Figure 6: Time course of mean ΔΔQTcF

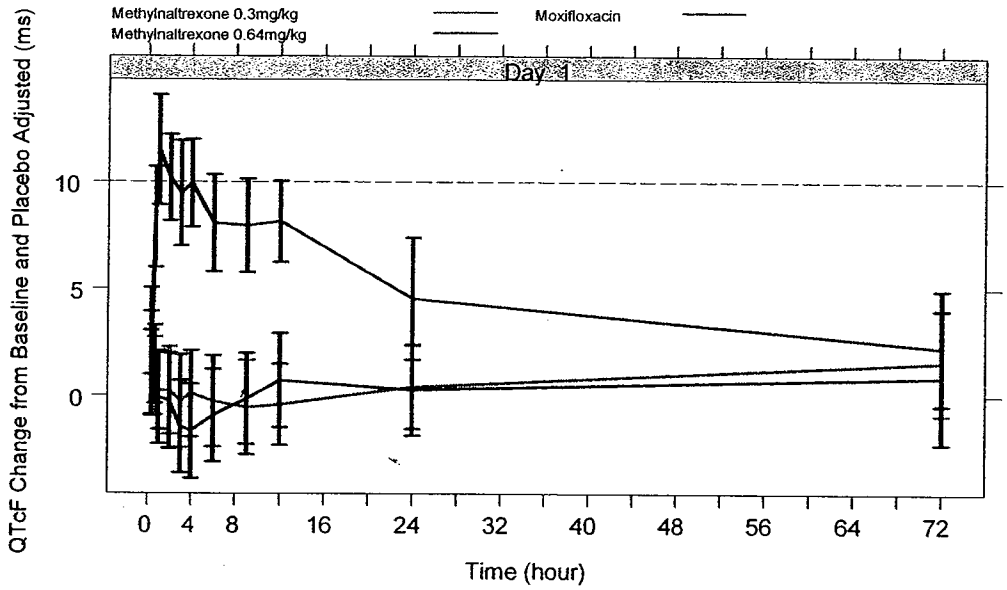
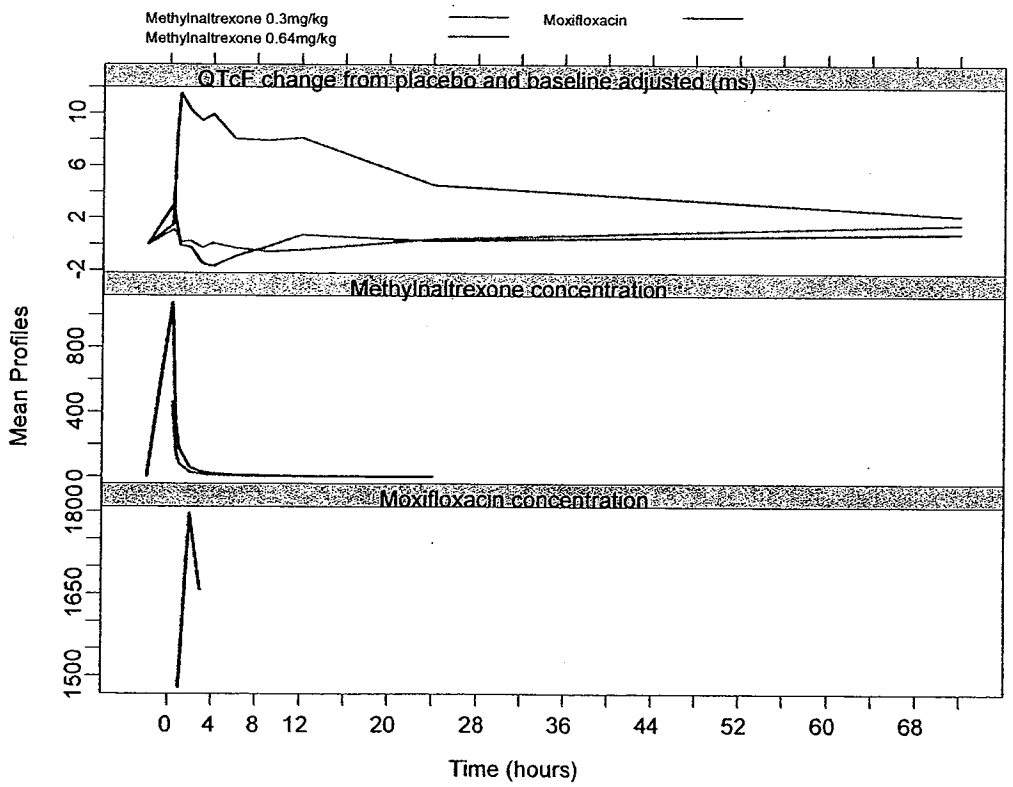
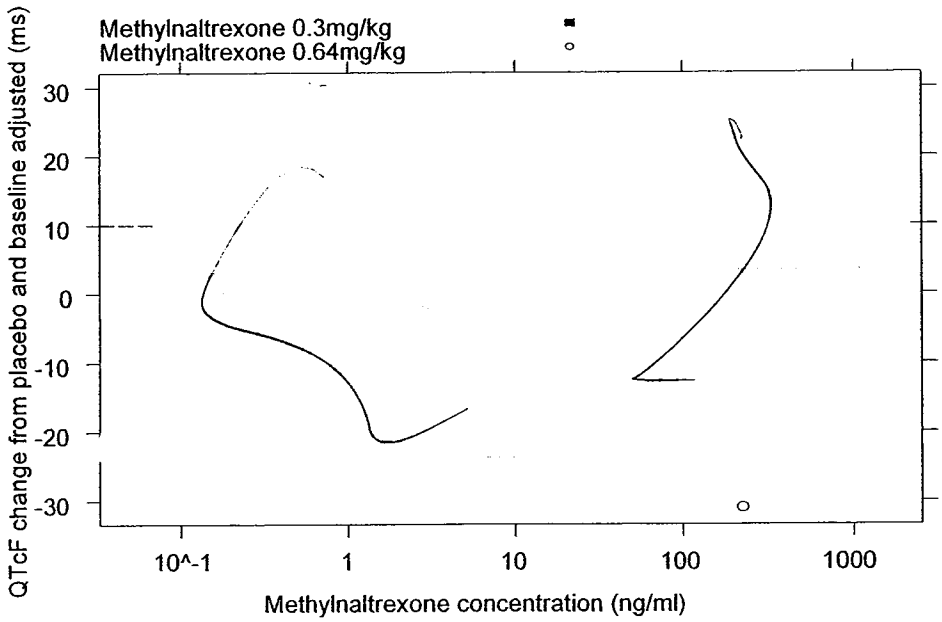


Figure 7: Time course of mean ΔΔQTcF and concentrations



Additional evidence based on Concentration-QTcF modeling from Figure 8, shows that methylnaltrexone does not prolong QT interval at the studied doses.

Figure 8: Log Concentration-ΔΔQTcF relationship



5.3 Clinical Assessments

None of the clinical events identified as of particular importance in ICH E14 (i.e. death, serious ventricular arrhythmia, syncope and seizure) were observed in this study with MOA-728

6 APPENDIX

6.1 Highlights of Clinical Pharmacology

Therapeutic dose Subcutaneous (SC)	• 8 mg for patients from 38 kg to < 62 kg • 12 mg for patients from 62 kg to 114 kg • 0.15 mg/kg for weights outside the indicated bands Each dose to be administered as a single SC dose not to exceed once daily.
Maximum tolerated dose	Not Determined for SC
Principal adverse events	Orthostatic hypotension at concentrations > 1400 ng/mL (variance not yet determined)

