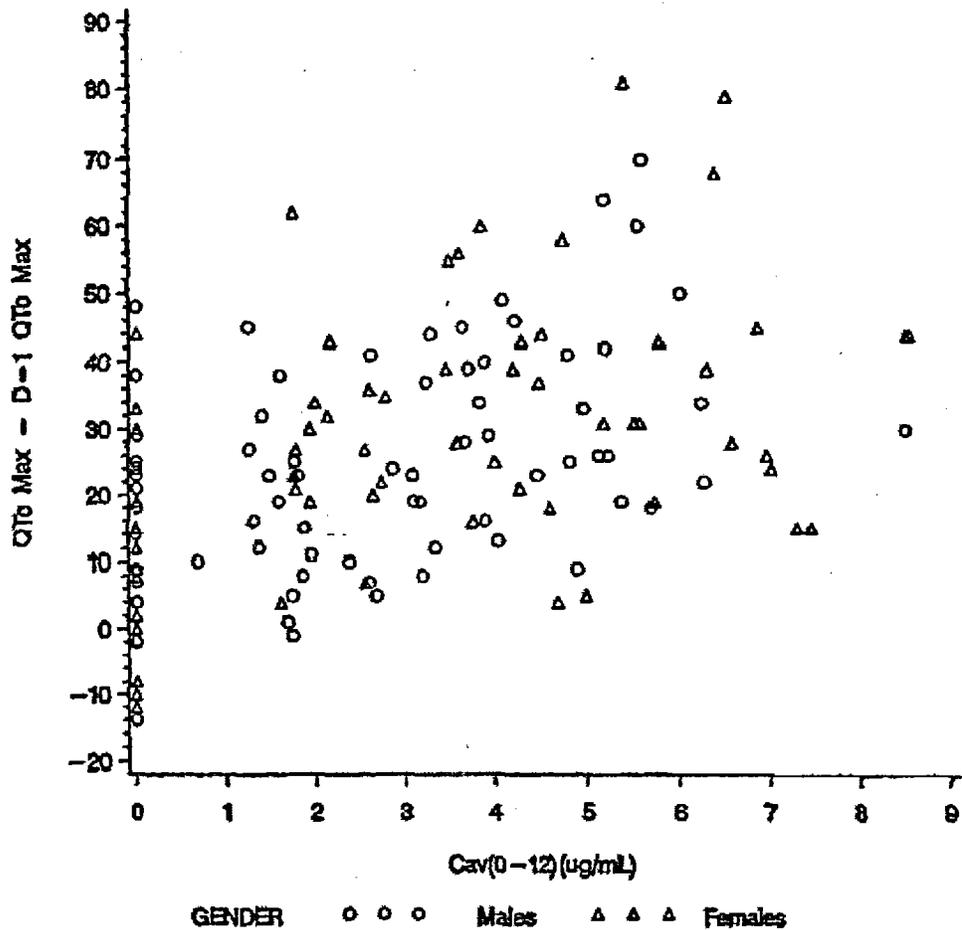
Linear Regression Parameters for Δ QTc Avg(0-12) vs. Cav(0-12):

Slope (95% CI): 2.5 (1.9, 3.2) msec/ μ g/mL

Intercept: 0.1 msec

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Figure 3. Change from Baseline (Day -1 without Gatifloxacin) in QTc Max vs. Average Plasma Concentrations of Gatifloxacin from 0 to 12 hr (Cav(0-12)) following Single Oral Doses of 400mg, 800mg and 1200mg to Healthy Male and Female Subjects

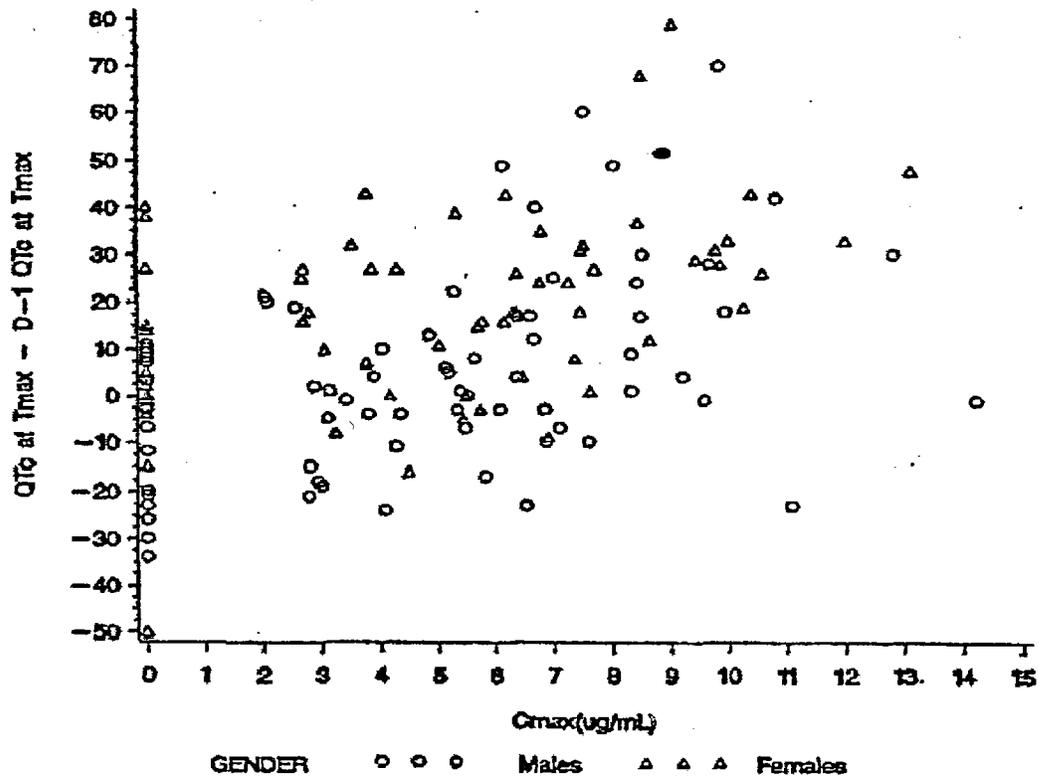


Linear Regression Parameters for Δ QTc Max vs. Cav(0-12):

Slope (95% CI): 3.1 (2.2, 4.1) msec/ μ g/mL

Intercept: 17.3 msec

Figure 4. Change from Baseline (Day -1 without Gatifloxacin) in QTc at Tmax vs. Maximum Plasma Concentrations of Gatifloxacin (Cmax) following Single Oral Doses of 400mg, 800mg and 1200mg to Healthy Male and Female Subjects



Linear Regression Parameters for ΔQTc at Tmax vs. Cmax:
 Slope (95% CI): 2.7 (1.6, 3.7) msec/ μ g/mL
 Intercept: -2.8 msec

2. **Study AI420-093: RANDOMIZED, OPEN LABEL, SINGLE DOSE, FOUR-WAY CROSSOVER STUDY OF THE EFFECTS OF GATIFLOXACIN, CIPROFLOXACIN, SPARFLOXACIN, AND CLARITHROMYCIN ON QTc INTERVAL IN ADULT VOLUNTEERS**

Study Dates: 7/24/2000 – 10/22/2000

Vol. 5-8; pp. 1-415

OBJECTIVES:

To compare the effects of gatifloxacin, ciprofloxacin, sparfloxacin and clarithromycin on QTc interval in adult volunteers.

To assess relative safety and tolerability of gatifloxacin 800 mg, ciprofloxacin 1000 mg, sparfloxacin 400 mg and clarithromycin 1000 mg.

To explore the relationship between QTc at Tmax and the measured plasma concentrations for each study drug.

TREATMENTS/FORMULATIONS:

Gatifloxacin 400mg Tablets (TEQUIN®); Batch #OF33942

Ciprofloxacin 500mg Tablets (CIPRO®); Batch #OCGD

Sparfloxacin 200mg Tablets (ZAGAM®); Batch #MN3414

Clarithromycin 500mg Tablets (BIAXIN®); Batch #02-798021RS

SUBJECTS:

40 healthy male (N=20) and female (N=20) subjects. Males: mean (range) age 38 (18-70) yr., mean (range) weight 75 (45-103) kg. Females: mean (range) age 31 (19-51) yr., mean (range) weight 65 (45-85) kg.

NOTE: N=1/20 males aged 70 yr.; no elderly females enrolled/studied

STUDY DESIGN AND METHODS:

Randomized, double blind, 4-way crossover, single dose study design. All subjects received each of the following single dose treatments; the multiple of the recommended clinical doses are provided:

Gatifloxacin 800mg (2x400mg tablets) = 2X Clinical Dose (400mg)

Ciprofloxacin 1000mg (2x500mg tablets) = 1.3X to 2X Clinical Dose (500mg to 750mg)

Sparfloxacin 400mg (2x200mg tablets) = Loading Dose; 2X Maintenance Dose (200mg)

Clarithromycin 1000mg (2x500mg tablets) = 2X to 4X Clinical Dose (250mg to 500mg)

Each treatment was separated by at least a 7-day washout period. During each of the 4 treatment periods, subjects were confined to the clinical facility for a total of 3 nights and 2 days. Subjects entered the clinical unit on Day -2. On **Day -1**, each subject had 11 ECG's (12-lead) at 0 hr and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 hrs to provide a baseline prior to each treatment. On **Day 1** each subject was administered one treatment in the sequence assigned according to the randomization schedule. ECG's (12-lead) were obtained immediately pre-dose (0 hr) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 hrs after dosing. The clock timing on **Day -1** and **Day 1** for ECG measurements was approximately the same.

Plasma samples for determination of drug concentrations were obtained on Day 1 immediately pre-dose (0 hr) for all drugs and at the average Tmax following administration of gatifloxacin, ciprofloxacin, and clarithromycin (i.e., at 2 hr postdose), and sparfloxacin (i.e., at 4 hr postdose).

Subjects were discharged from the clinical unit on **Day 2**. Following a 7-day outpatient washout period, subjects returned to the clinical unit for the next dosing period. This process was repeated 3 more times

until each subject had received all 4 treatments. All treatments were administered under fasting conditions and subjects remained fasting for at least 2 hrs post-treatment.

All 12-lead ECG's were performed under standardized conditions. Each subject was at rest for 5 minutes prior to each ECG recording (supine or 30° angle). The electrodes were placed on the subjects according to a diagram and instructions provided by an independent contract research organization, _____ and remained in place for 2 days. Prior to discharge from the clinical unit at the end of Treatment Periods 1, 2, and 3, the position of each electrode was marked with permanent marker and instructions were given to the subject not to excessively scrub the area during the 7-day washout period. Upon returning to the clinical unit for the next Treatment Period the electrode was placed at the site of the permanent marker and remained on for the 2 days in the clinical unit. The ECG recordings were monitored by the investigator during the conduct of the study to insure the safety of all participants. The ECG readings were forwarded to _____ for formal digital analysis and reporting as outlined in the study protocol.

Relevant criteria for exclusion from this study included the following:

- Use of any drugs known to affect any part of the electrocardiogram that will impact on measurement or interpretation of QTc interval.
- QTc interval > 450 msec for males or > 470 msec for females.
- Subjects receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents.
- Personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, or recent myocardial ischemia.

ANALYTICAL METHODS:

Gatifloxacin concentrations in plasma were determined by an HPLC-UV method. The assay was validated over a linear range from 0.01 to 5.0µg/mL (LLOQ 0.01µg/mL).

The validation and performance of the plasma assay for gatifloxacin was acceptable.

Ciprofloxacin concentrations in plasma were determined by an HPLC-UV method. The assay was validated over a linear range from 0.025 to 10.0µg/mL (LLOQ 0.025µg/mL).

The validation and performance of the plasma assay for ciprofloxacin was acceptable.

Sparfloxacin concentrations in plasma were determined by an HPLC-UV method. The assay was validated over a linear range from 0.025 to 20.0µg/mL (LLOQ 0.025µg/mL).

The validation and performance of the plasma assay for sparfloxacin was acceptable.

Clarithromycin concentrations in plasma were determined by an HPLC-UV method. The assay was validated over a linear range from 0.05 to 5.0µg/mL (LLOQ 0.05µg/mL).

The validation and performance of the plasma assay for clarithromycin was acceptable.

DATA ANALYSIS AND STATISTICAL METHODS:

Pharmacokinetics (PK)

Plasma drug concentrations at the average T_{max} were determined for gatifloxacin, ciprofloxacin, sparfloxacin, and clarithromycin (i.e., C_{max}).

Pharmacodynamics (PD)

ECG intervals were determined by trained technicians at _____ using the _____ ECG measurement system. This system utilizes a _____

_____, is translated into milliseconds and is automatically entered into a database. The _____ was calibrated for accuracy prior to each session by measuring a series of 200msec blocks from the background ECG paper grid and was found to be accurate to within ± 3 msec.

The onset of the QRS complex and the end of the T wave were identified to define the QT interval. R-R duration was similarly determined selecting the peak of 2 consecutive R waves. The presence of abnormal T or U waves in each ECG recording was determined by a single, board-certified cardiologist. Manual digitization of up to 3 beats, usually from Lead II, was performed using the _____

Measurements of the following intervals were reported for each ECG tracing:

- Three (3) PR \rightarrow mean PR Interval
- Three (3) QRS \rightarrow mean QRS Width
- Three (3) R-R \rightarrow mean R-R Interval
- Three (3) QT \rightarrow mean QT Interval
- Three (3) QTc \rightarrow mean QTc Interval

QTc values were calculated for each of 3 sets of R-R/QT measurements using Bazett's (B) and Fridericia's (F) heart rate correction formulae, i.e., $QTcB = QT/\sqrt{R-R}$ and $QTcF = QT/\sqrt[3]{R-R}$. The mean QTc equaled the sum of the 3 QTc measurements divided by 3.

