This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

1 SYNOPTIC STUDY REPORT TITLE PAGE

THOROUGH QT/QTC STUDY FOR GARENOXACIN (SCH 745737)

Other Study Information:	This was a two-part study. Part 1 was a randomized, placebo-controlled, third-party blind (within dose-level), multiple-dose, dose-escalation study to assess the safety, tolerability, and pharmacokinetics at the proposed top dose of garenoxacin in adult healthy volunteers. Part 2 was a randomized, open-label, multiple-dose, placebo- and positive-controlled, 4-period, 4-treatment cross-over study in adult healthy volunteers.
Name of Sponsor:	Schering-Plough Research Institute, a division of Schering Corporation
Included Protocol:	P04342
Development Phase of Study:	3
Study Initiation Date:	18 JAN 2007
Study Completion Date:	04 MAY 2007
Sponsor's Project Director:	[redacted]
Sponsor's Responsible Medical Officer:	[redacted]

Sponsor's Contact Person:

[redacted]
Telephone:
FAX:

GCP Compliance: This study was performed in compliance with good clinical practice, including the archiving of essential documents.

Date of the Synoptic Study Report: 20 NOV 2007

Doc ID: 3480121

2 SYNOPTIC STUDY REPORT

Title of Study:	Thorough QT/QTc Study for Garenoxacin (SCH 745737) (Protocol No. P04342)	
Investigator:	[redacted]	
Study Center:	[redacted] The Netherlands	
Publications:	None	
Studied Period:	18 JAN 2007 to 04 MAY 2007	**Clinical Phase:** 3

Objectives

Primary Objective: To evaluate QT/QTc prolongation and proarrhythmic potential for garenoxacin using a placebo control and moxifloxacin as the positive control in adult healthy volunteers.

Secondary Objective: To evaluate safety, tolerability and pharmacokinetics of garenoxacin at supra-therapeutic doses in adult healthy volunteers.

Methodology: This was a two-part study.

Part 1: Was a randomized, placebo-controlled, third-party blind (within dose-level), multiple-dose, dose-escalation study to assess the safety, tolerability, and pharmacokinetics at the proposed top dose of garenoxacin.

Part 2: Was a randomized, open-label, multiple-dose, placebo- and positive-controlled, 4-period, 4-treatment cross-over study in adult healthy volunteers. Both parts of the study were conducted at a single study center with adult healthy volunteers in conformance with Good Clinical Practices.

Thorough QTc Assessment: 12-lead ECGs were taken at different times relative to oral intake of the different treatments using a Digital Holter Recorder (Mortara H12+). These Digital Holter Recorders have the capacity to record continuous, high-resolution (1000 Hz), 12-lead ECG data on Compact Flash Memory Cards capable of storing 24 hours of 12-lead digital data. All doses of garenoxacin, moxifloxacin, and placebo were administered in the morning (starting at approximately 8:00) after an approximately 10-hour fast for 5 days. A physician was present at the time of dosing until 4 hours postdose. Subjects were instructed to remain in the supine position for at least 10 minutes before and after the nominal times identified below. ECGs recorded on Compact Flash memory cards were mailed to a central lab for processing and blinded third-party evaluation. ECG intervals were measured using the waveform from lead II.

For each treatment period, subjects were domiciled on Day -2 at least 12 hours prior to the start of the baseline ECG recordings (Day -1) and were to remain confined to the study site under appropriate supervision until 24 hours after the last dose of that period. Subjects were then discharged for an outpatient period to allow at least 7 days of washout between dosing (ie, last dose of previous period to first dose of subsequent period). Baseline digital ECGs were obtained for all randomized subjects on Day -1 using a 12-Lead Digital Holter Recorder after the subject had been in the supine position for at least 10 minutes before and after the nominal time identified below. Post-treatment digital ECGs were recorded for approximately 23 hours beginning predose on Day 5 of each treatment period, and Day 1 for treatment periods of moxifloxacin and placebo (Treatment A and B) and in the same manner obtained at Baseline. Triplicate ECGs were extracted and were evaluated at each of the following nominal time points: predose (0 hour), 1, 2, 3, 4, 6, 8, and 23 hours relative to dosing on Day 5 (±5 minutes) for all treatment groups and Day 1 for Treatment A (moxifloxacin) and B (placebo). Baseline ECGs were evaluated at each of the matching time points. ECGs were transferred to an independent third party [redacted] for final analysis. [redacted] was blinded to treatment. At each nominal time point, the triplicate ECGs were spaced approximately 1 minute apart, and the following parameters were measured: ventricular rate, RR, PR, QRS, and QT intervals. QT intervals were corrected to heart rate using Fridericia (QTcF) and Bazett (QTcB) methods as well as individually corrected using linear regression (QTcI). Both QTcF and QTcB were provided by [redacted] and QTcI was derived by the sponsor. The formulae for individual correction are derived from observed QT interval and RR interval.

Blood Pressure Assessment: Supine blood pressure and pulse were measured at 0, 1, 2, 4, and 24 hours relative to dosing on Days 1 and 5; and 2 hours postdose on Days 3 and 4.

Safety Assessment: Safety variables assessed included: adverse events, clinical laboratory tests, vital signs, and physical exams.

Pharmacokinetic Sampling: Plasma samples were collected at 0, 1, 2, 3, 4, 6, 8, and 24 hours relative to dosing on Day 5 for pharmacokinetic assessment.

Number of Subjects: A total of 55 healthy volunteers were enrolled into this study.

Part 1: A total of 18 subjects (with 9 subjects on each dose level) were enrolled.