Maximum dose tested	Single Dose	• SC ~ 0.5 mg/kg single dose (Study MNTX 1106) • IV ~ 0.64 mg/kg single dose (Study 3200L2 104 US) • IV ~ 24 mg as a 20 min IV infusion (Studies MNTX 1303, MNTX 1304)
	Multiple Dose	• SC ~ No multiple SC doses were studied. • IV ~ 0.45 mg/kg as a 20 min IV infusion q6h for 5 doses (Study MNTX 1108). • IV ~ 24 mg as a 20 min IV infusion q6h for 17 doses (Study MNTX 1303)
Exposures Achieved at Maximum Tested Dose	Single Dose (Mean±SD)	At 0.50 mg/kg SC (Study MNTX 1106) • AUC_{24} (Area under the curve from dosing to 24 hours) = 582±111 ng/mL*h • C_{max} = 392±148 ng/mL At 0.64 mg/kg IV (Study 3200L2-104-US) • AUC_{24} = 739±139 ng/mL*h • C_{max} = 1062±258 ng/mL
	Multiple Dose (Mean±SD) or (Mean±CV)	No multiple SC doses were studied. At 0.45 mg/kg as a 20 min IV infusion q6h for 5 doses(Study MNTX 1108) • $C_{ss,max}$ = 1061±198 ng/mL • AUC_{τ} = 690±104 ng/mL*h At 24 mg as a 20 min IV infusion q6h for 17 doses (Study MNTX 1303) • $C_{ss,max}$ = 496±23% ng/mL • AUC_{τ} = 339±14% ng/mL*h
Range of linear PK	Linearity was clearly established across the SC dose range of 0.15 mg/kg (N = 39), 0.30 mg/kg (N = 39), and 0.50 mg/kg (N = 41) (Study MNTX 1106)	
Accumulation at steady state	• SC ~ Accumulation factor (R) simulated for once daily SC dosing (0.30 mg/kg) = 1.07 (simulation report in Module 5.3.5.3) • IV ~ Accumulation factor (R) following 0.45 mg/kg as a 20 min IV infusion q6h for 5 doses = 1.19 (Study MNTX 1108) • IV ~ Accumulation factor (R) following 24 mg as a 20 min IV infusion q6h for 17 doses = 1.20 (Study MNTX 1303)	

Metabolites	Urinary and fecal metabolite profiles suggest only limited biotransformation of MNTX in human subjects after IV administration (Study MNTX 102, IV administration). Metabolites identified to date include: • M1 Methyl 6 naltrexol sulfate • M2 Methylnaltrexone sulfate • M3 Dihydroxy methyl 6 naltrexol • M4 Methyl 6 naltrexol isomer • M5 Methyl 6 naltrexol isomer Following an IV 0.30 mg/kg (99.975 μCi) dose of ^{14}C MNTX in six healthy adult male subjects with sampling to 120 h (Study MNTX 102), the most abundant metabolites identified, methyl 6 naltrexol isomer (M4), methylnaltrexone sulfate (M2), and methyl 6 naltrexol isomer (M5), accounted for 3.15% 6.37%, 0.72% 2.11%, and 0.07% 1.43% of administered radioactivity, respectively, during the initial 24 h interval. Avery low recovery of radioactivity in exhaled CO_2 (0.06%) indicates that *N*demethylation to naltrexone is not a significant pathway for the metabolism of MNTX in humans.	
Absorption	Absolute/Relative Bioavailability (Mean ± SD)	At 0.30 mg/kg SC vs IV (Study MNTX 103), Absolute Bioavailability ~ F = = 0.82 ± 0.08.
	t_{max} (Median and Range)	• t_{max} = 0.5 h (0.25 – 0.75 h) N = 119 (Study MNTX 1106)
Distribution	V_{area}/F or V_{area}	SC ~ V_{area}/F ~ 8 – 12 L/kg (Studies MNTX 102,103) IV ~ V_{ss} = 1.07 L/kg (Study MNTX 1108)
	% bound	The portion unbound in human plasma ranges from 84.7% to 89.0% in the human. These fractions were independent of the concentrations tested and indicate minimal binding to plasma proteins.
Elimination	Route (Mean±SD)	Following as IV dose of 0.30 mg/kg (100μCi), 58.6±18.2% was recovered as unchanged MNTX in the urine (Study MNTX 102). Less than 10% was recovered in urine & feces as MNTX metabolites (Study MNTX 102).

	Terminal $t_{½}$	SC ~ Reported apparent terminal $t_{½}$ values of MNTX following SC administration have ranged from six to 13 h, depending on the time of the final blood collection ($t_{½}$ = 6, 8, 13, and 12 h for final collection times of 24, 48, 120, and 120 h, respectively) (Studies MNTX 1106, MNTX 103,MNTX 1105, MNTX 1107). Overall, $t_{½}$ appears to be independent of dose and route of administration. IV ~ $t_{½}$ = 7 - 9 h (Studies MNTX 103, 1303,1304)
CL/F or CL (Mean±SD)	SC ~ Cl/F = 1.39±0.21 L/h/kg at 0.10 mg/kg and1.00±0.14 L/h/kg at 0.30 mg/kg SC (Study MNTX 103) IV ~ Cl = 10.5±1.5 mL/min/kg (Study MNTX102) and 11.1±1.9 mL/min/kg (Study MNTX1108)	
Intrinsic Factors	Age Gender Race	SC ~ A combined analysis of healthy subject data from Studies MNTX 103, MNTX 1105, MNTX1106, and MNTX 1107 (140 subjects, 150 PK profiles) revealed no clinically significant effects of gender, race, ethnicity, age, or body weight on MNTX pharmacokinetics. Completed studies involving subjects >65 years of age include: Study MNTX 1105 which enrolled 10 subjects≥65 years (four mild, two moderate, four severe renal impairment, no normals), and Study MNTX1107 which enrolled two subjects ≥65 years (one mild hepatic impairment, one normal). IV ~ Following 24 mg as a 20 min IV infusionq6h for 17 doses to healthy adult (18 45 yr) and elderly (≥65 yr) peak exposure (C_{max}) increased approximately 10% and total exposure increased approximately 25% (Study MNTX 1303).

	Hepatic & Renal Impairment (Mean±SD)	Impairment of renal function has a marked effect on the renal clearance (Cl_R) of MNTX. The extent of the effect on renal clearance (Cl_R) is consistent with the degree of renal function impairment. However, an eight to nine fold reduction of renal clearance in humans (normal renal function Cl_R = 441±149 mL/min, severe renal impairment Cl_R = 52±28 mL/min) affected only a two fold increase in total exposure (normal renal function AUC_∞ = 433±92 ng/mL*h, severe renal impairment AUC_∞ = 822±76 ng/mL*h) (Study MNTX 1105). Hepatic impairment has no clinically significant effect on the pharmacokinetics of MNTX (Study MNTX 1107).
Extrinsic Factors	Drug Drug Interactions	• No clinically significant effect on CYP2D6(Study MNTX 1108) • No clinically significant effect from drugs competing for OCT1/2 renal transporters(Study MNTX 1304)
	Food Effects	Not applicable
Expected High Clinical Exposure Scenario (Mean±SD)	• At 8 mg SC for body weights of 38 to 61 kg, AUC_∞ was estimated to be between 194 -148 ng/mL*h, or at 12 mg SC for body weights of 62 to114 kg, AUC_∞ was estimated to be between 220-169 ng/mL*h	

6.2 TABLE OF STUDY ASSESSMENTS

Table 5-1: Study Flowchart

Study Period	Screening Evaluation[a]	1	Interperiod Interval[b]	2	Interperiod Interval[b]	3	Interperiod Interval[b]	4	
Study Days	-21 to -3	-2 to 4		-2 to 4		-2 to 4		-2 to 3	4/FSE[c]
Informed consent	X								
Outpatient visit	X								
Inpatient confinement		X	X	X	X	X	X	X	X
Medical history	X								
Physical examination	X[d]								X
Brief physical assessment		X		X		X		X	
HIV screen, HCV antibody screen, and HBsAg screen	X								
Pregnancy test (women only)	X	X							X
Urine drug screen & Alcohol screen	X	X							
Laboratory evaluation[e]	X	X		X		X		X	X
Supine vital signs	X	X		X		X		X	X
12-Lead electrocardiogram (single)	X	X		X		X		X	X
12-Lead electrocardiogram (triplicate)		X		X		X		X	
Randomization		X							
Test article administration		X		X		X		X	
PK blood sample collection for MOA-728		X		X		X		X	
PK blood sample collection for moxifloxacin		X		X		X		X	
Pharmacogenomic blood sample collection		X							
Monitoring of adverse events	X	X	X	X	X	X	X	X	X
Nonstudy medication monitoring	X	X	X	X	X	X	X	X	X
Conclusion of subject participation									X
CPE number (for sponsor use only)	1	2-8	8	9-15	15	16-22	22	23-28	29

Table 5-1: Study Flowchart (Cont'd)

Study Period	Screening Evaluation[a]	1	Interperiod Interval[b]	2	Interperiod Interval[b]	3	Interperiod Interval[b]	4	
Study Days	-21 to -3	-2 to 4		-2 to 4		-2 to 4		-2 to 3	4/FSE[c]

Abbreviations: FSE = final study evaluation; PK = pharmacokinetic; HbsAg = hepatic B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency.

a. Within 21 days before test article administration.
b. The interperiod interval will be 1 day.
c. The FSE will be performed on day 4, period 4, or upon early withdrawal from the study.
d. Physical examination will include height (cm) and weight (kg).
e. Laboratory evaluation should be fasting with the exception of screening and day -2 (period 1 only). Includes hematology, coagulation, blood chemistry, and urinalysis.