A routine quality control program for the ECG interval measurement data was implemented by _____

PK/PD Analyses

The PD parameters for this study were defined as follows:

- *Delta QTc Avg (0-6)* = the change from baseline (Day -1 outcome) in time-averaged QTc during the first 6 hours after dosing on Day 1, i.e., the area under the QTc curve from 0 (predose) to 6 hr after dosing, divided by 6 hr.
- *Delta QTc Avg (0-12)* = the change from baseline (Day -1 outcome) in the time-averaged QTc during the first 12 hours after dosing on Day 1, i.e., the area under the QTc curve from 0 (predose) to 12 hr after dosing, divided by 12 hr.
- *Delta QTc Max* = the change from baseline (Day -1 outcome) in the longest QTc recorded after dosing on Day 1.
- *Delta QTc at Tmax* = the change from baseline (Day -1 outcome) in the QTc recorded at 2 hrs, the average time of peak gatifloxacin, ciprofloxacin, and clarithromycin concentrations on Day 1, and at 4 hrs, the average time of peak sparfloxacin concentrations on Day 1.

Five different baseline values were determined in each treatment period:

- 1) *Baseline QTc Avg(0-6)* = the time averaged QTc during the 6 hours on Day -1, i.e., the area under the QTc curve over 6 hours on Day -1, divided by 6 hours.

- 2) *Baseline QTc Avg(0-12)* = the time averaged QTc during the 12 hours on Day -1, i.e., the area under the QTc curve over 12 hours on Day -1, divided by 12 hours.
- 3) *Baseline QTc Max* = the QTc recorded on Day -1 at the time corresponding to the time of longest QTc recorded on Day 1.
- 4) *Baseline QTc at Tmax* = the QTc recorded on Day -1 at the expected/average Tmax for gatifloxacin, ciprofloxacin, and clarithromycin (i.e., 2 hr), and for sparfloxacin (i.e., 4 hr).
- 5) *QTc at 0 hr* = the mean of the QTc intervals recorded just prior to drug dosing on Day 1 and at the corresponding time 24 hours earlier on Day -1.

Baselines (1) and (5) were used in the analyses of the QTc Avg(0-6). Baselines (2) and (5) were used in the analyses of the QTc Avg (0-12). Baselines (1), (2), (3), (4), and (5) were used in the analyses of QTc Max and QTc at Tmax.

Analyses of covariance (ANCOVA) were performed to assess the effects of treatments on the changes from baseline in each of the above outcome measures. Factors in the analysis of variance were sequence, gender, sequence by gender, subject within sequence-by-gender, period, treatment, and gender by treatment interaction. The corresponding baseline QTc outcome was included as a covariate. The adjusted mean changes from baseline, based on the above model, were summarized by treatment for each of the derived QTc outcome measures.

The changes in each of the derived QTc outcome measures from the corresponding baseline values were summarized by treatment. Additionally, each of the derived QTc outcome measures was cross-tabulated against baseline, for each treatment. For males, QTc values were grouped as QTc <430msec, 430msec ≤ QTc ≤ 450msec, or QTc >450msec. For females, QTc outcome values were grouped as QTc <450msec, 450msec ≤ QTc ≤ 470msec, or QTc >470msec. Additionally, the values of changes in QTc Max from baseline were also tabulated as ΔQTc Max < 30 msec, 30 msec ≤ ΔQTc Max ≤ 60 msec, or ΔQTc Max > 60 msec.

Reviewer Comments:

These cross-tabulations were consistent with the previously published 1997 CPMP/EMEA Points to Consider document entitled, "The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products".

The cross-tabulations were to be presented by gender and age group, but due to the small numbers of subjects in the older age group (i.e., N=1), they are only presented by gender.

All subjects who received any study drug were included in the safety data sets and pharmacodynamic data listings. Only those subjects who had QTc data available in at least two Treatment Periods with gatifloxacin as one of the treatments were included in the statistical analysis.

RESULTS:

A total of 40 subjects entered the study and 39 subjects completed all 4 Treatment Periods. One subject discontinued from the study prior to completing all 4 Treatment Periods after having received gatifloxacin 800mg and clarithromycin 1000 mg. The table below provides a summary of subject demographics, by treatment, for which PK and QTc data was obtained.

Subject Demographics by Treatment for PK and QTc Data

Single Dose	N	M / F	≥65 Years
800mg Gatifloxacin	40	20 M 20 F	1 M (70 yr.) 0 F
1000mg Ciprofloxacin	39	20 M 19 F	1 M (70 yr.) 0 F

400mg Sparfloxacin	39	20 M 19 F	1 M (70 yr.) 0 F
1000mg Clarithromycin	40	20 M 20 F	1 M (70 yr.) 0 F

Reviewer Comment: Note that in the table above, there was only 1 elderly male subject and no female subjects evaluated for PK and QTc. Because of the small numbers, no conclusions can be made regarding the effects of gatifloxacin or the comparators on the QT / QTc interval in elderly subjects.

Pharmacokinetics

The plasma concentrations of gatifloxacin and the comparators at the expected Tmax following single dose administration of each drug are presented in the table below.

Plasma Drug Concentrations at Expected Tmax following Single Dose Oral Administration to Healthy Subjects; Data Expressed as Mean (%CV); [Min - Max]

Gatifloxacin 800mg at 2 hr (µg/mL)	Ciprofloxacin 1000mg at 2 hr (µg/mL)	Sparfloxacin 400mg at 4 hr (µg/mL)	Clarithromycin 1000mg at 2 hr (µg/mL)
6.5 (25%) [3.4-9.5]	4.1 (24%) [2.4-6.7]	1.2 (36%) [0.03-2.0]	3.4 (36%) [1.5-7.1]

The mean and range of gatifloxacin plasma concentrations at 2 hrs following 800mg were similar to that observed in the previously reviewed **Study AI420-092** (see above). It is noteworthy to mention that the mean and range of plasma concentrations for sparfloxacin at the expected Tmax are much lower than for the other antibiotic drugs.

Pharmacodynamics

Summaries of the statistical results are presented in the tables below for each derived QTc parameter and the change in each QTc parameter from the respective baselines.

Reviewer Comment: The sponsor focused on the QTc Avg(0-6) as the primary QTc parameter. While this was acceptable, it is the opinion of the reviewer that the QTc Avg(0-12) is equally important, since although both are time-averaged parameters, the QTc Avg(0-12) may represent a more robust time-averaged parameter, especially if the QTc exhibits diurnal variability greater than over a 6-hour time period. Thus, the reviewer will place greater emphasis on the QTc Avg(0-12) than the QTc Avg(0-6).

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1. QTc Values

Summary Statistics for QTc Parameters following Single Oral Dose Administration to Healthy Subjects; Data Expressed as Mean (SD); Min, Max

	Gatifloxacin 800mg	Ciprofloxacin 1000mg	Sparfloxacin 400mg	Clarithromycin 1000mg
QTc Avg(0-6) (msec)	397 (20) 358, 444	388 (19) 353, 426	397 (21) 359, 437	394 (16) 362, 428
QTc Avg(0-12) (msec)	396 (21) 356, 439	388 (17) 356, 426	398 (19) 361, 437	393 (16) 359, 428
QTc at Tmax (msec)	399 (25) 345, 445	385 (23) 332, 436	402 (25) 342, 447	388 (19) 350, 429
QTc Max (msec)	418 (23) 376, 461	407 (19) 364, 456	417 (19) 382, 453	415 (19) 372, 447

These results show overall similarities in the mean and ranges of the values for QTc Avg(0-6), QTc Avg(0-12), and QTc at Tmax between gatifloxacin and the other antibiotics. The mean and ranges of the QTc Avg(0-6) and QTc Avg(0-12) values were nearly identical across all drug treatments. With all of these three QTc parameters, there were no QTc values greater than 450 msec. The mean and ranges of QTc Max values were also relatively similar between gatifloxacin and the other antibiotics, but there were QTc Max values greater than 450 msec for gatifloxacin at 800mg (i.e., 461 msec), ciprofloxacin at 1000mg (i.e., 456 msec), and sparfloxacin at 400mg (i.e., 453 msec). All QTc Max values for clarithromycin at 1000mg were less than 450 msec.

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2. Change in QTc (Δ QTc) from Baseline (Day -1)

Summary Statistics for Δ QTc Parameters following Single Oral Dose Administration to Healthy Subjects

	Gatifloxacin 800 mg	Ciprofloxacin 1000 mg	Sparfloxacin 400 mg	Clarithromycin 1000 mg
	ΔQTc Avg(0-12) from Day -1 QTc Avg(0-12)			
Mean (Min, Max)	12.7 (-1.2, 28.9)	4.2 (-7.2, 18.3)	13.7 (-14.9, 31.6)	10.3 (-5.0, 30.0)
Difference (95% CI) from Gatifloxacin	--	-8.4 (-11.4, -5.3)	1.1 (-1.95, 4.1)	-2.6 (-5.6, 0.38)
p-Value	--	<0.001	0.48	0.09
	ΔQTc at Tmax from Day -1 QTc at Tmax			
Mean (Min, Max)	14.7 (-35.0, 42.0)	0.15 (-30.0, 42.0)	14.3 (-21.0, 47.0)	4.2 (-30.0, 28.0)
Difference (95% CI) from Gatifloxacin	--	-14.2 (-20.3, -8.1)	1.1 (-5.0, 7.2)	-10.8 (-16.8, -4.7)
p-Value	--	<0.001	0.73	0.001
	ΔQTc Max from Day -1 QTc Max			
Mean (Min, Max)	34.2 (6.0, 71.0)	23.7 (-13.0, 74.0)	27.7 (-21.0, 60.0)	33.2 (-12.0, 75.0)
Difference (95% CI) from Gatifloxacin	--	-10.5 (-15.7, -5.4)	-3.0 (-8.2, 2.3)	-3.1 (-8.2, 2.0)
p-Value	--	<0.001	0.26	0.23

For Δ QTc Avg(0-12) and Δ QTc Max, administration of a single oral 800mg dose of gatifloxacin resulted in similar changes compared to the administration of single oral doses of sparfloxacin 400mg and clarithromycin 1000mg. The differences in these two Δ QTc parameters were not statistically significant for either sparfloxacin or clarithromycin vs. gatifloxacin. The Δ QTc at Tmax for both clarithromycin and sparfloxacin was significantly less as compared to gatifloxacin at 800mg, but was not significantly different for sparfloxacin vs. gatifloxacin. Single oral dose administration of ciprofloxacin 1000mg had the least effect on all Δ QTc parameters and the differences in these Δ QTc parameters were significantly lower compared to the single oral 800mg dose of gatifloxacin.

Reviewer's Notes / Comments:

The values for the Δ QTc parameters derived in this study for gatifloxacin at 800mg were similar to those reported for the same dose from the previously reviewed Study AI420-092 (see above).

The Δ QTc Avg(0-12) and Δ QTc at Tmax values for sparfloxacin from this study are generally similar to Δ QTc values that have been previously reported in the literature at the same sparfloxacin dose. These relatively substantial changes in QTc occur despite the achievement of relatively low plasma sparfloxacin concentrations following a single 400mg oral dose, which suggests greater potency of sparfloxacin to prolong the QTc interval.

3. Exposure – Response Relationships

In general, there were no discernable relationships between any of the Δ QTc parameters and plasma concentrations for any of the drug treatments, including gatifloxacin. Because of this, the plots of these relationships are not shown in this review.

4. Outlier Analyses

QTc values and changes in QTc from baseline were categorized by the sponsor according to criteria published by the EMEA/CPMP Points to Consider document. These criteria are summarized below.

Categories for Absolute QTc Values

Classification	QTc Interval for Males (msec)	QTc Interval for Females (msec)
Normal	<430	<450
Borderline	430 to 450	450 to 470
Prolonged	>450	>470

Risk Categories for Changes in QTc from Baseline

Risk Classification for Drug to Induce Arrhythmia, Including <i>Torsades de Pointes</i>	Δ QTc (msec)
Unlikely – Non-Significant/Minimal Clinical Concern	<30
Likely – Moderate Clinical Concern	30 to 60
Highly Likely – Significant/High Clinical Concern	>60

The sponsor chose to use the QTc Max for the outlier analyses since this parameter represents the worst case scenario. The results for absolute QTc Max values and for Δ QTc Max in male and female subjects are shown in the tables below.