Part 2: A total of 37 subjects (including one replacement) were enrolled.

Title of Study: Thorough QT/QTc Study for Garenoxacin (SCH 745737) (Protocol No. P04342)

Diagnosis and Criteria for Inclusion: Adult healthy volunteers between the ages of 18 and 55 years were selected for the study.

Test Product, Dose, Mode of Administration, Batch No(s): Garenoxacin (SCH 745737) 600 mg, 1200 mg, or 1600 mg once per day, administered orally. Garenoxacin was provided as powder in bottle (Batch No. [redacted] and was dispensed as an oral suspension in 50 mL Ora-sweet syrup by the pharmacist at the investigative site.

Reference Therapy, Dose, Mode of Administration, Lot No(s): Placebo was matched to garenoxacin and was administered orally.

Moxifloxacin (moxifloxacine hydrochloride, AVELOX®, Bayer Pharmaceuticals Corporation) 200 mg tablets for oral administration were administered orally (Bayer Lot No. [redacted]

Duration of Treatment

Part 1: Garenoxacin at doses of 1200 mg or 1600 mg, or placebo administered orally once daily for 5 days.

Part 2:

- For moxifloxacin, 400 mg administered orally once daily in the morning for 5 days.
- For garenoxacin at therapeutic dose, 600 mg administered orally once daily in the morning for 5 days.
- For garenoxacin at supra-therapeutic dose, 1200 mg administered orally once daily in the morning for 5 days.
- For placebo, administered orally once daily in the morning for 5 days.
- There were 5 days of scheduled dosing in each of four treatment periods, so the total treatment duration was to be approximately 20 days.

Note: There was an approximate 7-day washout period between last dosing of the prior period and first dosing of the subsequent period.

Criteria for Evaluation: Safety was evaluated by adverse events (AE), vital signs, ECGs, and laboratory assessments.

Primary Endpoint

Part 1: To evaluate the safety, tolerability, and pharmacokinetics of garenoxacin at supra-therapeutic doses in normal healthy volunteers as determined by Cmax, AUC(0-24 hr), reported AE, vital signs, safety laboratory tests, ECG, and physical examinations.

Part 2: The effect of a supra-therapeutic dose of garenoxacin following 5 days of treatment on QT intervals, corrected with Fridericia's method (QTcF), as measured by the largest upper bound of 95% one-sided confidence intervals for the eight mean changes in QTcF from time-matched baseline ECG recordings, compared to placebo.

Secondary Endpoint(s)

- The effect of a therapeutic dose (600 mg) of garenoxacin following 5 days of treatment on QT intervals, corrected with Fridericia's method (QTcF), as measured by the largest upper bound of the eight 95% one-sided confidence intervals for the mean changes from time-matched baseline ECG recordings, compared to placebo.
- The effect of both supra-therapeutic and therapeutic doses of garenoxacin following 5 days of treatment on QT intervals without correction, with individual correction (QTcI), and with Bazett's correction method (QTcB), as measured by the largest upper bound of the eight 95% one-sided confidence intervals for the mean changes from time-matched baseline ECG recordings, compared to placebo.
- The effect of garenoxacin on PR interval and heart rate (HR) at both a therapeutic dose (600 mg) and a supra-therapeutic dose following 5 days of treatment as measured by average change from baseline ECG recordings, compared to placebo.
- Safety, tolerability, and pharmacokinetics of garenoxacin at supra-therapeutic doses (1200 mg or 1600 mg once daily).

Title of Study: Thorough QT/QTc Study for Garenoxacin (SCH 745737) (Protocol No. P04342)

Statistical Methods

Safety: Part 1 and Part 2: Adverse events were tabulated. Clinical safety laboratory values were listed by date and time and compared to baseline using summary statistics. Vital signs were listed and summarized. Plasma garenoxacin concentrations and pharmacokinetic parameters were listed and summarized by dose using descriptive statistics. ECG parameters from Part 1 were listed and summarized using descriptive statistics.

Pharmacodynamics (PD): Flash memory cards containing multiple continuous ECG recordings during each period (Day -1, Day 1 for Treatments A and B, and Day 5) were transferred to a blinded third-party for evaluation [redacted]). The final results of the third-party analysis were considered the definitive ECG data and were the only ECG data used in the analysis. Triplicate ECGs at each nominal time point were evaluated for RR, PR, QRS, and QT intervals, derivation of heart rate and QTc (QTcF, QTcB, and QTcI). The average of the triplicate ECG parameters was used for evaluation of the potential for QT prolongation as well as clinical interpretation (abnormal/normal). QT corrected by the Fridericia (QTcF) method was used as the primary measure of change in QT interval.

The derived QTc interval was separately analyzed by time using ANOVA model for 4-way crossover extracting the effects due to treatment, sequence, period, and subject. The differences in change from time-matched baseline QTc interval between garenoxacin or moxifloxacin and placebo, and corresponding 95% one-sided confidence interval were provided for each time point at Day 5 (with a total of eight confidence intervals for each comparison).

If the largest upper bound of all of the eight 95% one-sided confidence intervals for the difference in change from time-matched baseline QTc interval between garenoxacin and placebo is less than 10 msec, garenoxacin is considered having no QTc prolongation effect (negative). The primary comparison was garenoxacin at the supra-therapeutic dose vs. placebo and garenoxacin at the therapeutic dose vs. placebo was to be tested only if garenoxacin at the supra-therapeutic dose vs. placebo was positive. The comparison between moxifloxacin vs. placebo on Days 1 and 5 was used to verify the QTc prolongation effect of moxifloxacin and therefore to validate the study.