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joanne Zhang
2/4/2008 11:15:49 AM
BIOMETRICS

Kate L Dwyer
2/4/2008 11:22:04 AM
BIOMETRICS

Christine Garnett
2/4/2008 01:31:29 PM
BIOPHARMACEUTICS
Nitin Mehrotra was the clinical pharmacology reviewer.

Suchitra Balakrishnan
2/4/2008 02:00:25 PM
MEDICAL OFFICER

Norman Stockbridge
2/4/2008 03:05:46 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review

NDA	21-964 / N000
Generic Name	Methylnaltrexone Injection
Sponsor	Progenics Pharmaceuticals, Inc.
Proposed Indication	Treatment of Opioid Induced Constipation in Patients Receiving Palliative Care
Dosage Forms	• Solution for subcutaneous injection • [illegible] • [illegible]
Proposed Therapeutic Dose	• 8 mg/day SC for patients from 38 kg to < 62 kg • 12 mg/day SC for patients from 62 kg to 114 kg • 0.15 mg/kg/day SC for other weights
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	0.64 mg/kg IV bolus
Application Submission Date	3/30/2007
Review Classification	TQT Study report in Standard NDA
Date Consult Received	6/28/2007
Date Consult Due	8/15/2007
Clinical Division	Division of Gastrointestinal Products
PDUFA Date	1/30/2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

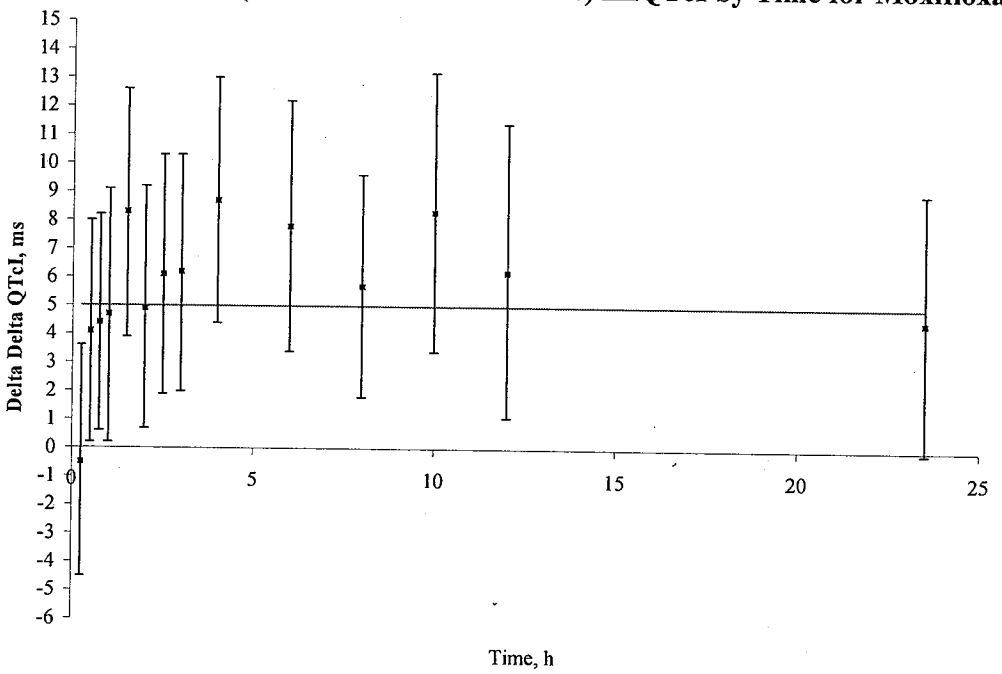
Progenics Pharmaceuticals, Inc. has submitted NDA 21964 seeking approval to market methylnaltrexone solution for subcutaneous injection (MNTX) as treatment for opioid induced constipation in patients receiving palliative care. In the NDA they included a study report for study 3200L2-104-US, a single-center, randomized, placebo and positive controlled, parallel group study designed to evaluate the effect of methylnaltrexone administration on the QT interval.

In this study the positive control, a single oral dose of 400 mg moxifloxacin, failed to have the expected effect on the QTc; at no time was the mean effect on the QTc greater than 5 ms as evidenced by a lower 90% confidence interval ≥ 5 ms. Therefore, the study lacked assay sensitivity, i.e. the ability to detect a mean effect of methylnaltrexone on the QTc of about 5 ms had it been present. We conclude that study 3200L2-104-US failed to provide adequate data to reach a conclusion about the effect of administering methylnaltrexone on the QT interval.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

1. In thorough QT studies, it is important to have a high degree of confidence in the ability of the study as designed and conducted to detect small QT effects. When moxifloxacin is used as the positive control, the mean effect on the QTc should be greater than 5 ms (as evidence by the lower 90% confidence interval ≥5 ms) at one timepoint. This study failed to demonstrate assay sensitivity because the greatest lower 90% confidence bound is 4.4 ms at 4 hours after dosing, as shown in Figure 1. Failure to detect the positive control's anticipated effect indicates that the study could not detect an effect of similar magnitude for methylnaltrexone.

Figure 1: Mean (90% Confidence Intervals) ΔΔQTcI by Time for Moxifloxacin



2. The moxifloxacin effect on the QTcF was prolonged well beyond the time the serum concentration of moxifloxacin is expected to have significantly declined, not returning to baseline for at least 12 hrs post dosing.

3. The confidence intervals for the placebo corrected mean change in QTc of moxifloxacin and MNTX are wide and overlapping indicating large variability in the study, as shown in figure 2. This large variability may be due in part to the use of a parallel group design instead of a crossover design, which limits variability by using each subject as their own control. Given the terminal half-life of injected methylnaltrexone of 6-13 hrs, the choice of a parallel group design was not good.

2.3 MARKET APPROVAL STATUS

Not approved for marketing in any country.

2.4 PRECLINICAL INFORMATION

In the 1 Mar 2006 IB the sponsor states:

"In an in vitro assay to examine ion currents in mammalian cells transfected with the cloned human ether-a-go-go related gene...to compare the effects to the positive control cisapride, the IC_{50} for MNTX was > 1000 μM, whereas the IC_{50} for cisapride was 0.051 μM. In isolated canine Purkinje fibers, MNTX caused a prolongation in action potential duration $(APD)_{60}$ (7% to 21%) and $(APD)_{90}$ (5% to 16%) at concentrations up to 10 μM MNTX. The changes recorded for MNTX in canine fibers were neither concentration-dependent nor rate-dependent. In isolated rabbit Purkinje fibers, MNTX at 1, 10, and 100 μM did not induce statistically significant prolongation when compared with controls.

Conscious, telemetrized dogs received single IV dosages of 1, 5, and 20 mg/kg MNTX.† MNTX did not produce any alteration in the QTc interval value in 3 of 4 dogs at any dosage; however, 1 dog did show a transient increase in QTc interval duration after administration of 20 mg/kg. The increase in QTc interval for this 1 animal was 38 msec (18%), 54 msec (24%), and 49 msec (22%) compared with vehicle control values at 60, 75, and 90 minutes after dosing, respectively. Similar increases were not seen in other animals at any time interval examined or at any dosage tested."

2.5 PREVIOUS CLINICAL EXPERIENCE

As of 31 Dec 2006, over 724 healthy subjects or patients have been exposed to injected doses up to 0.5 mg/kg and oral doses up to 900 mg of MNTX in studies sponsored by the current sponsor; 441 healthy subjects or subjects with renal or hepatic impairment in 15 Phase 1 studies and 220 patients in five phase 2 and 3 human clinical trials.

The most commonly reported AE was abdominal pain and nausea. No cardiac deaths or sudden deaths are reported.

2.6 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features of MNTX's clinical pharmacology.