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QTc MAX FOR MALES

Treatment	Pre-Dose	Post-Dose QTc MAX		
		<430 (msec)	>430 - <450 (msec)	>450 (msec)
Gatifloxacin 800 mg	<430 msec	16	4	0
	430-450 msec	0	0	0
	>450 msec	0	0	0
Ciprofloxacin 1000 mg	<430 msec	19	0	1
	430-450 msec	0	0	0
	>450 msec	0	0	0
Sparfloxacin 400 mg	<430 msec	16	3	0
	430-450 msec	0	1	0
	>450 msec	0	0	0
Clarithromycin 1000 mg	<430 msec	17	2	0
	430-450 msec	1	0	0
	>450 msec	0	0	0

QTc MAX FOR FEMALES

Treatment	Pre-Dose	Post-Dose QTc MAX		
		<450 (msec)	>450 - <470 (msec)	>470 (msec)
Gatifloxacin 800 mg	<450 msec	16	4	0
	450-470 msec	0	0	0
	>470 msec	0	0	0
Ciprofloxacin 1000 mg	<450 msec	18	1	0
	450-470 msec	0	0	0
	>470 msec	0	0	0
Sparfloxacin 400 mg	<450 msec	18	1	0
	450-470 msec	0	0	0
	>470 msec	0	0	0
Clarithromycin 1000 mg	<450 msec	20	0	0
	450-470 msec	0	0	0
	>470 msec	0	0	0

FREQUENCY DISTRIBUTION for ΔQTc MAX (USING DAY -1 QTc Avg(0-12) as BASELINE)

Treatment	Males			Females		
	< 30 (msec)	30-60 (msec)	> 60 (msec)	< 30 (msec)	30-60 (msec)	> 60 (msec)
Gatifloxacin 800 mg	11	9	0	5	15	0
Ciprofloxacin 1000 mg	17	3	0	18	1	0
Sparfloxacin 400 mg	6	14 ^b	0	9	9	1
Clarithromycin 1000 mg	14	5	1	9	8	3

^a one subject was ≥ 65 years old

The table of QTc Max values for males and females showed that the majority of subjects had QTc Max values <430 msec (males) or <450 msec (females) for all drugs; 1/20 males with Maximum QTc value >450 msec after single dose ciprofloxacin 1000mg. No subjects with QTc \geq 500 msec.

For the frequency distribution of Δ QTc Max, the majority of subjects had Maximum Δ QTc <30 msec after single oral doses of gatifloxacin, ciprofloxacin, and clarithromycin. There were no subjects with Maximum Δ QTc >60 msec at single oral doses of gatifloxacin and ciprofloxacin. Maximum Δ QTc >60 msec was observed in 1/19 and 3/20 females with sparfloxacin and clarithromycin, respectively and in 1/20 males with sparfloxacin. There were a greater number of subjects with Maximum Δ QTc between 30 to 60 msec with gatifloxacin, sparfloxacin, and clarithromycin vs. ciprofloxacin.

Reviewer Assessment of Time to Maximum QTc (QTc Max) vs. Time to Drug Cmax (i.e., Tmax)

This assessment was performed by the reviewer to evaluate whether the time of occurrence of the maximum QTc interval and the change in QTc Max from baseline coincided with the median plasma Tmax of gatifloxacin and the comparators. It has generally been assumed that the greatest change in the QTc would occur at time of Cmax (i.e., Tmax) for the fluoroquinolones and other non-cardiovascular drugs that prolong the QT interval. The table below summarizes the results.

Drug Plasma Tmax vs. Time to QTc Max and Time to Δ QTc Max

	Median Tmax (hr)* (Range)	Median Time to QTc Max (hr) (Min, Max)	Median Time to Δ QTc Max (hr) (Min, Max)
800mg Gatifloxacin	2.0	3.5 (0, 12)	3.0 (0, 12)
1000mg Ciprofloxacin	1.0 to 2.0	5.0 (0, 12)	5.0 (0.5, 12)
400mg Sparfloxacin	4.0 (3.0 to 6.0)	4.0 (0, 12)	3.0 (1.5, 12)
1000mg Clarithromycin	2.0	4.0 (0, 12)	4.0 (1.0, 12)

*Values as reported in approved labeling

This data shows that the median times to QTc Max and to Δ QTc Max were relatively similar to the median plasma Tmax values determined for gatifloxacin and sparfloxacin. There appeared to be a greater difference between the occurrence of the QTc Max parameters and the plasma Cmax for ciprofloxacin and clarithromycin. The ranges for the QTc Max parameters were wide, which lends support to the high degree of time variability that is observed in QTc.

Reviewer Comments:

This analysis is very limited and the results should be interpreted with caution.

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REVIWER CONCLUSIONS:

- The following multiples of the recommended clinical unit dose (oral) were employed in this study:
 - Gatifloxacin 800mg Single Dose = 2X (Clinical Dose 400mg)
 - Ciprofloxacin 1000mg Single Dose = 1.3X to 2X (Clinical Dose 500mg to 750mg)
 - Sparfloxacin 400mg Single Dose = Recommended Loading Dose; 2X Clinical Maintenance Dose
 - Clarithromycin 1000mg Single Dose = 2X to 4X (Clinical Dose 250mg to 500mg)
- For the Δ QTc parameters - Δ QTc at Cmax, Maximum Δ QTc, and Average Δ QTc(0-12) - administration of a single oral 800mg dose of gatifloxacin resulted in similar changes compared to administration of single oral doses of sparfloxacin 400mg and clarithromycin 1000mg.
 - **Δ QTc at Cmax and Average Δ QTc(0-12) values (mean (overall range)):**
Gatifloxacin 800mg → 12 to 15 (-18, 40) msec
Sparfloxacin 400mg → 14 to 18 (-18, 51) msec
Clarithromycin 1000mg → 5 to 10 (-16, 30) msec
 - **Maximum Δ QTc values (mean (range)):**
Gatifloxacin 800mg → 34 (23, 60) msec
Sparfloxacin 400mg → 33 (-1, 67) msec
Clarithromycin 1000mg → 32 (6, 88) msec
- Single oral dose administration of ciprofloxacin 1000mg had the least effect on Δ QTc parameters and the changes were significantly lower compared to single oral 800mg dose of gatifloxacin:
 - **Δ QTc at Cmax and Average Δ QTc(0-12) values (mean (overall range)):**
Gatifloxacin 800mg → 12 to 15 (-18, 40) msec
Ciprofloxacin 1000mg → 0.5 to 4 (-26, 29) msec
 - **Maximum Δ QTc values (mean (range)):**
Gatifloxacin 800mg → 34 (23, 60) msec
Ciprofloxacin 1000mg → 23 (6, 62) msec
- The majority of subjects had Maximum Δ QTc <30 msec after single oral doses of gatifloxacin, ciprofloxacin, and clarithromycin. No subjects with Maximum Δ QTc >60 msec at single oral doses of gatifloxacin and ciprofloxacin; 1/19 and 3/20 females with sparfloxacin and clarithromycin, respectively; 1/19 males with sparfloxacin had Maximum Δ QTc >60 msec. There were a greater number of subjects with Maximum Δ QTc between 30 to 60 msec with gatifloxacin, sparfloxacin, and clarithromycin vs. ciprofloxacin.
- The majority of subjects had Maximum QTc values <430 msec (males) or <450 msec (females) for all drugs; 1/20 males with Maximum QTc value >450 msec after single dose ciprofloxacin 1000mg. No subjects with QTc ≥500 msec.
- There was limited QTc data from elderly subjects (N = 1 male ≥65 years), and therefore, no conclusions can be made regarding the effects of gatifloxacin, ciprofloxacin, sparfloxacin, and clarithromycin on the QT / QTc interval in elderly subjects.
- Overall, Δ QTc and QTc parameters appeared to be most similar following a single oral clinical dose of gatifloxacin 400mg (**Study 092**) and a single oral dose of ciprofloxacin 1000mg (**Study 093**).

3. **Study AI420-095: AN OPEN LABEL, MULTICENTER, NONCOMPARATIVE, PHASE IV STUDY OF ORAL GATIFLOXACIN IN THE TREATMENT OF COMMUNITY ACQUIRED RESPIRATORY INFECTIONS – ANALYSIS OF EFFECTS ON THE QT INTERVAL OF THE ECG**

Study Dates: July 2000 – September 2000

Vol. 9; pp. 1-115

OBJECTIVES:

Primary: To evaluate the effect of a single oral dose of gatifloxacin on the QTc interval.

Secondary: To evaluate the clinical efficacy and safety of gatifloxacin at an oral dose of 400 mg QD for acute exacerbation of chronic bronchitis (AECB), community acquired pneumonia (CAP), and acute uncomplicated maxillary sinusitis (ABS). To assess bacteriologic efficacy of oral gatifloxacin at a dose of 400-mg QD in the treatment of community acquired respiratory tract infections.

NOTE: This review will focus only on the primary objective.

FORMULATIONS/TREATMENTS:

Gatifloxacin Tablets 400mg (TEQUIN®); Lot #9M15940

PATIENTS:

264 adult male and female patients with community acquired respiratory tract infections. The table below provides demographic details.

PATIENT DEMOGRAPHICS

	Total Enrolled = 264 Total Evaluated = 262*
	N (%)
Male	92 (35)
Female	172 (65)
Mean Age (Range)	42 years (18 to 90)
≤ 65 years	241 (91)
> 65 years	23 (9)
Sinusitis (ABS)	240 (91)
AECB	16 (6)
CAP	8 (3)

***NOTE:** 10 patients stratified into "High Risk" group – 1 with hypokalemia (not defined); 9 receiving concomitant medications recognized to prolong QT interval, i.e., tricyclic antidepressants (N=3), antihistamines (N=5), azole antifungal (N=1).

STUDY DESIGN AND METHODS:

Open label, non-comparative, multicenter study design. All patients received oral gatifloxacin 400mg QD (1 TEQUIN® tablet) for 7 to 14 days, depending on the indication. The following ECG and PK procedures were followed:

Day 1 (1st Day of Dosing):

"Baseline" 12-lead ECG @ 30 minutes prior to 1st dose

12-lead ECG @ 2 hours following 1st TEQUIN® dose

PK sample for determination of gatifloxacin plasma concentration @ 2 hours post-dose, immediately after the 2nd 12-lead ECG

If the post-dose QTc was greater than 500 msec, the patient was to discontinue study drug. QTc readings of less than 500 msec but greater than 450 msec for males or 470 msec for females or a change in QTc of greater than 60 msec required the subject to return for an ECG on **Day 3** of the study. In addition, patients were to be **excluded** if they met one of the following cardiac-related conditions:

- History of QTc intervals > 450 msec for males or > 470 msec for females (or > 500 msec for subjects with left bundle branch block)
- History of prolonged QT interval
- Receiving class IA or class III antiarrhythmic agents
- History of *Torsades de Pointes*

Sites were provided with automated ECG equipment and accessories for the generation of an electronic ECG that was submitted via modem to a central ECG laboratory - _____ where they were manually read by a cardiologist. A corrected QT interval was calculated using Bazett's formula:

$$QTc = QT \text{ (actual)} / \sqrt{RR \text{ interval}}$$

ANALYTICAL METHODS:

Gatifloxacin concentrations in plasma were determined by an HPLC-UV method. The assay was validated over a linear range from 0.01 to 5.0 µg/mL (LLOQ 0.01 µg/mL).

The validation and performance of the plasma assay for gatifloxacin was acceptable.

DATA ANALYSIS AND STATISTICAL METHODS:

Analyses of the QTc interval were performed using data from subjects who had both a pre- and post-dose QTc value and a plasma concentration that corresponded to the post-dose ECG reading.

Change from pre-dose QTc interval to post-dose QTc (i.e., $\Delta QTc = \text{post} - \text{pre}$) was computed for each subject and summary statistics presented. Mean change in QTc was estimated using a 95% confidence interval (assuming a normal distribution).

Pre- and post-dose QTc intervals were cross-tabulated for all treated subjects with paired ECG readings. As per the EMEA/CPMP Points to Consider document, the QTc intervals were classified into three categories - Normal, Borderline, and Prolonged - and were defined according to gender as follows:

Categories for Absolute QTc Values

Classification	QTc Interval (msec)	
	Male	Female
Normal	< 430	< 450
Borderline	430 - 450	450 - 470
Prolonged	> 450	> 470

In addition, the frequency of QTc changes (i.e., Δ QTc) were tabulated and classified, as per the EMEA/CPMP Points to Consider, document by pre-dose QTc category as follows:

Risk Categories for Changes in QTc from Baseline

Risk Classification for Drug to Induce Arrhythmia, Including <i>Torsades de Pointes</i>	Δ QTc (msec)
Unlikely – Non-Significant/Minimal Clinical Concern	<30
Likely – Moderate Clinical Concern	30 to 60
Highly Likely – Significant/High Clinical Concern	>60

Analyses were also performed by gender, age group (≤ 65 years and > 65 years) and risk group. Patients with hypokalemia or who used medications associated with QT prolongation were considered "High Risk". All other patients were considered "Low Risk".

The relationship between Δ QTc vs. plasma gatifloxacin concentration at 2 hr postdose was examined using linear regression analysis.

RESULTS:

PK and QTc data were obtained from 262 of the 264 patients enrolled in to this study and the results are provided in the tables below.