Additionally, the numbers of subjects with the average change in QTcF categorized as <0, 0 to 30, 31 to 60, and >60 msec was tabulated and summarized by treatment group as was the number of subjects with a QTc interval >480 to 500 and >500 msec. QT, QTcB, and QTcI were analyzed in a similar fashion.

Pharmacokinetics (PK): Plasma garenoxacin concentrations and PK parameters were listed and summarized using descriptive statistics

PK/PD: The relationship between drug exposure and QT/QTc interval changes was explored so QT/QTc risk at clinically relevant doses can be assessed.

SUMMARY - CONCLUSIONS:

RESULTS:

Demographic and Baseline Characteristics: A total of 55 adult subjects (25 men and 30 women) between the ages of 19 and 53 years were enrolled ( ). A total of 18 adult subjects (5 men and 13 women) between the ages of 19 and 38 years (mean age of 25.6 years) were enrolled into Part 1, and a total of 37 adult subjects (20 men and 17 women) between the ages of 19 and 53 years (mean age of 33.5 years) were enrolled into Part 2 of this study. In Part 2 of this study, 31 (84%) subjects were Caucasian; 2 (5%) were Asian; 3 (8%) were Black, and 1 (3%) was multiracial.

Subject Disposition: One placebo-treated subject discontinued from the study because of a serious adverse event in Part 1 ( ). Four subjects discontinued from the study in Part 2; three due to adverse events and one due to personal reasons. Among the three subjects who discontinued due to adverse events, one discontinued while receiving moxifloxacin (rectal bleeding) and two discontinued while receiving garenoxacin (one due to generalized skin rash and one due to moderate vomiting) ( ).

Clinical Pharmacology:

Pharmacodynamics

Garenoxacin Effect on QTc: The effect of garenoxacin on QTc was assessed at doses of 600 mg and 1200 mg, using moxifloxacin as a positive control. Since the primary end point is QTcF, statistical analysis and graphical representation of QTcF is the main focus in this report. The results for QTcB and QTcI are summarized in . Moxifloxacin was associated with QTc prolongation following both single-dose administration (Day 1) and multiple-dose administration once-daily for 5 days (**Figure 1**); thus, the assay sensitivity was established. In this study, there were no subjects with QTcF >500 msec or with an average change in QTcF >60 msec in QTcF (**Table 1** and). Compared to a mean increase of 17 msec to 18.4 msec (95% upper CI 21.2 to 22.1 msec) between 1 to 4 hours postdose noted with moxifloxacin,

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garenoxacin at 1200 mg was associated with a maximal increase of 14.4 msec (95% upper CI 18.5 msec) at 4 hours postdose (**Figure 1** and **Table 2**). The timing of maximal increase in QTc observed with the supra-therapeutic dose of garenoxacin 1200 mg coincided with the median Tmax following oral administration; the effect on QTc was transient and become less apparent at 23 hours postdose. Garenoxacin at a therapeutic dose of 600 mg was not associated with any noticeable effect on QTcF (maximal increase of 3.2 msec, 95% upper CI 6.7 msec), meeting the predefined criteria of "no effect on QTc". Similar results were obtained when QT was corrected by either Bazett's or individual corrections ( ). There was no apparent effect on QRS duration ( ). However, garenoxacin treatment appeared to be associated with a modest decrease in ventricular rate (**Figure 2** and).

Table 1 Frequency (Number of Subjects) of Maximum Categorical Change in QTcF From Time-Matched Baseline

Treatment	<0 msec[a]	0 to <30 msec	30 to <60 msec	≥60 msec
Moxifloxacin (n=33)	0	27	6	0
Placebo (n=35)	6	29	0	0
GRN 600 mg (n=31)	5	26	0	0
GRN 1200 mg (n=35)	2	27	6	0

a: Based on average of triplicates, the maximal changes on Day 5 were used.

Source Data: .

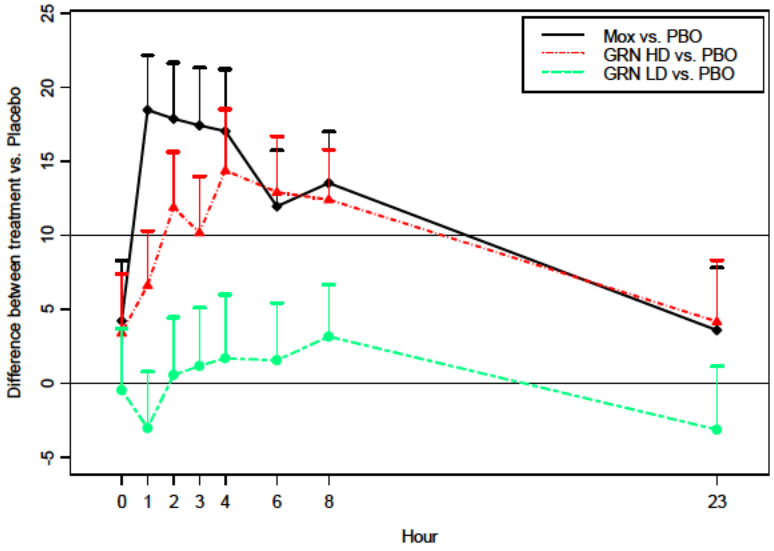

Figure 1 The Mean and Upper Boundary of 95% CI Changes in QTcF from Time-Matched Baseline at Different Times Postdose on Day 5
(Mox = moxifloxacin [400 mg], PBO = placebo, GRN LD = garenoxacin 600 mg, and GRN HD = garenoxacin 1200 mg)