Table 1: Highlights of Clinical Pharmacology

Therapeutic Dose (SC)	• 8 mg/day for patients from 38 kg to < 62 kg • 12 mg/day for patients from 62 kg to 114 kg • 0.15 mg/kg/day for weights outside the indicated bands
Maximum Tolerated Dose (MTD)	No MTD was determined for SC administration.
NOAEL	Rats, 3-month toxicity, IV 5 mg/kg Rats, perinatal/postnatal, SC 25 mg/kg Dogs, 3-month toxicity, IV 5 mg/kg
Principal AE's At SC doses of 0.075, 0.15, and 0.30 mg/kg in double-blind, placebo-	Abdominal pain (29% vs placebo 10%), flatulence (13% vs placebo 6%), nausea (12% vs placebo 5%), dizziness (7% vs placebo 2%), diarrhea (6% vs placebo 2%) [Studies MNTX-301, MNTX-302].

† [redacted]. MOA-728: A cardiovascular evaluation of methylnaltrexone in beagle dogs [redacted] Study Identification Number 940-GOI, 2002). Wyeth RPT-63423, 2006.

controlled studies.	
Dose-Limiting AE	Orthostatic hypotension ‡
Maximum Dose Tested (Single SC dose)	0.50 mg/kg SC [Study MNTX-1106]
Maximum Dose Tested (Multiple IV dose)	0.45 mg/kg as a 20-min IV infusion q6h for 5 doses [Study MNTX-1108]. No multiple SC doses were studied.
Exposures at Maximum Dose Tested (Single SC dose)	At 0.50 mg/kg SC [Study MNTX-1106] • AUC_{24} (Area under the curve from dosing to 24 hours) = 582±111 ng*h/mL • C_{max} = 392±148 ng/mL
Exposures at Maximum Dose Tested (Multiple IV dose)	At 0.45 mg/kg as a 20-min IV infusion q6h for 5 doses [Study MNTX-1108] • AUC_{τ} (Area under the curve within a dosing interval at steady-state) = 690±104 ng*h/mL • $C_{ss,max}$ (Peak exposure at steady-state) = 1061±198 ng/mL
Pharmacokinetic Linearity	Linearity was clearly established across the SC dose range of 0.15 mg/kg (N = 39), 0.30 mg/kg (N = 39), and 0.50 mg/kg (N = 41) [Study MNTX-1106]
Accumulation at Steady-State	At 0.45 mg/kg as a 20-min IV infusion q6h for 5 doses [Study MNTX-1108], R (accumulation index) = 1.19 R simulated for once daily SC dosing (0.30 mg/kg) = 1.07
Metabolites	Urinary and fecal metabolite profiles suggest only limited biotransformation of MNTX in human subjects after IV administration [Study MNTX-102]. Metabolites identified to date include: • M1 Methyl-6-naltrexol sulfate • M2 Methylnaltrexone sulfate • M3 Dihydroxy-methyl-6-naltrexol • M4 Methyl-6-naltrexol isomer • M5 Methyl-6-naltrexol isomer Following an IV 0.30 mg/kg (99.975 μCi) dose of ^{14}C-MNTX in six healthy adult male subjects with sampling to 120 h [Study MNTX-102], the most abundant metabolites identified, methyl-6-naltrexol isomer (M4), methylnaltrexone sulfate (M2), and methyl-6-naltrexol isomer (M5), accounted for 3.15% - 6.37%, 0.72% - 2.11%, and 0.07% - 1.43% of administered radioactivity, respectively, during the initial 24-h interval. A very low recovery of radioactivity in exhaled CO_2 (0.06%) indicates that *N*-demethylation to naltrexone is not a significant pathway for the metabolism of MNTX in humans. Metabolite pharmacokinetics was not studied.
Absorption	At 0.30 mg/kg SC vs IV [Study MNTX-103], F ~ Absolute Bioavailability = 0.82±0.08. Across studies t_{max} is consistently observed within 0.5 h.
Distribution	V_{area} = 7.92±1.54 L/kg [Study MNTX-102] V_{ss} = 1.0±0.21 L/kg [Study MNTX-1108] The portion unbound in human plasma ranges from 84.7% to 89.0% in the human. These fractions were independent of the concentrations tested and indicate minimal binding to plasma

‡ J. F. Foss, M. F. O'Connor, Chun-Su Yuan, M. Murphy, J. Moss, M. F. Roizen, *Safety and tolerance of methylnaltrexone in healthy humans: A randomized, placebo-controlled, intravenous, ascending-dose, pharmacokinetic study*, **J Clin Pharmacol**, 37, 25 – 30 (1997).

	proteins.
Clearance	Total clearance (Cl) = 10.5±1.5 mL/min/kg [Study MNTX-102] & 11.11±1.87 mL/min/kg [Study MNTX-1108]. Renal clearance (Cl_R) = 6.37±3.00 mL/min/kg [Study MNTX-102] Metabolism appears to account for < 10% of MNTX clearance.
Urinary & Fecal Recovery	Following an IV 0.30 mg/kg (99.975 µCi) dose of ^{14}C-MNTX, 53.6±6.2 % of administered radioactivity was recovered in the urine and 58.6±18.2 % of the 0.30 mg/kg dose was recovered as MNTX. Significant radioactivity in the feces suggested the involvement of hepatobiliary secretion and/or gastrointestinal efflux. [Study MNTX-102]
Terminal Half-Life ($t_{1/2}$)	Reported apparent terminal $t_{1/2}$ values of MNTX following SC administration have ranged from 6 to 13 h, depending on the time of the final blood collection ($t_{1/2}$ = 6, 8, 13, and 12 h for final collection times of 24, 48, 120, and 120 h, respectively) [Studies MNTX-1106, MNTX-103, MNTX-1105, MNTX-1107]. Overall, $t_{1/2}$ appears to be independent of dose and route of administration.
Intrinsic Factors Gender, race, ethnicity, age, body weight (SC Studies)	A combined analysis of healthy subject data from Studies MNTX-103 (0.30 mg/kg IV & 0.15, 0.30, & 0.45 mg/kg SC), MNTX-1105 (0.30 mg/kg SC), MNTX-1106 (0.15, 0.30, & 0.50 mg/kg SC), and MNTX-1107 (0.30 mg/kg SC) (140 subjects, 150 PK profiles) revealed no clinically significant effects of gender, race, ethnicity, age, or body weight on MNTX pharmacokinetics.
Intrinsic Factors Age (IV Study)	A double-blind, randomized, single-period, two-sequence, placebo-controlled, parallel group study [Study MNTX-1303], assessing the pharmacokinetics, safety and tolerability of MNTX following single doses (24 mg by 20-min IV infusion) and at steady state during multiple dosing (24 mg by 20-min IV infusion q6h) and evaluating the effects of aging on the pharmacokinetics, safety, and tolerability of MNTX was conducted after the submission cut-off of NDA 21964. Preliminary results, suggesting a slightly higher, but clinically insignificant, exposure in the elderly, will be submitted with the 120-day safety update.
Intrinsic Factors Renal Impairment	Renal function impairment had a marked effect on the pharmacokinetics of MNTX following single 0.3 mg/kg SC doses [Study MNTX-1105]. The extent of the effect on renal clearance (Cl_R) is consistent with the degree of renal function impairment. However, an eight- to nine-fold reduction of renal clearance in humans (normal renal function - Cl_R = 441±149 mL/min, severe renal impairment - Cl_R = 52±28 mL/min) affected only a two-fold increase in total exposure (normal renal function - AUC_∞ = 433±92 ng/mL*h, severe renal impairment - AUC_∞ = 822±76 ng/mL*h) [Study MNTX-1105].
Intrinsic Factors Hepatic Impairment	Mild to moderate hepatic impairment had no significant effect on the pharmacokinetics of MNTX following single 0.3 mg/kg SC doses [Study MNTX-1107]. Effects of severe hepatic impairment were not studied.
Extrinsic Factors Drug-Drug Interactions (CYP2D6)	MNTX, as a single 0.30 mg/kg SC dose and as 0.45 mg/kg by 20-min IV infusion q6h for 5 doses, had no effect on the