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1. QTc Assessments

QTc SUMMARY

Statistic	QTc Interval (msec) N = 262		
	Pre-Dose	Post-Dose	Change
Mean	396.7	405.8	9.1
Std Deviation	23.4	26.8	18.6
95% CI			(6.9, 11.4)
Minimum	313	305	-47
25th Percentile	380	389	-3
Median	399	406	10
75th Percentile	414	425	22
Maximum	456	471	63

QTc SUMMARY BY GENDER, AGE AND RISK

		N	Mean QTc (msec)		
			Pre-Dose	Post-Dose	Change
Gender	Male	91	384.3	391.0	6.7
	Female	171	403.2	413.7	10.4
Age (yr.)	≤ 65	241	395.0	404.4	9.4
	> 65	21	415.4	422.0	6.5
Risk	Low	252	396.4	405.5	9.1
	High	10	402.9	412.5	9.6

POST DOSE QTc DISTRIBUTION BY GENDER, AGE, AND RISK

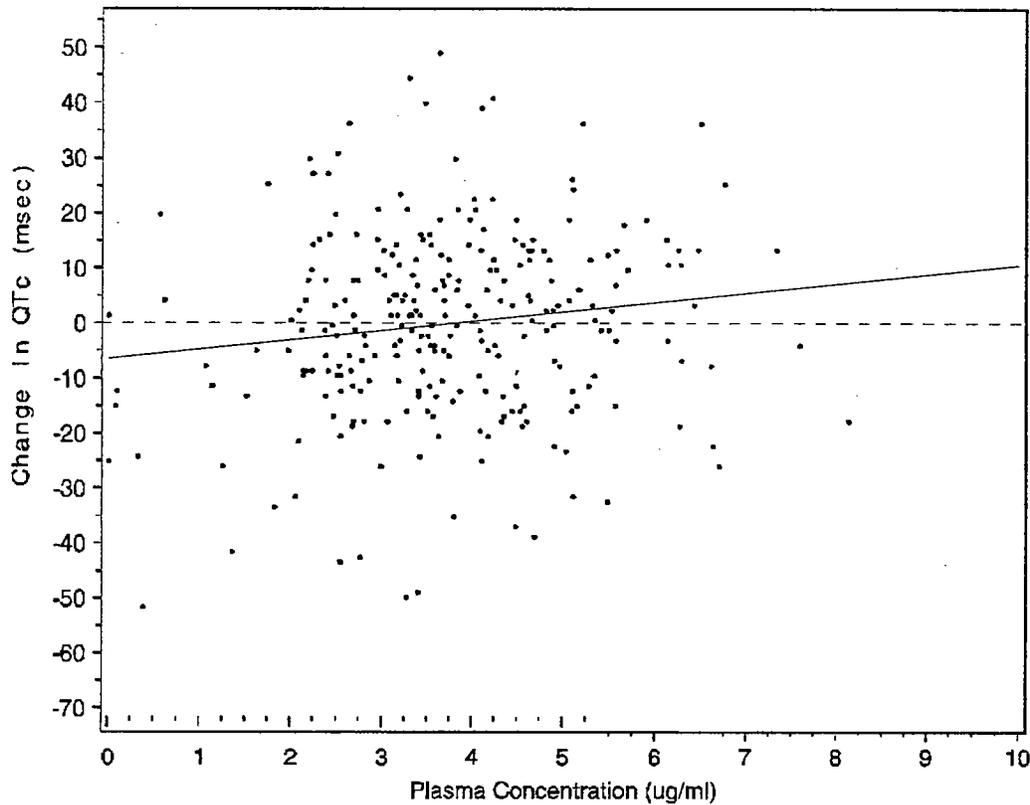
		N	N (%)		
			Normal <430 males <450 females	Borderline 430-450 msec males 450-470 msec females	Prolonged >450 males >470 females
Gender	Male	91	82 (90)	6 (7)	3 (3)
	Female	171	162 (95)	9 (5)	0
Age (yrs)	≤ 65	241	229 (95)	11 (5)	1 (<1)
	> 65	21	15 (71)	4 (19)	2 (10)
Risk	Low	252	234 (93)	15 (6)	3 (1)
	High	10	10 (100)	0	0

ΔQTc FREQUENCIES BY AGE, GENDER, AND RISK

		N	ΔQTc (msec)* N (%)			
			< 0	0 to 30	31 to 60	> 60
Gender	Male	91	31 (34)	48 (53)	12 (13)	0
	Female	171	44 (26)	113 (66)	13 (8)	1 (<1)
Age (yr.)	≤ 65	241	67 (28)	152 (63)	21 (9)	1 (<1)
	> 65	21	8 (38)	9 (43)	4 (19)	0
Risk	Low	252	72 (29)	154 (61)	25 (10)	1 (<1)
	High	10	3 (30)	7 (70)	0	0

*ΔQTc = Pre Dose QTc – Post Dose QTc

2. Assessment of Δ QTc vs. Plasma Gatifloxacin Concentration at 2 hr Postdose – Linear Regression Analysis



Solid Line = Estimated Regression Line with Slope 2.6 msec/ μ g/mL (95% CI: 1.0, 4.2)

The sponsor incorporated a term for the interaction between pre-dose QTc and concentration into the regression model. As shown in the table below, this resulted in a significant interaction effect.

Results of Regression Model of Δ QTc on Concentration and Pre-Dose QTc including Interaction Term

Factor	Slope Estimate	95% CI	p-value
Concentration ¹	2.7	(1.1, 4.3)	0.001
Pre-Dose QTc x Concentration ²	-0.8	(-1.5, -0.1)	0.02

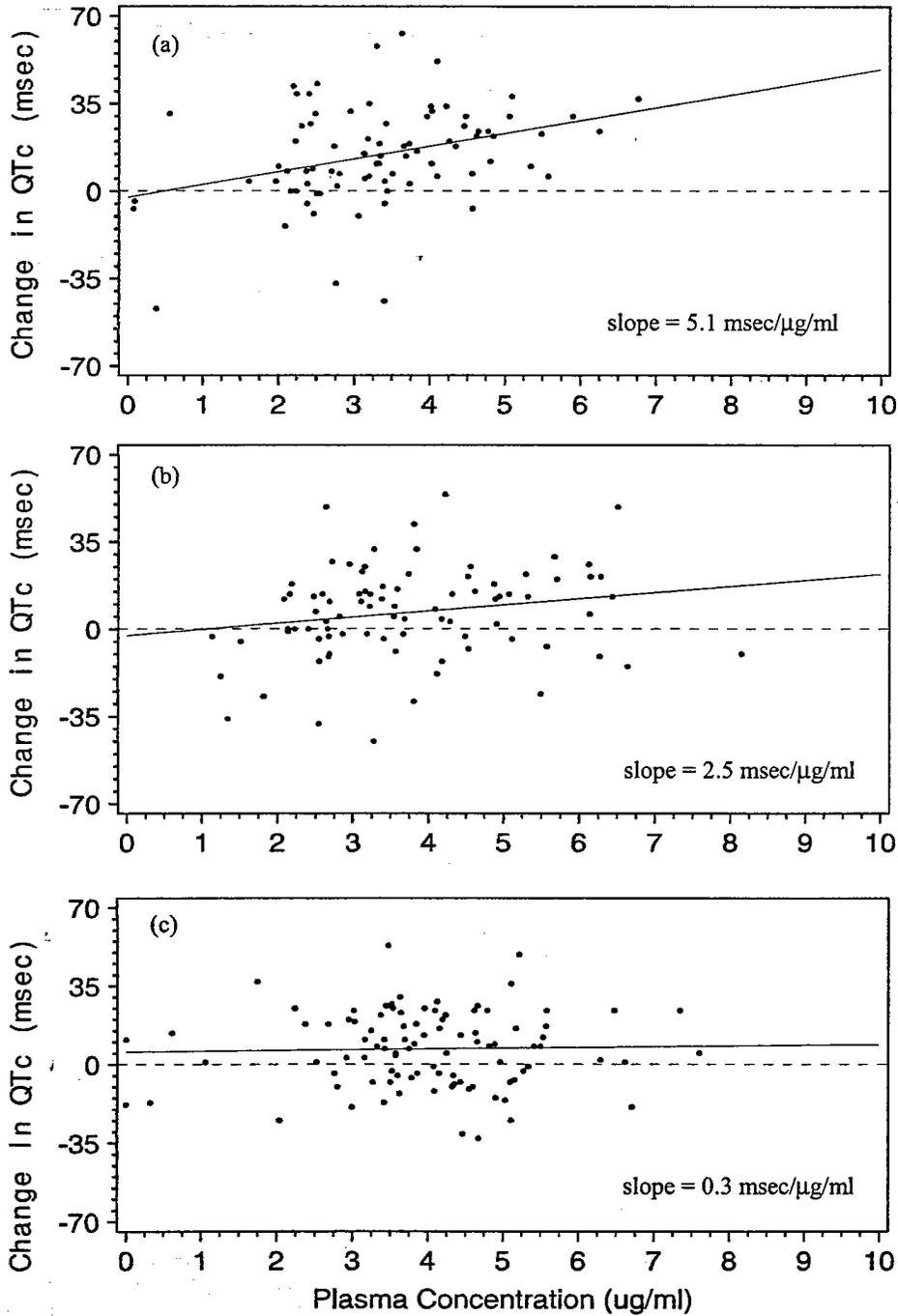
¹ Mean msec change in QTc per μ g/ml of plasma concentration at mean pre-dose (397 msec).

² Change in concentration slope for each 10 msec change in pre-dose QTc.

The impact of this interaction is that the concentration effect on change in QTc appeared to be **strongest at low pre-dose QTc and minimal at high pre-dose QTc**. This interaction effect was illustrated by the sponsor by sub-setting the data according to pre-dose QTc and performing regressions in these sub-groups, as shown in the 3 figures below.

Linear Regression Analysis of Change in QTc on Gatifloxacin Plasma Concentration Subsetted by Pre-dose QTc

Data were divided into three equally sized groups based on pre-dose QTc: (a) ≤ 385 msec, (b) >385 and ≤ 405 msec, (c) >405 msec. Dashed line represents zero change; solid line = estimated regression line.



REVIEWER SUMMARY OF RESULTS / CONCLUSIONS:

- Overall, the mean change between pre dose and post dose QTc at 2 hours after the first oral gatifloxacin dose of 400mg to 262 patients with respiratory tract infections (RTI) was 9 msec (95% CI: 6.9, 11.4). The median increase in QTc at 2 hours post gatifloxacin was similar at 10 msec, with 25% of the patients experiencing a QTc increase of 22 msec or greater.
- There was no apparent trend for greater prolongation of QTc by gatifloxacin in those patients >65 years of age vs. patients ≤65 years, in those patients classified as “high risk” for QTc prolongation (i.e., hypokalemia; concomitant medications known to prolong QT interval) vs. patients with “low risk”, nor in females vs. males.
- No patients had a pre or post dose QTc interval ≥500msec. The majority of patients had post dose QTc changes considered to be without clinical concern for males (<430 msec) and females (<450 msec). Few patients (≤10%) had post dose QTc changes that were considered to be prolonged and/or potentially significant for males (>450 msec, N=3) and females (>470 msec, N=0).
- The majority of patients also had post dose QTc changes of 30 msec or less. Approximately 10% of patients had ΔQTc of 30 to 60 msec and very few (<1%) of patients had changes >60 msec.
- There was an apparent linear relationship between ΔQTc (i.e., QTc at 30 minutes pre dose – QTc at 2 hours post dose) and plasma concentrations of gatifloxacin at 2 hours post dose, with the slope estimated at 2.6 msec/μg/mL (95% CI: 1.0, 4.2).
 - This relationship and slope in patients with RTI were similar to that determined from the single dose escalation study of healthy volunteers (**Study AI420-092**) and suggested similar QT responsiveness between healthy subjects and patients with RTI.
 - The upper range of plasma gatifloxacin concentrations at 2 hours post dose from this study, i.e., up to approximately 8 μg/mL, was consistent with the range of concentrations in healthy subjects following single oral doses of 400mg to 800mg (i.e., approximately 3 to 10 μg/mL, **Study AI420-092**).
 - A statistically significant (pre dose QTc x plasma concentration) interaction was detected in the regression model. The impact of this interaction was demonstrated as the effect of plasma concentrations tended to be *strongest* at low pre dose QTc values (i.e., at ≤385 msec, slope = 5.1 msec/μg/mL) and *weakest* at high pre dose QTc values (i.e., at >405 msec, slope = 0.3 msec/μg/mL). This regression to the mean effect suggested that patients with low “baseline” QTc intervals would experience the greatest prolongation, whereas those patients with high “baseline” QTc intervals may be at lower risk of further QTc prolongation by gatifloxacin.
- It should be noted that there were several limitations with this study and included the following:
 - There was no control group (active or placebo) employed
 - Only a single pre dose QTc (“baseline”) and a single post dose QTc were determined
 - The time of day for dosing was not strictly controlled
 - There was a relatively small number of elderly patients evaluated (N=21/262 – 8%)

4. **Study CV 123-229: PRAVASTATIN OR ATORVASTATIN EVALUATION AND INFECTION THERAPY (PROVE IT): ECG SUB-STUDY OF GATIFLOXACIN EFFECTS ON THE QTc INTERVAL**

Study Dates: 11/20/2000 – 6/6/2001

OBJECTIVES:

The primary objective of this ECG substudy was to demonstrate the clinical equivalence of the acute effect of gatifloxacin vs. placebo on the QTc interval on the first day of dosing of gatifloxacin or placebo (**Day 15**), where clinical equivalence was defined as a change from baseline in QTc between gatifloxacin and placebo of not more than 6 msec.

The secondary objective was to assess the steady-state effect, in the first 100 subjects, of gatifloxacin on the QTc interval on the 6th day of dosing of gatifloxacin or placebo (**Day 20**) compared with baseline on **Day 15**.

Tertiary objectives were to assess the acute-on-chronic effect, in the first 100 subjects, of gatifloxacin on the QTc interval on **Day 20** compared with baseline on **Day 20** and to assess the relationship between the change from baseline in QTc interval and gatifloxacin plasma concentration in the gatifloxacin treatment group on **Day 15** and **Day 20**.

TREATMENTS/FORMULATIONS:

Gatifloxacin 400 mg Tablets (TEQUIN®)
Matching Gatifloxacin Placebo Tablets

PATIENTS:

760 male and female patients with a qualifying acute coronary syndrome (ACS) and a total cholesterol ≤ 240 mg/dL. The table below provides the demographic details.