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Table 2 Mean QTcF and Changes From Time-Matched Baseline at Different Times Relative to Treatment on Day 5

Time	Placebo	Moxifloxacin		GRN 600 mg		GRN 1200 mg	
		QTcF[a]	Change[b]	QTcF[a]	Change[b]	QTcF[a]	Change[b]
0	404 ± 16	410 ± 15	4.2 (8.3)	402 ± 15	-0.5 (3.7)	409 ± 17	3.4 (7.4)
1	403 ± 17	421 ± 17	18.4 (22.1)	400 ± 14	-3.0 (0.8)	410 ±17	6.6 (10.3)
2	402 ± 18	420 ± 18	17.9 (21.7)	402 ± 14	0.6 (4.5)	412 ± 17	11.9 (15.6)
3	402 ± 16	420 ± 19	17.4 (21.3)	402 ± 14	1.2 (5.1)	414 ± 18	10.2 (14.0)
4	404 ± 15	419 ± 19	17.0 (21.2)	405 ± 16	1.7 (6.0)	417 ± 17	14.4 (18.5)
6	400 ± 16	412 ± 17	12.0 (15.7)	402 ± 15	1.5 (5.4)	412 ± 16	12.9 (16.7)
8	396 ± 16	409 ± 17	13.5 (17.0)	397 ± 13	3.2 (6.7)	407 ± 15	12.4 (15.8)
23	408 ±17	413 ± 16	3.6 (7.8)	406 ± 14	-3.1 (1.2)	412 ± 16	4.2 (8.3)

a: Mean of QTcF ± SD.

b: Mean change corrected for Placebo with upper boundary of 95% CI shown in parenthesis.

Source Data: .

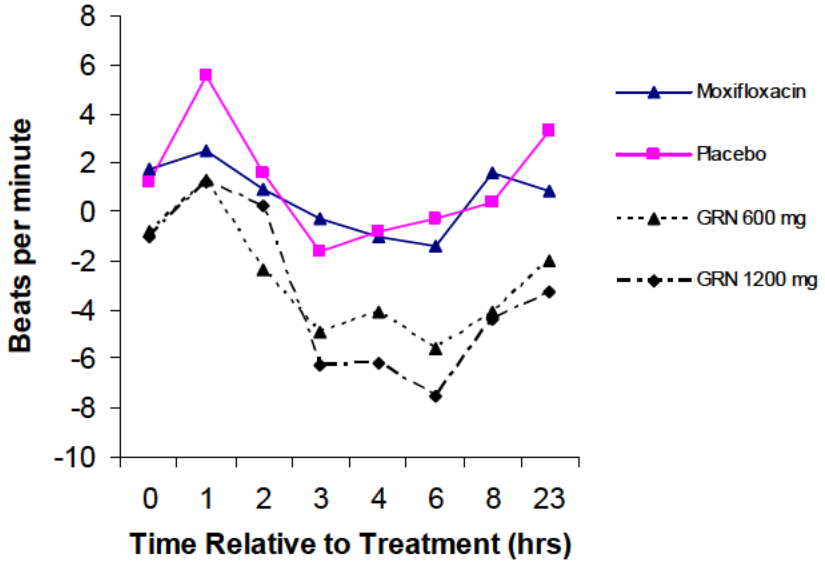

Figure 2 Mean Ventricular Rate Changes From Time-Matched Baseline on Day 5 (Based on ECG Readings, Source Data:)

For cross-study comparison, the effect of moxifloxacin on QTc was also monitored following single-dose administration of moxifloxacin. This study demonstrated a clear effect of QTc prolongation following single-dose administration of moxifloxacin ( ), but it appeared that the magnitude of prolongation following single-dose administration is less than that of multiple-dose administration.

Garenoxacin Effect on PR Interval: Preclinical data and initial clinical pharmacology studies suggested that garenoxacin administration is associated with a slight, nonclinically relevant effect on PR interval. The potential effect of garenoxacin on PR interval was also assessed in this study. A few subjects experienced PR interval above the upper limit of normal, but no subject experienced any second degree AV blockade or third degree AV blockade. Consistent with previous observation, a slight (an average of 10 to 12 msec) prolongation of PR interval was noted in garenoxacin-treated subjects (**Figure 3** and) with a similar effect observed between 600 mg and 1200 mg of garenoxacin. The maximal effect was noted between 1 to 4 hours postdose. Treatment with moxifloxacin was not associated with an apparent effect on PR interval.

Title of Study: Thorough QT/QTc Study for Garenoxacin (SCH 745737) (Protocol No. P04342)