	pharmacokinetics of dextromethorphan, a CYP2D6 substrate [Study MNTX-1108].
Extrinsic Factors Drug-Drug Interactions (Renal OCT1 & 2 Transporters)	An assessment of the effect of steady-state cimetidine, an inhibitor of the OCT1 & OCT2 renal transporters, on MNTX pharmacokinetics following a single dose of 24 mg by 20-min IV infusion [Study MNTX-1304] was conducted after the submission cut-off of NDA 21964. The study report is in preparation and preliminary results will be submitted with the 120-day safety update. These results indicate that cimetidine had no effect on the pharmacokinetics, safety, and tolerability of MNTX following 24 mg administered as a 20-min IV infusion in 18 healthy adult human subjects.
Extrinsic Factors Food Effects	NA
Expected High Clinical Exposure Scenario	At 8 mg, a 38 kg patient would receive 0.21 mg/kg and a 62 kg patient would receive 0.13 mg/kg. At 12 mg, a 62 kg patient would receive 0.19 mg/kg and a 114 kg patient would receive 0.11 mg/kg. Note that AUC per 1 mg/kg dose increases slightly as body weight increases (see section 5.3.5.3.5 of the NDA). For a simple comparison, the table below provides exposures at doses of 0.15, 0.30, & 0.50 mg/kg [MNTX-1106, N = 119]: **Mean (SD) Pharmacokinetic Metrics of MNTX Following Single Subcutaneous Doses [mean (SD), MNTX-1106]** **Metric** | **0.15 mg/kg N =39** | **0.30 mg/kg N = 39** | **0.50 mg/kg N = 41** AUC_{24} (ng*h/mL) | 175 (37) | 362 (64) | 582 (111) C_{max} (ng/mL) | 117 (33) | 239 (62) | 392 (148) t_{max} (h) | 0.5 (0.25-0.75) | 0.5 (0.25-0.75) | 0.5 (0.25-0.75) t_{max} expressed as median (range) Daily administration would not result in significant accumulation. Accordingly the Expected High Clinical Exposure Scenario during repeated daily dose administration would not differ significantly from that following a single SC dose.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The following were submitted by the sponsor and reviewed by the QT-IRT: TQT study report, 1 Mar 2007 Investigator's brochure, sponsor supplied Highlights of Clinical Pharmacology Table, Raw SQT and PK datasets

3.2 QT STUDY

3.2.1 Title

A Randomized, Double-Blind, Placebo/Positive Controlled Evaluation of the Effects of MNTX on ECG Parameters and Cardiac Repolarization in Normal Volunteers

3.2.2 Protocol Number

3200L2-104-US

3.2.3 Objectives

3.2.3.1 Primary Objective

Compare the effects of clinical and supratherapeutic doses of MNTX with the effects of placebo on QTcI duration

3.2.3.2 Secondary Objectives

Evaluate the effects of MNTX on QTcB, QTcF, and other electrocardiographic parameters, such as heart rate, pulse rate, QRS and QT intervals, and morphological changes

3.2.4 Design

3.2.4.1 Description

Single-center, randomized, placebo and positive controlled, parallel group phase 1 study in which subjects were randomized 1:1:1:1:1 to one of five treatments.

Eligible subjects checked into the clinic approximately 36 hours before dosing (Day -2) and were randomized. On the day before dosing, all subjects were fitted with a digital 12-lead ECG recorder. On the morning of Day 1, subjects received randomized treatment and began a second 24-hour continuous digital ECG. Serial blood samples were obtained over a 24-hour period during baseline and again after dosing on Day 1. Post dose samples from subjects administered MNTX were assayed for drug concentration for pharmacokinetics and PK-PD analyses. Predose samples and those from subjects administered moxifloxacin and placebo were not analyzed.

3.2.4.2 Sponsor's Justification for Design

Positive and negative control groups are essential to define the ECG effects of MNTX in light of the large degree of spontaneous inter- and intrasubject variability in QT interval duration. A blinded placebo group served as the negative control. Moxifloxacin was used as the positive control to demonstrate that the study had adequate sensitivity to detect small changes in QT intervals.

3.2.4.3 Controls

The sponsor used both negative (placebo) and positive (moxifloxacin) controls.

3.2.4.4 Blinding

MNTX (0.15 mg/kg, 0.30 mg/kg, and 0.50 mg/kg) and placebo treatments were administered double-blinded; moxifloxacin was administered in an open-label manner.

The central laboratory personnel responsible for measurement and interpretation of the digital ECG data were blinded to study treatment. Plasma samples obtained from all subjects remained blinded and were shipped to the bioanalytical laboratory.

3.2.5 Dosing Regimens

3.2.5.1 Treatment Arms

Each subject received one of the five treatments described in Table 2:

Table 2: Description of Study Treatments

Treatment Group	Planned Number of Subjects (N)	Study Treatment	Method of Administration
1	40	MNTX 0.15 mg/kg	single SC injection
2	40	MNTX 0.30 mg/kg	single SC injection
3	40	MNTX 0.50 mg/kg	single SC injection
4	40	Placebo (matching MNTX)	single SC injection
5	40	Moxifloxacin 400 mg	single 400 mg tablet PO

(Source: Clinical Study Report: Study MNTX 1106; Table 2, page 20)

3.2.5.2 Sponsor's Justification for Doses

Single doses of MNTX, 0.64 mg/kg and delivered by IV push, elicited transient, symptomatic orthostatic hypotension in 37.5% of a population of healthy, normal volunteers.[§] In discussions between the sponsor and the FDA, it was agreed that the supratherapeutic dose to be used in this study should be 0.50 mg/kg (below the dose that resulted in dose-limiting toxicity). In accordance with the ICH E14 guidance, two doses within the therapeutic dose range (0.15 mg/kg and 0.30 mg/kg) were also evaluated. The dose of moxifloxacin used in this study (400 mg) is known to prolong the QT interval, which makes it appropriate for an active control.

3.2.5.3 Instructions with regard to meals

Standard meals were provided during confinement to the Clinical Research Unit. Subjects fasted from midnight on Day -1 prior to the start of baseline assessments and for 4 hours thereafter, and again from midnight on Day 1 until 4 hours after dosing with study drug.

3.2.6 Study Assessments

Table 3: Highlights of Schedule of Interventions

Study Day	-2 (-36 to -24 hr)	-1 (-24 to 0 hr)	1 (0-24 hr)	2 (24+ hr)
Intervention	Check-in	Baseline	Single dose	Discharge
12-Lead ECGs[3]		Record ECGs	Record ECGs	
PK Samples for drug[4]		Collected	Collected	

[§] Foss J, O.Connor M, Yuan C, et al. (1997) Safety and tolerance of methylnaltrexone in healthy humans: a randomized, placebo-controlled, intravenous, ascending-dose, pharmacokinetic study. J Clin Pharmacol, Jan; 37(1):25-30.

(3) To allow for replacement of [redacted] flash memory cards, actual elapsed time for recording Baseline ECG data could be 23.75 to 24 hr, starting at -24 hr (predose). Data from the second flash memory card encompassed "time zero" (time of study drug administration) and ended at 23.75 to 24 hr post dose.
(4) Blood samples were drawn at Baseline (Day -1 to Day 1) at time 0 (within 30 minutes of the initiation of [redacted] ECG recording), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 23.75 hours after initiation of 24-hr ECG. Samples on Day 1 were taken before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours following dosing. The predose sample corresponded to the 23.75-hr sample from the Baseline Period. Two samples were not taken for this time point. Deviations from nominal sampling times were documented.

3.2.6.1 Sponsor's justification for sampling schedule

None provided.

3.2.6.2 Baseline

Both time-matched and time-averaged baselines were used in the study.

3.2.6.3 ECG Collection

Digital 12-lead ECG data were acquired an ECG sample every 10-15 seconds using a continuous ECG recorder. The digital ECG data were collected on a compact flash memory card for all 12 leads simultaneously.

Three discrete digital ECG recordings were taken approximately 1 minute apart at each scheduled time point. High resolution measurement of the cardiac intervals and morphological assessment were made by personnel at a central laboratory blinded to study treatment. Measurements were initially performed by trained analysts using a validated electronic caliper system applied to a computer monitor screen. The central expert cardiologist subsequently verified the interval durations and performed the ECG wave form analysis.

A total of 45 ECGs (corresponding to triplicate measurements at 15 time points) were analyzed for baseline and 42 ECGs (14 time points) on Day 1, for a total of 87 ECGs for each subject.

3.2.7 Sponsor's Results

3.2.7.1 Study Subjects

207 healthy male and female subjects 18 - 45 years of age with normal baseline ECGs and BMIs were enrolled in the study between 22 Nov 2004 and 13 Jan 2005. One subject withdrew consent after receiving moxifloxacin on Day 1; all other subjects completed the study discharge assessments. As a result of technical problems encountered with the Holter ECG recordings, 7 subjects were not included in ECG population due to inadequate ECG data for analysis; 2 randomized to moxifloxacin, 4 to placebo, and 1 to high dose MNTX.