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Demographic Characteristics of Randomized ECG Substudy Patients			
Characteristics	Treatment		
	Gatifloxacin N = 374	Placebo N = 386	Total N = 760
Age (years) Mean (SD) (Min, Max)	58 (11.3) (33, 84)	58 (11.1) (30, 89)	58 (11.2) (30, 89)
Age (years), n(%) Elderly (≥ 65) Non-Elderly (< 65)	107 (28.6%) 267 (71.4%)	112 (29.0%) 274 (71.0%)	219 (28.8%) 541 (71.2%)
Gender, ^e n (%) Male Female	295 (78.9%) 79 (21.1%)	288 (74.6%) 97 (25.1%)	583 (76.7%) 176 (23.2%)
Diabetes Mellitus, n (%)	85 (22.7%)	57 (14.8%)	142 (18.7%)
Qualifying Coronary Syndrome, n (%) Unstable angina pectoris (UAP) Acute myocardial infarction (AMI)	140 (37.4%) 233 (62.3%)	121 (31.3%) 264 (68.4%)	261 (34.3%) 497 (65.4%)
Antiarrhythmics, ^f n (%)	14 (3.7%)	11 (2.8%)	25 (3.3%)
Antihistamines, n (%)	93 (24.9%)	97 (25.1%)	190 (25.0%)
Antibiotics, ^g n (%)	17 (4.5%)	13 (3.4%)	30 (3.9%)
CNS Agents, ^h n (%)	27 (7.2%)	30 (7.8%)	57 (7.5%)

^e Reflects missing gender data in one subject

^f Class IA and Class III antiarrhythmics taken during the 2 weeks prior to the qualifying event

^g Fluoroquinolone and macrolide antibiotics taken during the 2 weeks prior to the qualifying event

^h Selective serotonin re-uptake inhibitor (SSRI) and tricyclic antidepressants taken during the 2 weeks prior to the qualifying event

The following **exclusion criteria** were pertinent to participation in the **ECG substudy**:

- QTc interval (Lead II) >450 msec or QTc >500 msec for subjects with intraventricular conduction delay (e.g., LBBB) using Bazett's formula for heart rate correction
- History of prolonged QT interval
- Current or anticipated need for treatment with Class IA or III antiarrhythmic agents (e.g., quinidine, procainamide, sotalol, amiodarone) or history of prior episode of *torsade de pointes*
- Uncorrected hypokalemia
- Renal insufficiency, defined as calculated creatinine clearance < 40 mL/min
- Treatment with any of the following agents (some of which are known to prolong the QTc interval) within the last month, or likelihood of requiring such treatment during the study period:
 - Oral or parenteral Corticosteroids
 - Immunosuppressive agents (e.g., Cyclosporine)
 - Estrogens, Progestogens and Androgens (except hormone replacement therapy)
 - Erythromycin or Clarithromycin

- Probenecid
- Orlistat
- Terfenadine
- Cisapride
- Antipsychotics
- Tricyclic Antidepressants
- Protease Inhibitors

- Atrial fibrillation (these subjects were excluded from participation in the **ECG substudy** although they were allowed into the **PROVE IT** trial)

STUDY DESIGN AND METHODS:

The **PROVE IT** trial is an international, multicenter, randomized, double-blind, 2x2 factorial, parallel group design trial comparing pravastatin vs. atorvastatin, and comparing gatifloxacin vs. placebo in patients with a total cholesterol \leq 240 mg/dL following an acute coronary syndrome (ACS). A total of 175 sites participated in the study under a uniform protocol: 6 in Australia, 13 in Canada, 1 in France, 1 in Germany, 1 in United Kingdom, and 153 in the United States. The **PROVE IT** trial is currently ongoing. Its primary objective is to address all-cause death or major cardiovascular events after a minimum treatment period of 18 months with pravastatin and gatifloxacin or placebo vs. atorvastatin and gatifloxacin or placebo.

This **ECG substudy** was designed to assess the effects of gatifloxacin on the QTc interval in patients with an ACS. The duration for the **ECG substudy** was 20 days. The first 500 randomized subjects in the **PROVE IT** trial were targeted for enrollment into the **ECG substudy**. Within 10 days of the onset of the qualifying ACS, subjects were randomized to the following treatments:

Day 1 – Treatment A:

Pravastatin 40 mg PO QD or Atorvastatin 80 mg PO QD (1:1 ratio)

Days 15 to 28 – Treatment B:

Statin QD + Gatifloxacin 400 mg QD x 14 Days or Statin QD + Placebo QD x 14 Days (1:1 ratio Gatifloxacin:Placebo)

The first dose of antibiotic/placebo treatment was administered at the **Day 15** visit. Subjects randomized to gatifloxacin or placebo received an initial 14-day course for the first month (with a month defined as 30 consecutive days) followed by a 10-day course every month for the duration of the **PROVE IT** trial.

The following procedures were employed for the **ECG substudy** (duration of 20 days):

Day 15 – 1st day of QD Treatment B Dosing:

- Baseline 12-lead ECG prior to 1st dose of study drug (pre-dose)
- 12-lead ECG at 2 hr postdose (median Tmax for Gatifloxacin)
- Plasma sample for measurement of gatifloxacin plasma concentration at 2 hr postdose (i.e., gatifloxacin Cmax)

Day 20 – 6th day of QD Treatment B Dosing

- First 100 ECG substudy participants were to have 12-lead ECG's at pre-dose (baseline) and at 2 hr postdose; plasma sample for measurement of gatifloxacin plasma concentration at 2 hr postdose

ECG Monitoring and Processing:

Standard paper 12-lead ECG's were collected at all participating sites and the QTc intervals were determined by a Central ECG Laboratory - The use of ECG machines with automated measurement capabilities (i.e., measurement of QT and calculation of corrected QT interval) was strongly encouraged. If an ECG machine with these capabilities was unavailable, then the QTc interval was to be manually calculated according to Bazett's formula:

$$QTc = QT(\text{actual}) / \sqrt{RR \text{ interval (seconds)}}$$

To standardize the ECG collection across sites, the following specifications were required:

- Generation of an original ECG and an original duplicate ECG at baseline and 2 hours following the administration of study drug.
- Paper speed set at 25 mm/second.
- Lead II rhythm strips at least 10 seconds in duration and each lead were to be identified by a lead label.
- Sensitivity selection at 10 mm/mV.
- A 1-mV rectangular calibration signal recorded on each 12-lead and lead II rhythm strip.
- Properly completed ECG label affixed to the upper margin of the original ECG tracing (provided by the Central ECG Lab).

On the days when ECG's were scheduled for the **ECG substudy**, patients were to refrain from morning exercise and caffeine, and whenever possible, the morning dose of all concomitant medications was held. The patient was instructed to remain in the supine position for five minutes with the leads on prior to the ECG recording and to refrain from moving during the ECG recording. **Treatment B study medication was to be administered within 1 hour after the baseline ECG. The 2-hr postdose ECG was to be recorded within 2-3 hours after the administration of study medication. The 2-hr postdose plasma sample was to be collected immediately (within 30 minutes) after the ECG was recorded.**

ANALYTICAL METHODS:

Gatifloxacin concentrations in plasma at 2 hr postdose were determined by an HPLC-UV method. The assay was validated over a linear range from 0.01 to 5.0µg/mL (LLOQ 0.01µg/mL).

The validation and performance of the plasma assay for gatifloxacin was acceptable.

DATA ANALYSIS AND STATISTICAL METHODS:

PK/PD Analyses

Regression analysis was used to assess the relationship between the change from baseline in QTc versus plasma concentration for the gatifloxacin treatment group only. These assessments occurred on **Day 15** to examine the acute effect of gatifloxacin dosing on QTc interval and on **Day 20** to examine the steady-state effect of gatifloxacin dosing on QTc interval. Change from baseline in QTc was the dependent variable in the regression model; plasma concentration and baseline QTc served as independent variables.

ECG Datasets:

Analyses of QTc included all randomized subjects with evaluable ECG's including at least one of the following pairs of ECG's:

- Both Day 15 post-dose and Day 15 baseline ECG's
- Both Day 20 post-dose and Day 15 baseline ECG's
- Both Day 20 post-dose and Day 20 baseline ECG's

The primary safety dataset consisted of the subjects with evaluable ECG's prior to dosing on **Day 15** and 2 hours post dosing on **Day 15**.

The secondary safety dataset consisted of the subjects with evaluable ECG's prior to dosing on **Day 15** and 2 hours post dosing on **Day 20**.

The tertiary safety dataset consisted of subjects with evaluable ECG's prior to dosing on **Day 20** and 2 hours post dosing on **Day 20**.

Changes from baseline were analyzed using an ANCOVA (analysis of covariance) model to compare gatifloxacin to placebo at 2 hours post-dose. The analysis model consisted of treatment as the main factor and baseline QTc (**Day 15 or Day 20**) as the covariate. A 90% two-sided confidence interval was constructed for the estimated mean difference between gatifloxacin and placebo from the ANCOVA model. **To demonstrate clinical equivalence of the effect of gatifloxacin and placebo on QTc, the upper bound of the 90% two-sided confidence interval of the estimated mean difference (gatifloxacin - placebo) adjusted for baseline was expected to be less than 6 msec.**

This definition of clinical equivalence was based in part on studies in subjects treated with terfenadine. Compared to baseline, terfenadine was associated with a QTc increase of 6 msec in normal healthy subjects and an increase of 12 msec in subjects with cardiovascular disease.

Reviewer Comment:

This appeared to be reasonable since the QTc change with gatifloxacin at the clinical dose of 400 mg has been shown to be <10 msec in healthy subjects (mean Δ QTc range from 4 to 9 msec).

The table below provides an overview of the ECG analyses.

Overview of ECG Dataset Analyses		
Variable	Analysis Method	Sample Dataset
Primary Safety Variable		
Δ QTc at 2 hr post-dose on Day 15 from baseline QTc on Day 15	ANCOVA on QTc, mean, 90% two-sided CI; median, 25th & 75th percentile (raw data)	Primary safety dataset
Secondary Safety Variable		
Δ QTc at 2 hr post-dose on Day 20 from baseline QTc on Day 15	ANCOVA on QTc, mean, 90% two-sided CI; median, 25th & 75th percentile (raw data)	Secondary safety dataset
Tertiary Safety Variable		
Δ QTc at 2 hr post-dose on Day 20 from baseline QTc on Day 20	ANCOVA on QTc, mean, 90% two-sided CI; median, 25th & 75th percentile (raw data)	Tertiary safety dataset

Baseline was defined as the last ECG measurement prior to the dose of gatifloxacin or placebo on either **Day 15 or Day 20**.

For each subject, the 2 hours post-dose measurement on **Day 15 and Day 20** was defined as the measurement closest in time to 2 hours post administration of antibiotic study drug. If multiple measurements occurred post administration of antibiotic study drug or placebo on the same day at different time points, the one closest to 2 hours post-dose was used. In the event that the two nearest assessments were equally close to the 2 hours post-dose time point, then the later one was used. Only measurements between 1.5 and 3 hours post-dose were used.

Subjects did not always adhere to the visit schedule timings in the protocol. Therefore, the designation of visits was based on the day of evaluation relative to the trial (day of first dose of gatifloxacin or placebo) rather than the nominal visit day recorded in the case report form. For all analyses of change from baseline, the following mutually exclusive relative day windows were defined to provide derived visits that corresponded to the time points specified in the protocol.

Analyses Time Points		
Dose Administration	Target Visit Day	Day-Range
First dose of antibiotic administration (gatifloxacin or placebo)	15	1st dose of gatifloxacin or placebo
Five days post 1st dose of antibiotic administration (gatifloxacin or placebo)	20	5-14 days post 1st dose of gatifloxacin or placebo (i.e., during steady-state dosing)

Statistical checks on the ANCOVA models were performed and included assessment of treatment by baseline interaction, assessment of distributional assumptions and QTc outliers, and adjustments for prognostic/demographic factors. With respect to the latter, prognostic factors were identified as those baseline characteristics for which a clinically important imbalance exists between the treatment groups. Adjustments for such imbalances were made by including terms for all such prognostic factors in the ANCOVA model. A single prognostic factor was identified in the gatifloxacin treated group – the presence of diabetes (see previous **Table of Demographic Characteristics**) – and thus, it was the only factor included in this analysis.

RESULTS:

The following table outlines the number of patients studied for the primary, secondary, and tertiary safety endpoints / ECG datasets.

Overview of Number of Patients per ECG Dataset			
	N Gatifloxacin	N Placebo	Total N
Primary Safety Dataset / Variable			
Δ QTc at 2 hr post-dose on Day 15 from baseline QTc on Day 15	372	384	756
Secondary Safety Dataset / Variable			
Δ QTc at 2 hr post-dose on Day 20 from baseline QTc on Day 15	36	37	73
Tertiary Safety Dataset / Variable			
Δ QTc at 2 hr post-dose on Day 20 from baseline QTc on Day 20	38	39	77

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Treatment Effect on Heart Rate

There was no clinically significant change in heart rate from baseline to 2 hours post-dose for the gatifloxacin-treated or placebo-treated subjects on either **Day 15** or **Day 20**. These results are shown in the tables below.