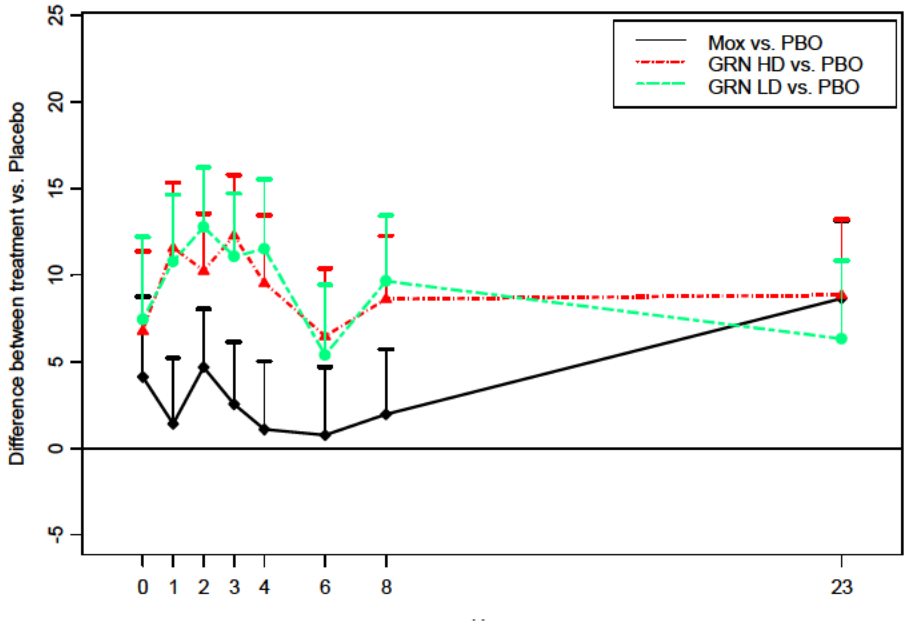

Figure 3 The Mean and Upper Boundary of 95%CI Changes in PR From Time-Matched Baseline at Different Times Postdose on Day 5
(Mox = moxifloxacin [400 mg], PBO = placebo, GRN LD = garenoxacin 600 mg, and GRN HD = garenoxacin 1200 mg)

Garenoxacin Effect on Blood Pressure: Since intravenous administration of garenoxacin was associated with a decrease in systolic blood pressure, the potential effect of garenoxacin administered orally was assessed at different times relative to garenoxacin intake in this study. Supine blood pressure and pulse rate were taken after subjects were in the supine position for at least 3 minutes. There was no symptomatic hypotension reported in this study. Mean changes of systolic blood pressure are shown in **Figure 4** and mean changes for diastolic blood pressure and heart rate are shown in and . It appeared that on average, garenoxacin at a dose of 600 mg was associated with an approximate 5 mm Hg decrease in systolic blood pressure in healthy subjects, and there was no apparent effect on diastolic blood pressure (DBP) or pulse rate. The effect of garenoxacin on systolic blood pressure appeared to be comparable between the 600 mg and 1200 mg doses, with the exception of one time point (approximately 9 mm Hg decrease was noted at 1200 mg; 4 hours postdose on Day 1). The magnitude of effect of garenoxacin was further analyzed using a categorical approach. Consistent with mean data, a slightly higher number of garenoxacin-treated subjects experienced a systolic blood pressure <90 mm Hg or >20 mm Hg decrease from baseline (**Table 3** and **Table 4**). However, it appeared that the maximum magnitude of systolic blood pressure (SBP) decrease observed in garenoxacin-treated subjects is similar to that in the placebo-treated group (**Table 3**, **Table 4**, and **Figure 5**).

Title of Study: Thorough QT/QTc Study for Garenoxacin (SCH 745737) (Protocol No. P04342)

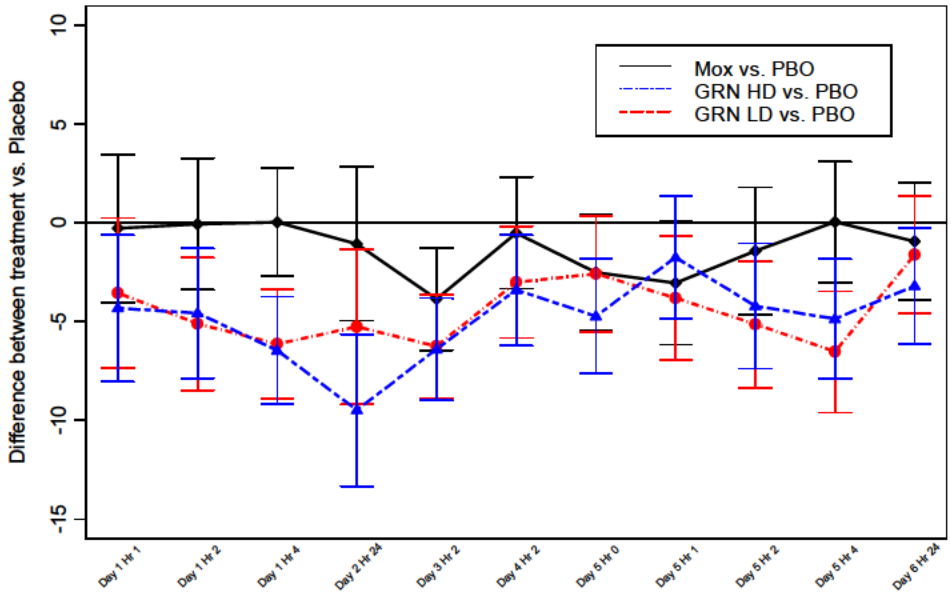

Figure 4 The Mean and 95% CI Changes From Baseline in SBP at Different Times Postdose (Mox = moxifloxacin [400 mg], PBO = placebo, GRN LD = garenoxacin 600 mg, and GRN HD = garenoxacin 1200 mg)

Table 3 Frequency Table of Maximum Systolic Blood Pressure Decrease From Baseline by Treatment

Range of Decrease (mmHg)	Treatment			
	Moxifloxacin (n=34)	Placebo (n=35)	GRN 600 mg (n=34)	GRN 1200 mg (n=37)
0 to <10[a]	7 (21%)	3 (9%)	0	0
-10 to <0	14 (41%)	18 (51%)	11 (32%)	11 (30%)
-20 to <-10	7 (21%)	9 (26%)	16 (47%)	17 (46%)
-30 to <-20	6 (18%)	2 (6%)	6 (18%)	8 (22%)
-50 to <-30	0	3 (9%)	1 (3%)	1 (3%)

a: Counts in the "0 to <10" category represent subjects whose post-baseline values increased.