Reviewer comment: The sponsor does not stipulate the nature of the technical problems. Having uninterpretable ECGs from 7 subjects is unusual and may indicate a more widespread problem with ECG acquisition in this study.

The analysis populations are summarized by treatment in Table 4.

Table 4: Analysis Populations

Analysis population	MNTX 0.15 mg/kg N = 40	MNTX 0.30 mg/kg N = 39	MNTX 0.50 mg/kg N = 41	Placebo N = 44	Moxifloxacin N = 43	Overall N = 207
Total enrolled	40	39	41	44	43	207
Safety	40	39	41	44	43	207
PK[a]	39	39	41	NA	NA	119
ECG[b]	40	39	40	40	40	199

NA = not applicable.

a Excludes Subject 01-368 who received placebo as the result of a dosing error.

b Subject 01-066 (moxifloxacin) withdrew consent. Subjects 01-044 (0.50 mg/kg MNTX), 01-064 (moxifloxacin), 01-065 (placebo), 01-142 (placebo), 01-216 (placebo), 01-253 (placebo), and 01-394 (moxifloxacin) were excluded from the analysis because of inadequate ECG data.

Reference: Table 14.1-2, Table 14.2-1.1.1, and Table 14.4.2.

(Source: Clinical Study Report: Study MNTX 1106; Table 7, page 37)

3.2.7.2 Statistical Analyses

3.2.7.2.1 Populations

Safety population: All subjects who received study drug.

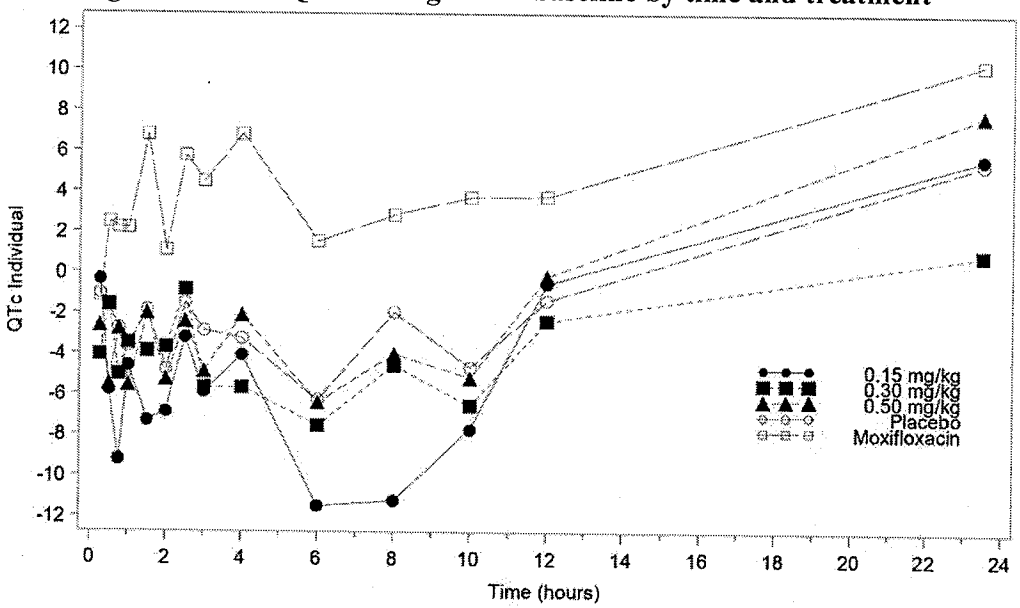
PK Population: All subjects who received MNTX, completed the study, and had sufficient plasma concentration data for analysis.

ECG Population: All subjects who received study drug, and had adequate baseline and post-dose digital ECG data.

3.2.7.2.2 Primary Analysis

The time-matched mean change from baseline QTcI is plotted in Figure 3 and summarized by treatment in Table 5. A change from baseline of up to 8 ms for QTcI and QTcF was observed at the 23.5-hour time point for placebo, as well as the 0.15 and 0.50 mg/kg MNTX treatment groups. The change for the 0.30 mg/kg MNTX treatment group was 0-1 ms, which is similar to the general change (-2 to 0 ms) at the 12-hour time point for all MNTX treatment groups and placebo. The change from baseline at the 23.5-hour time point for moxifloxacin was 8-10 ms compared to a 4 ms change at the 12-hour time point.

Figure 3: Mean QTcI change from baseline by time and treatment



(Source: Clinical Study Report: Study MNTX 1106; Figure 1, page 42)

Reviewer comment: A plot of the central tendency is not a plot of the mean; the sponsor should have indicated the 90% confidence interval within which the true mean would be found; see figure 2 above.

Table 5: Mean (SD) QTcI change from baseline by time and treatment

Time post-dose (hours)	MNTX 0.15 mg/kg N = 40	MNTX 0.30 mg/kg N = 39	MNTX 0.50 mg/kg N = 40	Placebo N = 40	Moxifloxacin N = 40
	Mean QTcI (SD) msec				
0.25	-0.35 (14.0)	-4.05 (13.1)	-2.62 (11.2)	-1.03 (11.7)	-1.17 (11.3)
0.5	-5.81 (13.3)	-1.57 (12.1)	-5.48 (10.5)	-1.72 (11.0)	2.49 (11.8)
0.75	-9.22 (9.96)	-5.02 (9.88)	-2.77 (11.4)	-2.75 (10.3)	2.22 (11.6)
1	-4.61 (11.2)	-3.46 (13.1)	-5.58 (10.6)	-3.65 (13.3)	2.18 (11.2)
1.5	-7.31 (13.5)	-3.88 (11.0)	-1.99 (9.80)	-1.85 (10.8)	6.79 (12.5)
2	-6.88 (10.8)	-3.68 (10.1)	-5.27 (12.7)	-4.78 (12.2)	1.10 (12.7)
2.5	-3.20 (13.6)	-0.84 (12.9)	-2.41 (13.3)	-1.51 (11.8)	5.74 (14.0)
3	-5.88 (13.2)	-5.68 (9.78)	-4.87 (12.5)	-2.87 (9.71)	4.50 (14.6)
4	-4.07 (10.2)	-5.67 (11.9)	-2.10 (10.3)	-3.25 (10.8)	6.82 (14.0)
6	-11.5 (17.1)	-7.54 (16.6)	-6.40 (15.0)	-6.28 (12.5)	1.53 (12.0)
8	-11.2 (11.2)	-4.56 (13.2)	-3.99 (9.62)	-1.94 (11.7)	2.87 (10.8)
10	-7.73 (12.5)	-6.56 (12.0)	-5.17 (14.5)	-4.66 (12.4)	3.74 (14.4)
12	-0.52 (11.4)	-2.37 (11.3)	-0.17 (10.4)	-1.36 (14.0)	3.78 (13.9)
23.5	5.66 (11.8)	0.91 (12.9)	7.81 (11.2)	5.40 (13.9)	10.31 (13.3)

SD = standard deviation

Subjects 01-044 (0.50 mg/kg MNTX), 01-064 (moxifloxacin), 01-065 (placebo), 01-142 (placebo), 01-216 (placebo), 01-253 (placebo), and 01-394 (moxifloxacin) were excluded from the analysis because of inadequate ECG data.

Reference: Table 14.2-1.1.1. (The "error corrected" results excluding Subjects 01-364 and 01-368 are displayed in Table 14.2-1.1.2.)

(Source: Clinical Study Report: Study MNTX 1106; Table 10, page 43)

The between-treatment comparisons of the LS mean change from baseline QT/QTc are presented in Table 6 for the overall population.