Summary of Change in Heart Rate from Baseline on Day 15 to 2 Hours Post-Dose on Day 15 (Subjects with QTc and Heart Rate Measurements at Baseline on Day 15 and 2 Hours Post-dose on Day 15)

Heart Rate (bpm)	Gatifloxacin (N= 372)	Placebo (N= 384)
BASELINE HR (Day 15)		
n	372	384
Mean (SD)	63.9 (10.7)	63.2 (11.0)
Median (25 th , 75 th %tiles)	62.0 (57.0, 70.0)	61.5 (55.0, 69.0)
POST DOSE HR (Day 15)		
n	372	384
Mean (SD)	64.4 (11.0)	63.1 (10.8)
Median (25 th , 75 th %tiles)	62.5 (57.0, 71.0)	62.0 (55.0, 69.0)
HR CHANGE from BASELINE at 2 HR POST DOSE (Day 15)		
n	372	384
Mean (SD)	0.5 (7.4)	-0.1 (7.1)
Median (25 th , 75 th %tiles)	1.0 (-4.0, 5.0)	0.0 (-4.0, 4.0)

Summary of Change in Heart Rate from Baseline on Day 15 to 2 Hours Post-Dose on Day 20 (Subjects with QTc and Heart Rate Measurements at Baseline on Day 15 and 2 Hours Post-dose on Day 20)

Heart Rate (bpm)	Gatifloxacin (N= 36)	Placebo (N= 37)
BASELINE HR (Day 15)		
n	36	37
Mean (SD)	63.4 (11.2)	65.9 (11.9)
Median (25 th , 75 th %tiles)	61.0 (55.0, 68.0)	66.0 (57.5, 72.0)
POST DOSE HR (Day 20)		
n	36	37
Mean (SD)	63.3 (12.1)	65.6 (11.9)
Median (25 th , 75 th %tiles)	64.0 (52.5, 69.0)	65.0 (58.0, 72.0)
HR CHANGE from BASELINE at 2 HR POST DOSE (Day 20)		
n	36	37
Mean (SD)	0.6 (8.5)	-0.3 (8.3)
Median (25 th , 75 th %tiles)	0.0 (-5.5, 7.5)	0.0 (-6.0, 7.0)

Summary of Change in Heart Rate from Baseline on Day 20 to 2 Hours Post-Dose on Day 20 (Subjects with QTc and Heart Rate Measurements at Baseline on Day 20 and 2 Hours Post-dose on Day 20)

Heart Rate (bpm)	Gatifloxacin (N= 38)	Placebo (N= 39)
BASELINE HR (Day 20)		
n	38	39
Mean (SD)	63.0 (10.4)	65.7 (12.9)
Median (25 th , 75 th %tiles)	61.5 (54.0, 70.0)	64.0 (57.0, 69.0)
POST DOSE HR (Day 20)		
n	38	39
Mean (SD)	63.3 (12.1)	65.2 (11.7)
Median (25 th , 75 th %tiles)	64.0 (52.0, 69.0)	65.0 (57.0, 72.0)
HR CHANGE from BASELINE at 2 HR POST DOSE (Day 20)		
n	38	39
Mean (SD)	0.2 (8.4)	-0.5 (8.1)
Median (25 th , 75 th %tiles)	-0.5 (-6.0, 7.0)	-1.0 (-6.0, 7.0)

The sponsor corrected the QT interval using both the Bazett and Fridericia correction formulas. However, because of the lack of effect of gatifloxacin and placebo treatments on heart rate, the QTc data provided in the final study report and shown in this review will be that using Bazett's correction. The sponsor also provided the QTc data corrected using the Fridericia correction and inspection of the two QTc data sets did not reveal any appreciable differences between the two correction methods.

Primary Safety Variable: Day 15 QTc Following Single Dose Gatifloxacin or Placebo

The table below provides an overall summary of the results for the Day 15 changes in QTc at 2 hr postdose from pre-dose baseline on Day 15.

Summary of Changes in QTc from Baseline on Day 15 to 2 hr Postdose on Day 15

	QTc (msec) Gatifloxacin 400mg x 1 Dose	QTc (msec) Placebo x 1 Dose
Overall		
Number of subjects:	372	384
Baseline mean (sd):	395.2 (25.9)	393.2 (26.2)
2 hours post-dose (sd):	401.4 (26.3)	395.8 (26.8)
Adjusted mean (se):	6.5 (0.94)	2.4 (0.92)
Median (25 th , 75 th percentile)	8.0 (-6.0, 19.0)	2.0 (-8.0, 14.0)
Adjusted mean difference from placebo (90% two-sided CI):	4.2 (2.00, 6.34)	
Non-elderly (< 65 years)		
Number of subjects:	265	273
Baseline mean (sd):	393.9 (26.3)	391.6 (25.6)
2 hours post-dose mean (sd):	399.2 (26.7)	394.8 (26.3)
Adjusted mean (se):	5.6 (1.09)	2.9 (1.07)
Adjusted mean difference from placebo (90% two-sided CI):	2.7 (0.19, 5.21)	
Elderly (≥ 65 years)		
Number of subjects:	107	111
Baseline mean (sd):	398.3 (24.7)	397.1 (27.2)
2 hours post-dose mean (sd):	406.8 (24.7)	398.2 (27.8)
Adjusted mean (se):	8.7 (1.85)	0.9 (1.81)
Adjusted mean difference from placebo (90% two-sided CI):	7.8 (3.49, 12.04)	
Male		
Number of subjects:	293	288
Baseline mean (sd):	392.2 (25.0)	390.2 (25.6)
2 hours post-dose mean (sd):	398.5 (25.8)	392.6 (26.2)
Adjusted mean (se):	6.5 (1.06)	2.1 (1.07)
Adjusted mean difference from placebo (90% two-sided CI):	4.4 (1.94, 6.89)	
Female		
Number of subjects:	79	95
Baseline mean (sd):	406.1 (26.4)	402.3 (26.2)
2 hours post-dose mean (sd):	412.4 (25.5)	405.6 (26.2)
Adjusted mean (se):	6.9 (2.04)	2.8 (1.86)
Adjusted mean difference from placebo (90% two-sided CI):	4.1 (-0.48, 8.65)	

Overall, gatifloxacin 400 mg prolonged the QTc by an average of 6.5 msec, relative to baseline, following first dose administration in coronary artery disease (CAD) patients presenting with an acute coronary syndrome (N=372). The QTc was prolonged by an average of 2.4 msec (relative to baseline) for those CAD patients presenting with an acute coronary syndrome who received placebo (N=384). The overall placebo-adjusted mean difference (and 90% CI) in the QTc following the single 400mg dose of gatifloxacin was 4.2 (2.00, 6.34) msec. The upper bound of the CI exceeded the pre-specified clinical equivalence criterion of < 6.0 msec and the CI did not include zero. Thus, the changes in QTc for the gatifloxacin-treated and placebo-treated patients were not demonstrated to be clinically equivalent, and also suggested that the QTc effect of gatifloxacin was statistically different (i.e., greater) vs. placebo.

It should be noted however, that the actual clinical significance of an average prolongation in QTc from baseline of 6.5 msec cannot be determined.

There appeared to be a greater prolongation of the QTc interval, from baseline, following single dose gatifloxacin in the elderly CAD patients (mean adjusted QTc 8.7 msec) presenting with an acute coronary syndrome vs. the younger/non-elderly CAD patients (mean adjusted QTc 5.6 msec). The QTc changes from baseline with the placebo treated elderly and non-elderly patients showed the opposite trend, with smaller QTc changes in the elderly group (mean adjusted QTc 0.9 msec) and larger changes in the younger group (mean adjusted QTc 2.9 msec). The upper bound of the 90% CI for the adjusted mean difference from placebo for the non-elderly patients met the pre-specified criterion of < 6 msec and suggested clinical equivalence between gatifloxacin and placebo treatments for the non-elderly group. However, the upper bound of the same 90% CI for the elderly patients exceeded this criterion of 6 msec and suggested that the QTc prolonging effects of gatifloxacin and placebo were not clinically equivalent in these elderly CAD patients.

There were no apparent gender-related differences in the changes in QTc following single dose gatifloxacin administration on **Day 15**. Similar adjusted mean QTc differences from placebo were determined for males and females. For both genders the upper bounds of the 90% CI of these placebo adjusted means exceeded the pre-specified clinical equivalence criterion of < 6 msec and suggested that the changes in QTc for the gatifloxacin-treated males and females were not clinically equivalent to the placebo-treated males and females.

The cross tabulation of the **Day 15** QTc interval at baseline and 2 hours post dose by treatment are presented in the table below. A summary of the absolute change in the QTc interval from baseline to 2 hours post dose on **Day 15** is also presented below. As seen from these tables, there were no patients who had prolongation of the QTc interval >500msec or experienced an increase in QTc from baseline >60msec with either gatifloxacin or placebo treatment at 2 hour post dose. The greatest changes in QTc from baseline were between 450 to 480 msec at 2 hours following gatifloxacin (3.2% of patients) and placebo (2.3% of patients) administration. The majority of patients had changes in absolute QTc at 2 hr post dose of <30 msec (~93% for placebo; ~90% for gatifloxacin). The % of patients with QTc changes between 30 to 60 msec was slightly greater for gatifloxacin (10.5%) vs. placebo (7.3%).

Cross-tabulation of Baseline QTc on Day 15 and 2 Hours Post-Dose QTc on Day 15 by Treatment

Baseline QTc (msec) (Day 15)	2 Hours Post-Dose (Day 15)	Treatment		
		Gatifloxacin N = 372 n (%)	Placebo N = 384 n (%)	Total N = 756 n (%)
< 450	< 450	356 (95.7%)	370 (96.4%)	726 (96.0%)
	450-480	8 (2.2%)	7 (1.8%)	15 (2.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	364 (97.8%)	377 (98.2%)	741 (98.0%)
450-480	< 450	4 (1.1%)	3 (0.8%)	7 (0.9%)
	450-480	3 (0.8%)	2 (0.5%)	5 (0.7%)
	> 480-500	0 (0.0%)	2 (0.5%)	2 (0.3%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	7 (1.9%)	7 (1.8%)	14 (1.9%)
> 480-500	< 450	0 (0.0%)	0 (0.0%)	0 (0.0%)
	450-480	1 (0.3%)	0 (0.0%)	1 (0.1%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	1 (0.3%)	0 (0.0%)	1 (0.1%)
> 500	< 450	0 (0.0%)	0 (0.0%)	0 (0.0%)
	450-480	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	< 450	360 (96.8%)	373 (97.1%)	733 (97.0%)
	450-480	12 (3.2%)	9 (2.3%)	21 (2.8%)
	> 480-500	0 (0.0%)	2 (0.5%)	2 (0.3%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)

Summary of Absolute Change in QTc from Baseline on Day 15 to 2 Hours Post-dose on Day 15 by Treatment

Change in QTc (msec) from Baseline at 2 hours Post Dose (Day 15)	N	< 30 msec	30 - 60 msec	> 60 msec
Placebo	384	356 (92.7%)	28 (7.3%)	0 (0.0%)
Gatifloxacin	372	333 (89.5%)	39 (10.5%)	0 (0.0%)
Total	756	689 (91.1%)	67 (8.9%)	0 (0.0%)

226 gatifloxacin-treated patients had paired ECG's and a blood sample collected for the measurement of gatifloxacin plasma concentration on **Day 15**. The table below provides a summary of the plasma gatifloxacin concentration data.

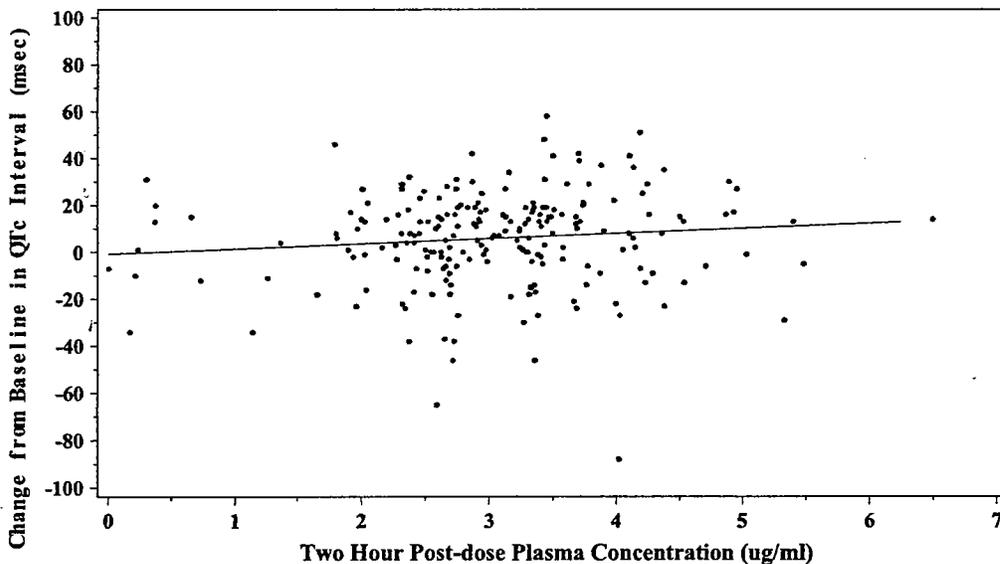
Gatifloxacin Plasma Concentrations at Approximately 2 Hours Following a Single 400 mg Oral Dose on Day 15 (Patients with Plasma Concentrations at 2 Hours Post-dosing and ECG Measurements at Two Hours Post-dosing and at Baseline)

CONCENTRATION ($\mu\text{g/mL}$)	N (%)
0 (<0.01 $\mu\text{g/mL}$)	3 (1.3)
> 0.0 - 1.0	8 (3.5)
> 1.0 - 2.0	14 (6.2)
> 2.0 - 3.0	90 (39.8)
> 3.0 - 4.0	79 (35.0)
> 4.0 - 5.0	26 (11.5)
> 5.0	6 (2.7)
N	226
MEAN (SD) CONC. ($\mu\text{g/mL}$)	3.00 (1.03)
MEDIAN CONC. ($\mu\text{g/mL}$)	2.98
QUARTILES ($\mu\text{g/mL}$)	2.5 - 3.5
CONC. RANGE ($\mu\text{g/mL}$)	0.0 - 6.5

The majority of patients had plasma gatifloxacin concentrations between 2 and 4 $\mu\text{g/mL}$ at approximately 2 hours postdose; the highest concentration achieved was 6.5 $\mu\text{g/mL}$.