Source Data:

Table 4 Frequency Table of Systolic Blood Pressure Values Below or Above the Specified Values

Range	Treatment			
	Moxifloxacin (n=34)	Placebo (n=35)	GRN 600 mg (n=34)	GRN 1200 mg (n=37)
SBP <90 mm Hg	6 (18%)	5 (14%)	10 (29%)	9 (24%)
SBP <100 mm Hg	21 (62%)	23 (66%)	29 (85%)	34 (92%)
SBP >140 mm Hg	3 (9%)	2 (6%)	0	0
DBP <45 mm Hg	6 (18%)	5 (14%)	6 (18%)	3 (8%)
Pulse <45 bpm	3 (9%)	4 (11%)	4 (12%)	7 (19%)
Pulse <50 bpm	9 (26%)	8 (23%)	13 (38%)	14 (38%)

Source Data: and

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Pharmacokinetics: The exposure to garenoxacin administered by oral suspension was comparable to that observed after administration of garenoxacin capsules; refer to for PK summary tables. Following oral administration of garenoxacin 1200 mg or 1600 mg QD for 5 days, the median Tmax was about 3 to 4 hours. The exposure to garenoxacin appeared to be dose proportional. Based on the findings from Part 1, 1200 mg was chosen as the supratherapeutic dose. The PK parameters are shown in **Table 5** for Part 1 and in **Table 6** for Part 2. Following oral administration, the median Tmax was about 2 to 3 hours. The exposure to garenoxacin was dose proportional in the dose ranging from 600 mg to 1200 mg.

Table 5 Garenoxacin Pharmacokinetic Parameters Following Oral Administration of 1200 mg or 1600 mg Garenoxacin for 5 Days (Part 1)

	Dose		Cmax (µg/mL)	Tmax (hr)	AUC(0-24hr) (hr·µg/mL)	CL/F (L/hr)
Part 1	1200 mg	N	6	6	6	6
		Mean	20.7	3.50	279	4.48
		CV%	18		20	25
		Min.	14.1	2.00	182	3.54
		Max.	24.7	4.00	339	6.60
		Median	21.9	4.00	291	4.12
		GM	20.4		273	4.39
	1600 mg	N	5	5	5	5
		Mean	27.7	3.20	373	4.37
		CV%	9		14	17
		Min.	24.4	2.00	280	3.91
		Max.	31.1	4.00	410	5.72
		Median	27.8	3.00	389	4.11
		GM	27.6		370	4.33

Abbreviation: AUC(0-24hr) = area under the plasma concentration versus time curve from 0 to 24 hour; Cmax = maximum observed plasma concentration; CL/F = apparent total body clearance (adjusted for bioavailability); CV = coefficient of variation, expressed as a percent (%); Tmax = time of maximum observed plasma concentration; GM = geometric mean.

Table 6 Garenoxacin Pharmacokinetic Parameters Following Oral Administration of 600 mg or 1200 mg Garenoxacin for 5 Days (Part 2)

	Dose		Cmax (µg/mL)	Tmax (hr)	AUC(0-24 hr) (hr·µg/mL)	CL/F (L/hr)
Part 2	600 mg	N	33	33	33	33
		Mean	9.56	2.27	123	5.05
		CV%	20		20	19
		Min	6.38	1.00	90.8	3.45
		Max	14.0	4.00	174	6.61
		Median	9.07	2.00	116	5.17
		GM	9.38		121	4.96
	1200 mg	N	36	36	36	36
		Mean	18.7	2.58	258	4.86
		CV%	20		23	20
		Min	13.5	1.00	172	2.69
		Max	29.3	4.00	446	6.97
		Median	17.6	3.00	240	4.99
		GM	18.4		252	4.76

Abbreviations: AUC(0-24 hr) = area under the plasma concentration versus time curve from 0 to 24 hours; Cmax = maximum observed plasma concentration; CL/F = apparent total body clearance (adjusted for

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bioavailability); CV = coefficient of variation, expressed as a percent (%); Tmax = time of maximum observed plasma concentration; GM=geometric mean.

See for summary tables/figures for ECG data; for listings of ECG data; for summary tables, by-subject listings, and plots of PK data; for PK-PD figures; and for the bioanalytical report.

Pharmacokinetic-Pharmacodynamic Relationship: The changes in systolic blood pressure at 4 hours postdose on Day 1 and Day 5 vs corresponding garenoxacin exposure on Day 5 were further examined (**Figure 5**). Compared to the placebo-treated period, more healthy subjects experienced a decrease in SBP on both Day 1 and Day 5, and there was no apparent association between exposure and change in SBP, suggesting that the effect on SBP may not be minimized effectively by decreasing exposure or reducing the dose within the dose range between 600 mg and 1200 mg, and higher exposure is not likely to lead to a greater decrease in systolic blood pressure. Vital signs data are summarized in .