Table 6: Between-treatment analysis (ANCOVA) of QTcI change from baseline

Treatment Comparison		Change from baseline QTcI (msec) LS Means (SEM)		Difference (95% CI)	p-value [a]
Treatment 1	Treatment 2	Treatment 1	Treatment 2		
0.15 mg/kg MNTX	0.30 mg/kg MNTX	-5.00 (0.77)	-3.77 (0.78)	-1.23 (-3.36, 0.90)	0.2588
0.15 mg/kg MNTX	0.50 mg/kg MNTX	-5.00 (0.77)	-3.07 (0.76)	-1.93 (-4.07, 0.20)	0.0754
0.15 mg/kg MNTX	placebo	-5.00 (0.77)	-2.40 (0.77)	-2.60 (-4.74, -0.46)	0.0172
0.15 mg/kg MNTX	moxifloxacin	-5.00 (0.77)	3.38 (0.77)	-8.38 (-10.52, -6.23)	<.0001
0.30 mg/kg MNTX	0.50 mg/kg MNTX	-3.77 (0.78)	-3.07 (0.76)	-0.71 (-2.85, 1.43)	0.5172
0.30 mg/kg MNTX	placebo	-3.77 (0.78)	-2.40 (0.77)	-1.37 (-3.52, 0.77)	0.2094
0.30 mg/kg MNTX	moxifloxacin	-3.77 (0.78)	3.38 (0.77)	-7.15 (-9.30, -5.00)	<.0001
0.50 mg/kg MNTX	placebo	-3.07 (0.76)	-2.40 (0.77)	-0.67 (-2.79, 1.45)	0.5372
0.50 mg/kg MNTX	moxifloxacin	-3.07 (0.76)	3.38 (0.77)	-6.44 (-8.56, -4.32)	<.0001
placebo	moxifloxacin	-2.40 (0.77)	3.38 (0.77)	-5.77 (-7.89, -3.66)	<.0001

SEM = standard error of the means

a The p-value was calculated using an analysis of covariance (ANCOVA) model with treatment as the fixed effect and baseline QTc, time, and gender as covariates. Treatment-by-gender interaction was not significant at the <0.10 level and was dropped from the model.

Subjects 01-044 (0.50 mg/kg MNTX), 01-064 (moxifloxacin), 01-065 (placebo), 01-142 (placebo), 01-216 (placebo), 01-253 (placebo), and 01-394 (moxifloxacin) were excluded from the analysis because of inadequate ECG data.

Reference: Table 14.2-4.2.1 (The "error corrected" results excluding Subjects 01-364 and 01-368 are displayed in Table 14.2-4.2.2.)

(Source: Clinical Study Report: Study MNTX 1106; Table 11, page 44)

3.2.7.2.3 Categorical Analysis

The frequency distributions of subjects meeting predefined categorical criteria for cardiac conduction intervals are summarized in Table 7 for all subjects.

Table 7: Frequency of new categorical ECG outliers

ECG interval (msec)		MNTX 0.15 mg/kg N = 40 n (%)	MNTX 0.30 mg/kg N = 39 n (%)	MNTX 0.50 mg/kg N = 40 n (%)	Placebo N = 40 n (%)	Moxifloxacin N = 40 n (%)
New onset QT/QTc outliers [a]						
QT	>500	0	0	0	0	0
	>450	0	0	0	0	0
QTcI	>500	0	0	0	0	0
	>450	1 (2.5%)	0	0	0	0
QTcF	>500	0	0	0	0	0
	>450	1 (2.5%)	0	0	0	0
QTcB	>500	0	0	0	0	0
	>450	2 (5.0%)	3 (7.7%)	3 (7.5%)	1 (2.5%)	7 (17.5%)
Maximum change from baseline						
QT	<30	33 (82.5%)	37 (94.9%)	35 (87.5%)	35 (87.5%)	26 (65.0%)
	≥30 to ≤60	7 (17.5%)	2 (5.1%)	5 (12.5%)	5 (12.5%)	12 (30.0%)
	>60	0	0	0	0	2 (5.0%)
QTcI	<30	39 (97.5%)	39 (100%)	40 (100%)	39 (97.5%)	37 (92.5%)
	≥30 to ≤60	1 (2.5%)	0	0	1 (2.5%)	3 (7.5%)
	>60	0	0	0	0	0
QTcF	<30	39 (97.5%)	39 (100%)	40 (100%)	40 (100%)	36 (90.0%)
	≥30 to ≤60	1 (2.5%)	0	0	0	4 (10.0%)
	>60	0	0	0	0	0
QTcB	<30	35 (87.5%)	38 (97.4%)	35 (87.5%)	36 (90.0%)	24 (60.0%)
	≥30 to ≤60	5 (12.5%)	1 (2.6%)	5 (12.5%)	4 (10.0%)	16 (40.0%)
	>60	0	0	0	0	0
Heart Rate						
bradycardia [b]		0	0	0	0	0
tachycardia [c]		7 (17.5%)	6 (15.4%)	5 (12.5%)	6 (15.0%)	9 (22.5%)
PR (>200 and 25% inc from baseline)		0	0	0	0	0
QRS (>100 and 25% inc from baseline)		0	0	0	0	0

a baseline ≤ 500 msec and on-treatment >500 msec; baseline ≤ 450 msec and on-treatment >450 msec
b on-treatment <50 bpm and representing a 25% decrease from baseline
c on-treatment >100 bpm and representing a 25% increase from baseline
Subjects 01-044 (0.50 mg/kg MNTX), 01-064 (moxifloxacin), 01-065 (placebo), 01-142 (placebo), 01-216 (placebo), 01-253 (placebo), and 01-394 (moxifloxacin) were excluded from the analysis because of inadequate ECG data
Reference: Table 14.2-2.1.1 (The "error corrected" results excluding Subjects 01-364 and 01-368 are displayed in Table 14.2-2.1.2.)

(Source: Clinical Study Report: Study MNTX 1106; Table 12, page 46)

3.2.7.2.4 Additional Analyses

The time-averaged central tendency results are summarized in Table 8.

Table 8: Time-averaged mean (SD) change from baseline ECG intervals by treatment

ECG interval msec (SD)	MNTX 0.15 mg/kg N = 40	MNTX 0.30 mg/kg N = 39	MNTX 0.50 mg/kg N = 40	Placebo N = 40	Moxifloxacin N = 40
QT					
baseline	367.4 (23.6)	364.1 (20.2)	359.7 (18.7)	360.8 (17.7)	354.1 (17.8)
change	-8.21 (6.62)	-8.05 (8.48)	-5.47 (6.77)	-4.21 (7.34)	-0.27 (10.3)
QTcI					
baseline	389.9 (20.1)	388.3 (17.2)	383.8 (20.8)	382.8 (13.9)	381.4 (18.6)
change	-5.28 (4.26)	-3.98 (4.99)	-2.98 (4.24)	-2.20 (5.03)	3.59 (5.91)
QTcF					
baseline	392.6 (16.9)	395.0 (15.3)	388.9 (17.2)	389.6 (11.6)	387.4 (15.1)
change	-4.55 (4.00)	-3.28 (4.96)	-2.11 (4.22)	-1.96 (5.07)	3.85 (4.93)
PR					
baseline	143.6 (15.7)	142.6 (16.0)	142.0 (15.2)	143.6 (18.0)	145.4 (16.8)
change	-0.89 (3.61)	-2.49 (3.65)	-2.61 (4.15)	-0.99 (2.90)	-3.60 (4.64)
QRS					
baseline	85.70 (4.75)	88.56 (6.95)	87.14 (5.43)	85.85 (5.30)	85.89 (4.72)
change	-0.95 (2.00)	-0.77 (2.47)	-1.46 (2.45)	-0.60 (3.02)	0.09 (2.08)
RR					
baseline	828.3 (98.5)	792.2 (94.1)	799.9 (81.0)	802.9 (85.2)	772.7 (86.3)
change	-27.9 (32.6)	-34.4 (44.2)	-24.4 (36.4)	-16.6 (34.7)	-24.9 (49.9)
HR [bpm]					
baseline	74.85 (9.04)	78.19 (9.15)	77.05 (8.21)	76.92 (7.60)	79.94 (8.73)
change	2.47 (3.00)	3.16 (3.96)	2.33 (3.53)	1.44 (3.20)	2.68 (5.26)

SD = standard deviation.

Subjects 01-044 (0.50 mg/kg MNTX), 01-064 (moxifloxacin), 01-065 (placebo), 01-142 (placebo), 01-216 (placebo), 01-253 (placebo), and 01-394 (moxifloxacin) were excluded from the analysis because of inadequate ECG data.

Reference: Table 14.2-1.1.1.

(Source: Clinical Study Report: Study MNTX 1106; Table 9, page 40)

3.2.7.3 Safety Analysis

No deaths or SAEs are reported. No subjects are reported to have withdrawn due to AEs. Only 8 AEs are reported, all assessed by the investigator as mild. 2 subjects reported tachycardia, one in the MNTX low dose group (heart rhythm was normal sinus) and one in the MNTX mid-dose group (the heart rhythm was sinus tachycardia). Sinus bradycardia was noted in one subject in the MNTX low dose group.