The relationship between QTc change and gatifloxacin concentrations at 2 hr postdose on Day 15 is shown in the figure below; the regression parameters are summarized in the table that follows after the figure.

Change in QTc Interval from Baseline on Day 15 to 2 Hours Post-Dose on Day 15 and Drug Plasma Concentration (Solid Line = Best Fit Regression Line)



Linear Regression Parameters for Change in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 15

Model	Factor	Estimate	95% CI	p-value
Adjusted	Baseline QTc slope ^a	-0.299	(-0.3990 , -0.1990)	0.0001
	Concentration slope ^b	2.189	(-0.3720 , 4.7510)	0.0935

^a Mean msec change in QTc per msec of pre-dose QTc

^b Mean msec in QTc per µg/mL of plasma concentration

There was a weak relationship between change in QTc from baseline and plasma gatifloxacin concentration at 2 hr postdose in these patients on **Day 15** after the first 400mg gatifloxacin dose. Although the concentration slope of the regression line was positive, the relationship was not statistically significant. The concentration slope estimate in these gatifloxacin-treated patients with CAD was similar to that reported for the healthy subjects studied in the single dose escalation **Study AI420-092** (slope estimates from 2.5 to 3.1 msec/µg/mL). The significant inverse relationship between baseline QTc interval and change in QTc interval on **Day 15** (baseline QTc slope) may reflect regression to the mean or a decreased drug effect in those patients with a higher baseline QTc interval.

Secondary Safety Variable: Day 20 QTc Following Repeat Dose Gatifloxacin or Placebo Compared to Day 15 Baseline QTc

Day 20 represented the 6th day of gatifloxacin dosing (400 mg QD) and plasma concentrations were presumed to be at steady state. 73 patients (36 gatifloxacin, 37 placebo) underwent ECG recording on **Day 20** for inclusion in the comparison with baseline on **Day 15**. The table below provides an overall summary of change in QTc from baseline on **Day 15** to 2 hours post-dose on **Day 20** in these patients.

Summary of Changes in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 20		
	QTc (msec) Gatifloxacin 400mg QD x 6 Days	QTc (msec) Placebo QD x 6 Days
Number of subjects:	36	37
Day 15 baseline mean (sd) QTc:	398.2 (25.7)	399.6 (22.3)
Day 20 2 hr post-dose mean (sd) QTc:	404.8 (32.8)	393.4 (25.2)
Adjusted mean (se) QTc:	6.5 (3.51)	-6.0 (3.46)
Median (25 th , 75 th percentile) QTc:	4.5 (-8.0, 20.0)	-1.0 (-15.0, 5.0)
Adjusted mean QTc difference from placebo (90% two-sided CI):	12.5 (4.31, 27.73)	

The mean QTc increased by 6.5 msec in gatifloxacin-treated subjects on **Day 20** compared with the **Day 15** baseline. This mean increase was the same as that observed for the primary analysis of the 372 patients after single dose administration of 400mg gatifloxacin on **Day 15** (i.e., adjusted mean QTc 6.5 msec). However, on **Day 20** the increase in QTc in the gatifloxacin-treated group on was accompanied by a **decrease** in QTc in the placebo group of nearly equal magnitude. The mean QTc in the placebo group at 2 hours post-dose on **Day 20**, compared to baseline on **Day 15**, **decreased** by 6.0 msec. The placebo-adjusted mean QTc increase with gatifloxacin on **Day 20**, compared with **Day 15** baseline, was therefore 12.5 msec (90% CI: 4.31, 27.73). In the primary analysis on **Day 15**, the QTc in the 384 placebo-treated patients **increased** by 2.4 msec from baseline to 2 hours post-dose.

For both gatifloxacin and placebo treatment groups, the variability (as standard error) in the adjusted mean QTc values for the secondary **Day 20** analyses was high and more substantial than that for primary **Day 15** analyses. The sponsor noted that while the inherent variability in QTc appeared to be adequately

"countered" by employing a large number of subjects for the **Day 15** primary analyses (>370 patients per group), the variability in QTc may not have been adequately "countered" in the **Day 20** secondary analyses of smaller treatment groups (<40 patients per group).

Summaries of the cross tabulations of QTc at baseline on **Day 15** and 2 hours post-dose on **Day 20** and of the change in absolute QTc, each by treatment, are shown in the tables below. As can be seen from the tables below, the QTc intervals at 2 hr postdose were <450msec for the majority of patients receiving gatifloxacin 400mg QD x 6 days (94.4%) or placebo QD x 6 days (100%). In addition, the absolute change in QTc at 2-hr postdose was <30msec for the majority of patients in both treatment groups (gatifloxacin 88.9%; placebo 97.3%). There were no placebo-treated patients with QTc >60msec and one gatifloxacin-treated patient with QTc change >60msec (see below).

There were 3 gatifloxacin-treated patients and 1 placebo-treated patient with an absolute change in QTc at 2-hr postdose of 30-60msec. There was one patient in the gatifloxacin-treated group with QTc >500msec at 2 hr postdose on **Day 20** and had a baseline QTc on **Day 15** <450msec. This was also the same patient with an absolute change in QTc at 2 hr post-gatifloxacin >60msec. This patient was a 50 year old white female with a history of angina pectoris, percutaneous coronary intervention, and syncope who presented with high risk unstable angina and underwent balloon angioplasty of the right coronary artery. The gatifloxacin 2-hr postdose plasma concentrations were 4.24 and 4.33 µg/mL on **Days 15 and 20**, respectively. An adverse event of prolonged QTc interval of mild intensity was reported on **Day 20** (the 6th day of gatifloxacin therapy) and subsequently resulted in **Treatment B** discontinuation 24 days later. This was reported by the investigator to be unrelated to the study treatment (i.e., **Treatment B**), but per protocol, the antibiotic study drug was discontinued due to QTc >500 msec.

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Cross-tabulation of Baseline QTc on Day 15 and 2 Hours Post-Dose QTc on Day 20 by Treatment

Baseline (Day 15)	2 Hours Post-Dose (Day 20)	Treatment		
		Gatifloxacin N = 36 n (%)	Placebo N = 37 n (%)	Total N = 73 n (%)
< 450	< 450	33 (91.7%)	36 (97.3%)	69 (94.5 %)
	450-480	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	1 (2.8%)	0 (0.0%)	1 (1.4%)
	Total	34 (94.4%)	36 (97.3%)	70 (95.9%)
450-480	< 450	1 (2.8%)	1 (2.7%)	2 (2.7%)
	450-480	1 (2.8%)	0 (0.0%)	1 (1.4%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	2 (5.6%)	1 (2.7%)	3 (4.1%)
> 480-500	< 450	0 (0.0%)	0 (0.0%)	0 (0.0%)
	450-480	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)
> 500	< 450	0 (0.0%)	0 (0.0%)	0 (0.0%)
	450-480	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	< 450	34 (94.4%)	37 (100%)	71 (97.3%)
	450-480	1 (2.8%)	0 (0.0%)	1 (1.4%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	1 (2.8%)	0 (0.0%)	1 (1.4%)

Summary of Absolute Change in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 20

Change from Baseline at 2 hours Post Dose (Day 15)	N	< 30 msec	30 - 60 msec	> 60 msec
Placebo	37	36 (97.3%)	1 (2.7%)	0 (0.0%)
Gatifloxacin	36	32 (88.9%)	3 (8.3%)	1 (2.8%)
Total	73	68 (93.2%)	4 (5.5%)	1 (1.4%)

24 gatifloxacin-treated patients had paired ECG's (baseline **Day 15** and 2 hr postdose **Day 20**) and a blood sample collected for the measurement of gatifloxacin plasma concentration on **Day 20**. The table below provides a summary of the plasma gatifloxacin concentration data.

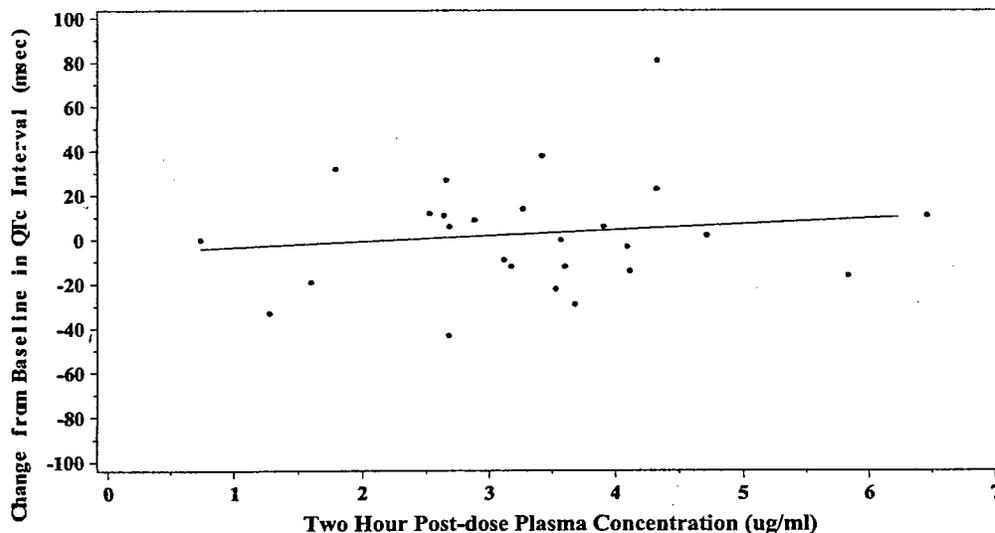
Gatifloxacin Plasma Concentrations at Approximately 2 Hours Following 400 mg QD on Day 20 (6th Dose)

CONCENTRATION (µg/mL)	N (%)
> 0.0 - 1.0	1 (4.2)
> 1.0 - 2.0	2 (8.5)
> 2.0 - 3.0	5 (20.8)
> 3.0 - 4.0	9 (37.5)
> 4.0 - 5.0	5 (20.8)
> 5.0	2 (8.3)
N	24
MEAN (SD) CONC. (µg/mL)	3.43 (1.27)
MEDIAN CONC. (µg/mL)	3.47
QUARTILES (µg/mL)	2.7 - 4.1
CONC. RANGE (µg/mL)	0.7 - 6.5

The majority of patients had plasma gatifloxacin concentrations between 2 and 5 µg/mL at approximately 2 hours postdose; the highest concentration achieved was 6.5 µg/mL.

The relationship between QTc change (2 hr postdose **Day 20** – baseline **Day 15**) and gatifloxacin concentrations at 2 hr postdose on **Day 20** is shown in the figure below; the regression parameters are summarized in the table that follows after the figure.

Change in QTc Interval from Baseline on Day 15 to 2 Hours Post-Dose on Day 20 and Gatifloxacin Plasma Concentration at 2 Hours Postdose on Day 20 (Solid Line = Best Fit Regression Line; N=24)



Linear Regression Analysis for Change in QTc from Baseline on Day 15 to 2 Hours Post-Dose on Day 20

Model	Factor	Estimate	95% CI	p-value
Adjusted	Baseline QTc slope ^a	-0.135	(-0.6570, 0.3870)	0.5980
	Plasma Concentration slope ^b	2.866	(-6.6290, 12.3620)	0.5390

^a Mean msec change in QTc per msec of pre-dose QTc

^b Mean msec in QTc per µg/mL of plasma concentration

Due to the relatively small number of patients included in this analysis the relationship of QTc with concentration was weak and no definitive conclusions can be made.

Tertiary Safety Variable: Day 20 QTc Following Repeat Dose Gatifloxacin or Placebo Compared to Day 20 Baseline QTc

77 patients (38 gatifloxacin, 39 placebo) were included in this analysis. The table below provides an overall summary of change in QTc from baseline on Day 20 to 2 hours post-dose on Day 20 in these patients.

Summary of Changes in QTc from Baseline on Day 20 to 2 Hours Post-Dose on Day 20		
	QTc (msec) Gatifloxacin 400mg QD x 6 Days	QTc (msec) Placebo QD x 6 Days
Number of subjects:	38	39
Day 20 baseline mean (sd) QTc:	400.1 (25.2)	400.7 (24.1)
Day 20 2 hr post-dose mean (sd) QTc:	404.4 (32.1)	393.9 (24.7)
Adjusted mean (se) QTc:	4.3 (3.41)	-6.7 (3.37)
Median (25 th , 75 th percentile) QTc:	4.0 (-13.0, 17.0)	-4.0 (-18.0, 3.0)
Adjusted mean QTc difference from placebo (90% two-sided CI):	11.0 (3.02, 18.98)	

These results are comparable to those for the secondary QTc analysis of 2-hr postdose Day 20 – baseline Day 15.