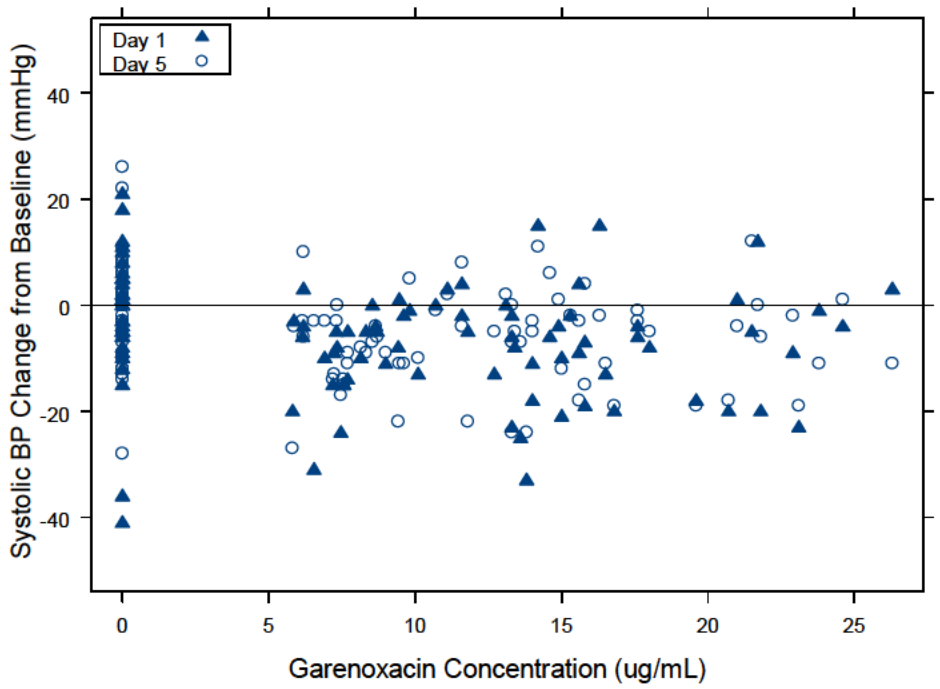

Figure 5 Changes in Systolic Blood Pressure From Predose Baseline vs Garenoxacin Plasma Concentration at 4 Hours Postdose (4 hours postdose represents the median Tmax for garenoxacin 1200 mg administered orally)
Concentration for placebo treatment was assigned as "0". Since garenoxacin blood samples were not collected on Day 1, changes in systolic blood pressure were plotted against concentration from Day 5.

The changes in QTcF vs garenoxacin exposure are shown in **Figure 6**. Exposure to garenoxacin 1200 mg was associated with some QTcF prolongation, but this relationship was not apparent at the exposure corresponding to the 600 mg dose (**Figure 7**), indicating that garenoxacin at 600 mg is not associated with QTc prolongation.

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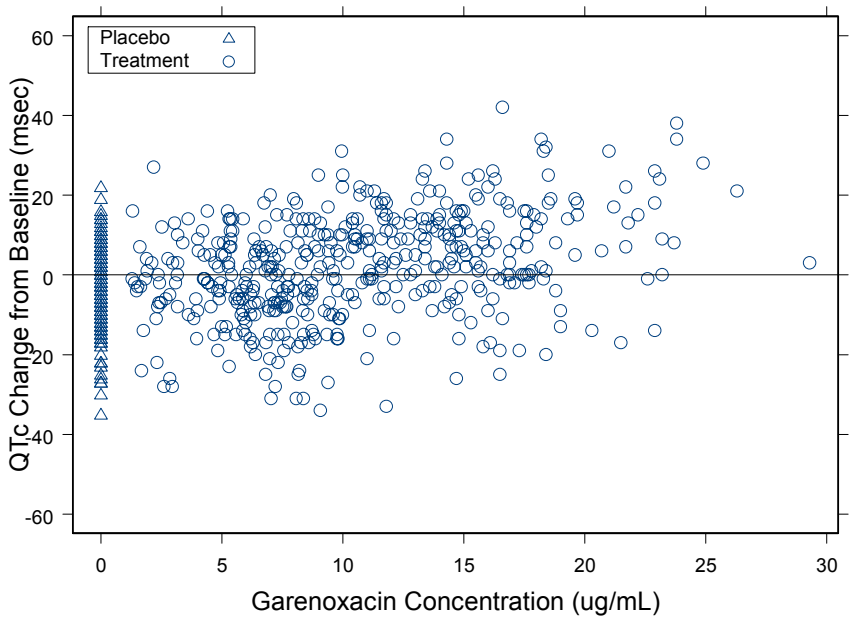

Figure 6 Changes in QTcF From Time-Matched ECGs vs Plasma Concentration of Garenoxacin Following Once-Daily Dosing for 5 Days

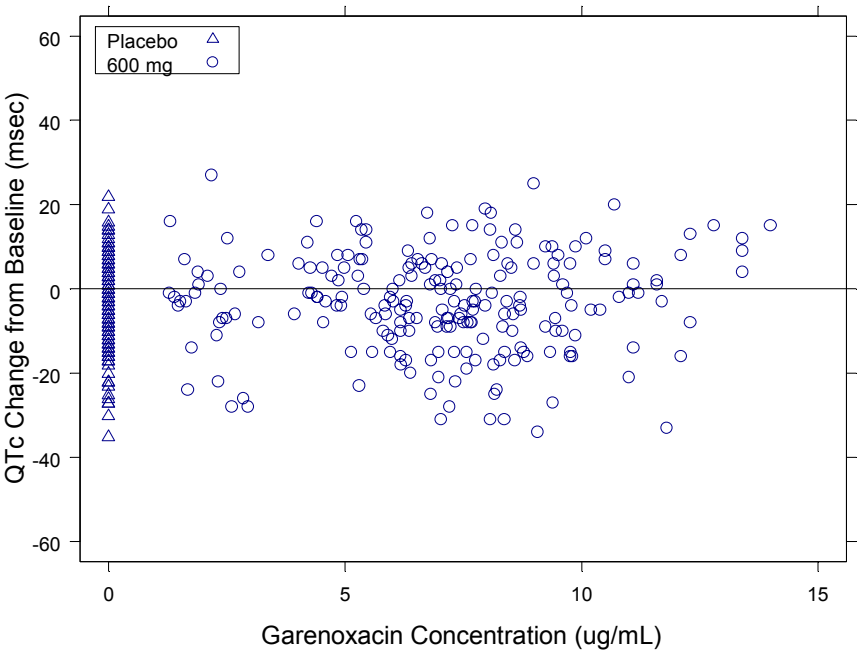

Figure 7 Changes in QTcF From Time-Matched ECGs vs Plasma Concentration of Garenoxacin Following Once-Daily Dosing at 600 mg for 5 Days

Pharmacogenetics: Blood samples were collected and stored, but not analyzed.