Summaries of the cross tabulations of QTc at baseline on Day 20 and 2 hours post-dose on Day 20 and of the change in absolute QTc, each by treatment, are shown in the tables below. Similar to the secondary QTc results, the majority of patients had QTc intervals <450 msec and changes in QTc <30 msec following gatifloxacin (95% and 87%, respectively) and placebo (100% and 95%, respectively) administration. One gatifloxacin treated patient had QTc >500msec and change in QTc >60 msec. This is the same patient described above in the secondary QTc analysis.

Cross-tabulation of Baseline QTc on Day 20 and 2 Hours Post-Dose QTc on Day 20 by Treatment

Baseline QTc (msec) (Day 20)	2 hours Post-Dose (Day 20)	Treatment		
		Gatifloxacin N = 38 n (%)	Placebo N = 39 n (%)	Total N = 77 n (%)
< 450	< 450	36 (94.7%)	38 (97.4%)	74 (96.1%)
	450-480	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	1 (2.6%)	0 (0.0%)	1 (1.3%)
	Total	37 (97.4%)	38 (97.4%)	75 (97.4%)
450-480	< 450	0 (0.0%)	1 (2.6%)	1 (1.3%)
	450-480	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	0 (0.0%)	1 (2.6%)	1 (1.3%)
> 480-500	< 450	0 (0.0%)	0 (0.0%)	0 (0.0%)
	450-480	1 (2.6%)	0 (0.0%)	1 (1.3%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	1 (2.6%)	0 (0.0%)	1 (1.3%)
> 500	< 450	0 (0.0%)	0 (0.0%)	0 (0.0%)
	450-480	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	< 450	36 (94.7%)	39 (100%)	75 (97.4%)
	450-480	1 (2.6%)	0 (0.0%)	1 (1.3%)
	> 480-500	0 (0.0%)	0 (0.0%)	0 (0.0%)
	> 500	1 (2.6%)	0 (0.0%)	1 (1.3%)

Summary of Absolute Change in QTc from Baseline on Day 20 to 2 Hours Post-Dose on Day 20 by Treatment

Change from Baseline at 2 hours Post Dose (Day 15)	N	< 30 msec	30 - 60 msec	> 60 msec
Placebo	39	37 (94.9%)	2 (5.1%)	0 (0.0%)
Gatifloxacin	38	33 (86.8%)	4 (10.5%)	1 (2.6%)
Total	77	70 (90.9%)	6 (7.8%)	1 (1.3%)

26 gatifloxacin-treated patients had paired ECG's (baseline **Day 20** and 2 hr postdose **Day 20**) and a blood sample collected for the measurement of gatifloxacin plasma concentration on **Day 20**. The table below provides a summary of the plasma gatifloxacin concentration data.

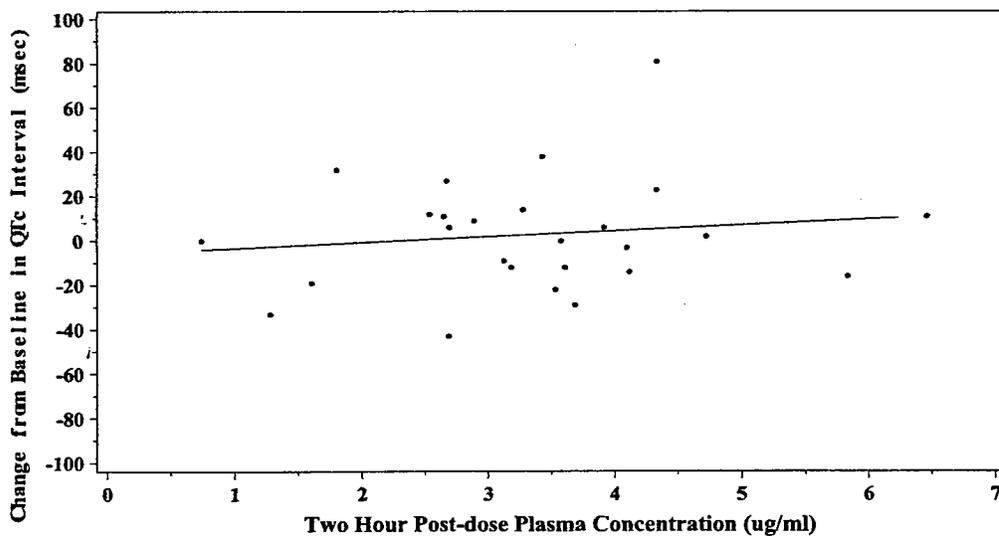
Gatifloxacin Plasma Concentrations at Approximately 2 Hours Following 400 mg QD on Day 20 (6th Dose)

CONCENTRATION ($\mu\text{g/mL}$)	N (%)
> 0.0 - 1.0	1 (3.8)
> 1.0 - 2.0	3 (11.5)
> 2.0 - 3.0	6 (23.1)
> 3.0 - 4.0	9 (34.6)
> 4.0 - 5.0	5 (19.2)
> 5.0	2 (7.7)
N	26
MEAN (SD) CONC. ($\mu\text{g/mL}$)	3.33 (1.28)
MEDIAN CONC. ($\mu\text{g/mL}$)	3.34
QUARTILES ($\mu\text{g/mL}$)	2.7 - 4.1
CONC. RANGE ($\mu\text{g/mL}$)	0.7 - 6.5

The majority of patients had plasma gatifloxacin concentrations between 2 and 5 $\mu\text{g/mL}$ at approximately 2 hours postdose; the highest concentration achieved was 6.5 $\mu\text{g/mL}$.

The relationship between QTc change (2 hr postdose **Day 20** – baseline **Day 20**) and gatifloxacin concentrations at 2 hr postdose on **Day 20** is shown in the figure below; the regression parameters are summarized in the table that follows after the figure.

Change in QTc Interval from Baseline on Day 20 to 2 Hours Post-Dose on Day 20 and Gatifloxacin Plasma Concentration at 2 Hours Postdose on Day 20 (Solid Line = Best Fit Regression Line; N=26)



Linear Regression Analysis for Change in QTc from Baseline on Day 20 to 2 Hours Post-Dose on Day 20

Model	Factor	Estimate	95% CI	p-value
Adjusted	Baseline QTc slope ^a	-0.111	(-0.6080, 0.3860)	0.6497
	Plasma Concentration slope ^b	2.607	(-5.9310, 11.1460)	0.5356

^a Mean msec change in QTc per msec of pre-dose QTc

^b Mean msec in QTc per µg/mL of plasma concentration

There were no substantial differences in the regression results between the secondary and tertiary QTc analyses. Due to the relatively small number of patients included with the tertiary analysis, the relationship between plasma gatifloxacin concentration and change in QTc interval is weak and no definitive conclusions may be made.

REVIEWER CONCLUSIONS:

The following conclusions may be made regarding the effects of gatifloxacin on the QTc interval in patients with coronary artery disease (CAD) who were being treated with gatifloxacin (400mg QD x 14 days; N=374) or placebo (QD x 14 days; N=386) following an acute coronary syndrome (post-ACS) in the ECG substudy of the PROVE-IT study:

- No clinically significant changes in heart rate were observed following either the 1st dose (**Day 15**) or the 6th dose (**Day 20**) of gatifloxacin or placebo. Thus, the use of Bazett's formula to correct the QT appeared to be appropriate for these patients.
- Mean plasma concentrations of gatifloxacin determined at approximately 2 hr following 1st dose (**Day 15**) and 6th dose (**Day 20**) administration of 400mg were similar at 3.0 µg/mL and 3.3-3.4 µg/mL, respectively. The majority of gatifloxacin-treated patients had plasma concentrations at approximately 2 hr postdose between 2 µg/mL and 5 µg/mL after the 1st and 6th doses. This indicated minimal accumulation of gatifloxacin in plasma (i.e., 10-13%) and is consistent with the PK characteristics observed in healthy subjects.
- Following 1st dose administration of 400mg gatifloxacin on **Day 15** (at 2 hr postdose) the mean (SD) increase in the QTc from **Day 15** baseline was 6.5 (18.1) msec in all patients (N=374). Following the 1st dose of placebo on **Day 15** (at 2 hr postdose) the mean (SD) increase in the QTc from **Day 15** baseline was 2.4 (18.0) msec in all patients (N=386). The mean (90% CI) placebo-adjusted increase in QTc following 1st dose administration of 400mg gatifloxacin on **Day 15** was 4.2 (2.0, 6.3) msec. **It should be noted that the actual clinical significance of an average prolongation in QTc from baseline of 6.5 msec cannot be ascertained.**
- There appeared to be a greater prolongation of the QTc interval, from **Day 15** baseline, following 1st dose gatifloxacin on **Day 15** in the elderly CAD post-ACS patients (N=107 ≥65 yr.) - mean (SD) QTc 8.7 (19.1) msec vs. non-elderly CAD post-ACS patients (N=265 <65 yr.) - mean (SD) QTc 5.6 (17.7) msec. The mean (90% CI) placebo-adjusted increases in QTc following 1st dose administration of 400mg gatifloxacin on **Day 15** in the elderly patients vs. non-elderly were 7.8 (3.5, 12.0) msec vs. 2.7 (0.2, 5.2) msec, respectively.
- There were no apparent gender-related differences in the change in QTc following 1st dose gatifloxacin administration on **Day 15**. Similar mean (SD) QTc increases from **Day 15** baseline were determined for males (i.e., 6.5 (18.1) msec; N=293) and females (i.e., 6.9 (18.1) msec; N=79). The

mean (90% CI) placebo-adjusted increases in QTc following 1st dose administration of 400mg gatifloxacin on **Day 15** in the male patients vs. female patients were 4.4 (1.9, 6.9) msec vs. 4.1 (-0.5, 8.7) msec, respectively.

- Following 1st dose administration of either gatifloxacin 400mg or placebo on **Day 15** there were no patients who had prolongation of the QTc interval >500msec nor experienced an increase in QTc from baseline >60msec with either gatifloxacin or placebo treatment at 2 hr post dose. The majority of patients had QTc intervals <450 msec at 2 hr following 1st dose administration of either gatifloxacin (97%) or placebo (97%). In addition, the majority of patients had changes in QTc at 2 hr post dose <30 msec (~93% for placebo; ~90% for gatifloxacin).
- Following the 6th dose of gatifloxacin 400mg (i.e., at presumed steady-state) to 36 CAD post-ACS patients on **Day 20** the average increase in QTc (from **Day 15** baseline) was the same as that after the 1st dose, i.e., mean (SD) QTc change on **Day 20** = 6.5 (21.1) msec. The mean (90% CI) placebo-adjusted increase in QTc following 6th dose administration of 400mg gatifloxacin on **Day 20** was 12.5 (4.3, 27.7) msec.
*This latter placebo-adjusted change in QTc after the 6th gatifloxacin dose on **Day 20** was greater than after 1st dose administration on **Day 15** because the mean QTc in the placebo group at 2 hr post-dose on **Day 20** (compared to baseline on **Day 15**) decreased by nearly equal magnitude (i.e., -6.0 msec) as the increase in the gatifloxacin-treated QTc.*
- On **Day 20** the QTc intervals at 2 hr postdose were <450msec for the majority of patients receiving repeat dose gatifloxacin 400mg QD x 6 days (94.4%; n/N = 34/36) or placebo QD x 6 days (100%; n/N = 37/37). In addition, the change in QTc at 2 hr postdose was <30msec for the majority of patients in both treatment groups (gatifloxacin 89%; placebo 97%). There were no placebo-treated patients with QTc >500msec or with change in QTc >60msec. However, there was one 50 year old female gatifloxacin-treated patient with QTc >500msec who also had a change in QTc >60msec. No clinical signs or symptoms of any cardiac abnormalities were associated with these QTc changes in this patient.
- The overall results of the assessment of QTc interval prolongation and changes in QTc after the 6th dose of gatifloxacin were similar when employing the baseline QTc on either **Day 15** (i.e., at the initiation of gatifloxacin or placebo treatment) or on **Day 20** (i.e., after the 6th day of QD dosing with either treatment).
- Linear regression analysis of the change in QTc (from baseline) vs. plasma gatifloxacin at 2 hr postdose on **Day 15** (i.e., 1st dose administration) and on **Day 20** (i.e., 6th dose administration) showed a relatively weak relationship, with the slopes for the regression lines not significantly different from zero (range of slope estimates 2.2-2.9 msec/μg/mL. These slope estimates are consistent with those determined from the single dose escalation study in healthy subjects (**Study AI420-092**).

REVIEWER COMMENTS:

There are some major limitations to this study that are noteworthy and may make interpretation of the findings difficult/ambiguous:

- Baseline QTc was determined using only a single ECG recording performed pre-dose on **Day 15** after 1st dose administration of gatifloxacin or placebo and pre-dose on **Day 20** after the 6th dose of each treatment. It is generally preferable to determine baseline QTc from several ECG recordings taken over a range of times during the day.
- Postdose QTc was determined at only a single timepoint, i.e., 2 hr postdose on **Days 15 and 20**. This assumes that the greatest change in QTc would occur around the time of maximum plasma gatifloxacin concentration (i.e., median Tmax for gatifloxacin is 2 hr). However, in the single dose escalation study evaluating QTc changes with gatifloxacin in healthy subjects, the greatest QTc changes occurred from 0 to 12 hr postdose (**Study AI420-092**).
- There were a relatively limited number of patients evaluated in the repeat dose phase of this ECG substudy (i.e., N <100).

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8/12/02 11:16:52 AM
BIOPHARMACEUTICS

BMD - you already received the hard copy; I
also cc'ed John and Arzu

Barbara Davit
8/12/02 05:05:08 PM
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