Title of Study: Thorough QT/QTc Study for Garenoxacin (SCH 745737) (Protocol No. P04342)

Safety: This study consisted of two parts and the adverse events for each part are summarized separately. Garenoxacin was safe and well tolerated at the therapeutic dose of 600 mg. A higher incidence of headache and gastrointestinal-related adverse events were noted with the supra-therapeutic dose levels (>600 mg). One placebo-treated subject from Part 1 experienced a serious adverse event of abdominal pain, and the abdominal pain was also associated with an anxiety attack that was treated with intravenous clonazepam. Similar adverse event profiles were observed in both Part 1 and Part 2. Majority of adverse events were mild to moderate in severity. The adverse event profile is consistent with previous experience with garenoxacin. Summaries of treatment-emergent adverse events can be found in .

For Part 1: Similar incidences of adverse events were reported among the treatment groups of garenoxacin at 1200 mg or 1600 mg and placebo. Compared to placebo, garenoxacin-treated subjects experienced a higher incidence of gastrointestinal related side effects, such as abdominal pain, diarrhea, nausea, and fatigue ( ). No symptomatic hypotension was reported in subjects who received garenoxacin treatment.

For Part 2: The summary of treatment-emergent adverse events can be found in **Table 7** and). Compared with 51% of placebo-treated subjects, garenoxacin-treated subjects reported a slightly higher incidence of treatment-emergent adverse events (71% with 600 mg, 84% with 1200 mg, and 74% with moxifloxacin). The adverse event profile was similar with placebo, garenoxacin, and moxifloxacin, except that more subjects reported fatigue and nausea with garenoxacin. It appeared that headache and gastrointestinal related adverse events were more prevalent with garenoxacin 1200 mg than with garenoxacin 600 mg. In addition, one placebo-treated subject and 3 subjects treated with garenoxacin 1200 mg experienced mild palpitation. These adverse event profiles are consistent with previously reported adverse event profiles. There was no clinically relevant effect on safety laboratory tests noted in this study ( ).

Table 7 Treatment-Emergent Adverse Events in Part 2 (Thorough QT Evaluation)

Adverse Event[a]	Moxifloxacin (n=34)	Placebo (n=35)	GRN 600 mg (n=34)	GRN 1200 mg (n=37)
Subjects reporting any adverse events	25 (74%)	18 (51%)	24 (71%)	31 (84%)
Palpitation	0	1 (3%)	0	3 (8%)
Abdominal pain	4 (12%)	2 (6%)	2 (6%)	7 (19%)
Diarrhea	9 (26%)	5 (14%)	4 (12%)	7 (19%)
Nausea	2 (6%)	1 (3%)	7 (21%)	14 (38%)
Vomiting	1 (3%)	0	1 (3%)	2 (5%)
Fatigue	4 (12%)	3 (9%)	7 (21%)	13 (35%)
Feeling cold	0	0	0	2 (5%)
Irritability	0	0	2 (6%)	0
Rhinitis	1 (3%)	0	2 (6%)	0
Myalgia	0	1 (3%)	3 (9%)	2 (5%)
Disturbance in attention	0	1 (3%)	3 (9%)	1 (3%)
Dizziness	4 (12%)	2 (6%)	2 (6%)	5 (14%)
Dysgeusia	2 (6%)	0	1 (3%)	1 (3%)
Headache	2 (6%)	1 (3%)	1 (3%)	6 (16%)
Attention deficiency/ hyperactivity disorder	2 (6%)	1 (3%)	1 (3%)	0
Dysmenorrhoea	0	0	0	2 (5%)
Pharyngolaryngeal pain	2 (6%)	0	2 (6%)	3 (8%)
Skin irritation	7 (21%)	7 (20%)	4 (12%)	2 (5%)

a: Events ≥2 subjects are listed in this table.

Source Data: .

Title of Study: Thorough QT/QTc Study for Garenoxacin (SCH 745737) (Protocol No. P04342)

CONCLUSIONS:

- Moxifloxacin at 400 mg was associated with increase in QTc, establishing the assay sensitivity.
- Garenoxacin at 1200 mg was associated with increase in QTc.
- Garenoxacin at 600 mg had no apparent effect on QTc.
- Oral administration of garenoxacin was associated with a mean decrease of 5 mm Hg in systolic blood pressure without an apparent effect on diastolic blood pressure or pulse rate. The effect on systolic blood pressure appeared to be comparable between garenoxacin 600 mg and 1200 mg.
- Garenoxacin administration appeared to be associated with a mild, nonclinically relevant prolongation of PR interval.
- In healthy subjects, garenoxacin at 600 mg was safe and well tolerated and garenoxacin at doses up to 1600 mg was safe and generally tolerated.

Date of the Synoptic Study Report: 20 NOV 2007