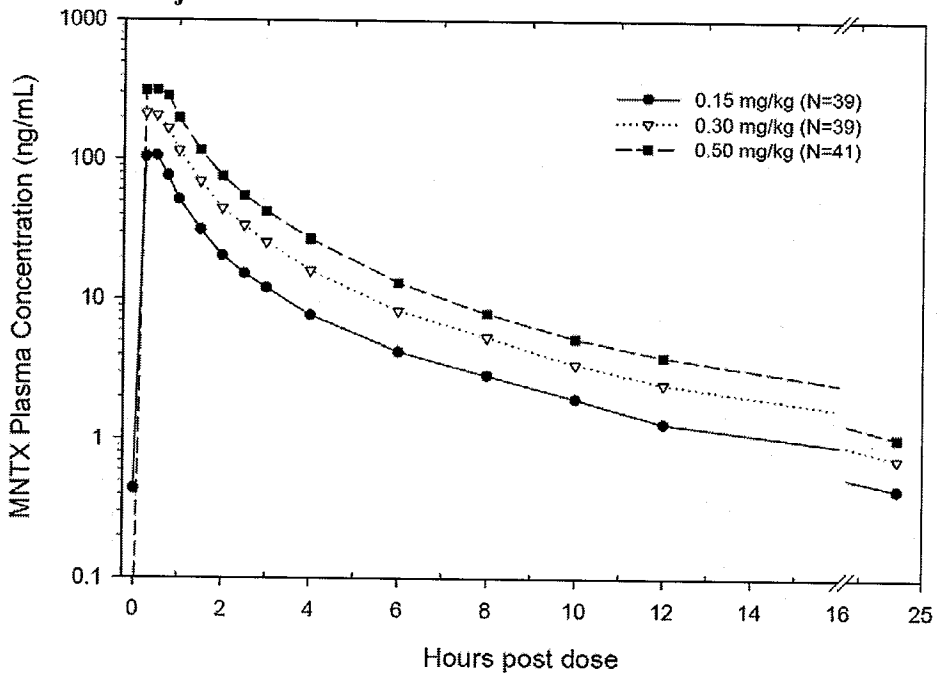
3.2.7.4 Clinical Pharmacology

3.2.7.4.1 Pharmacokinetic Analysis

Concentrations of MNTX were determined in plasma using a fully validated (LC-MS/MS) method by [redacted] in compliance with GLP. The method was validated over the range 0.05-250 ng/mL with a lower limit of quantification (LOQ) of 0.05 ng/mL. Mean plasma concentrations of MNTX over 24

hours following a single subcutaneous dose of 0.15 mg/kg, 0.30 mg/kg, or 0.50 mg/kg are plotted on a semi-log scale in Figure 4. Calculation of the mean plasma concentrations of MNTX for the 0.15 mg/kg dose group excludes subject 01-368 as the result of a dosing error.

Figure 4: Mean plasma concentrations (ng/mL) of MNTX after a single subcutaneous injection



(Source: Clinical Study Report: Study MNTX 1106; Figure 2, page 51)

3.2.7.4.2 Exposure-Response Analysis

The mean PK parameters for MNTX are summarized by dose group in Table 9.

Table 9: Mean (SD) pharmacokinetic parameters for MNTX after a single subcutaneous injection

Parameter	0.15 mg/kg N = 39[a]	0.30 mg/kg N = 39	0.50 mg/kg N = 41
AUC_{0-24} (ng*hr/mL) (± SD)	175 (36.6)	362 (63.8)	582 (111.2)
Cmax (ng/mL) (± SD)	117 (32.7)	239 (62.2)	392 (147.9)
Tmax (hr) [b] (min, max)	0.5 (0.25-0.75)	0.5 (0.25-0.75)	0.5 (0.25-0.75)

a Excludes Subject 01-368 who received placebo as the result of a dosing error
b Tmax expressed as median (range)
Reference: Table 14.4-2.

(Source: Clinical Study Report: Study MNTX 1106; Table 15, page 51)

4 REVIEWERS' ASSESSMENT

4.1 STATISTICAL ASSESSMENTS

This was a parallel, double blind, placebo and positive (moxifloxacin) controlled study in healthy male and female subjects to evaluate the effects of three doses of MNTX (0.15 mg/kg, 0.30 mg/kg, and 0.50 mg/kg SC) on ECG intervals. The moxifloxacin group was used as a positive control to determine the assay sensitivity of this study.

The sponsor used the change from baseline in QTcI for the primary analysis. However, the sponsor did not provide the upper limit of one-sided 95% CI for mean differences between respective MNTX (0.15 mg/kg, 0.30 mg/kg, and 0.50 mg/kg SC) and placebo by time point. We conducted a GLM statistical model which included the baseline QTc as a covariate, treatment, gender and gender by treatment interaction as factors at each time point. We used the ITT population without excluding any of the subjects. The results are presented in Table. It shows that the upper limits of the two sided 90% CI for the QTcI intervals for the difference in least square means between the respective MNTX (0.15 mg/kg, 0.30 mg/kg, and 0.50 mg/kg SC) and placebo were all less than 10 ms. The differences in treatment least square means were less than 5 ms for all time points except for the MNTX 0.50 mg/kg group at 23.5 hrs. As showed in Table 10, there was an unusual increase in QTc at time point 23.5 in all treatment groups except for MNTX 0.30 mg/kg.

Table 10: Upper boundary of the one-sided 95% ANOVA model based confidence interval for the placebo and baseline corrected values (delta delta analysis) of QTcI

Time post-dose (hrs)	Least Square Means				Treatment Difference			95% One-sided Upper Limit		
	MNTX			Placebo	MNTX	MNTX	MNTX	MNTX	MNTX	MNTX
	0.15 mg/kg (n = 40)	0.30 mg/kg (n = 39)	0.50 mg/kg (n = 41)	(n = 44)	0.15 mg/kg - Placebo	0.30 mg/kg - Placebo	0.50 mg/kg - Placebo	0.15 mg/kg - Placebo	0.30 mg/kg - Placebo	0.50 mg/kg - Placebo
0.25	0.2	-3.5	-2.6	-1.9	2.1	-1.6	-0.7	7.8	4.1	4.9
0.5	-5.0	-1.1	-5.9	-2.9	-2.2	1.7	-3.0	3.1	7.0	2.2
0.75	-8.1	-4.7	-3.7	-3.5	-4.5	-1.2	-0.2	0.0	3.4	4.3
1	-4.0	-3.2	-5.8	-3.7	-0.3	0.5	-2.1	5.0	5.9	3.2
1.5	-5.9	-3.7	-2.9	-3.6	-2.3	-0.2	0.7	2.4	4.5	5.3
2	-6.3	-3.3	-6.2	-5.6	-0.7	2.3	-0.6	4.3	7.2	4.3
2.5	-2.5	-0.5	-3.5	-2.9	0.4	2.4	-0.7	5.9	8.0	4.9
3	-5.3	-5.1	-5.2	-3.6	-1.7	-1.5	-1.6	3.4	3.5	3.4
4	-3.5	-5.1	-2.8	-3.8	0.3	-1.3	1.1	5.2	3.6	5.9
6	-9.5	-6.8	-7.4	-8.0	-1.5	1.2	0.6	4.6	7.3	6.6
8	-9.7	-4.2	-4.5	-3.6	-6.2	-0.6	-1.0	-0.9	4.5	4.1
10	-6.7	-5.7	-6.0	-5.8	-0.8	0.2	-0.1	4.9	5.9	5.5
12	-0.1	-1.9	-0.5	-2.1	2.0	0.2	1.6	7.3	5.5	6.8
23.5	5.7	1.5	7.1	5.3	0.4	-3.8	1.8	5.9	1.8	7.3

A similar analysis conducted for QTcF did not reach the same conclusion as for QTcI. At least at one time point, the differences in least square means between the respective MNTX (0.15 mg/kg, 0.30 mg/kg, and 0.50 mg/kg SC) and placebo were equal or greater than 10 ms (see Table 11).

Table 11: Upper boundary of the one-sided 95% ANOVA model based confidence interval for the placebo and baseline corrected values (delta delta analysis) of QTcF

Time post-dose (hrs)	Least Square Means				Treatment Difference			95% One-sided Upper Limit		
	MNTX			Placebo	MNTX	MNTX	MNTX	MNTX	MNTX	MNTX
	0.15 mg/kg (n = 40)	0.30 mg/kg (n = 39)	0.50 mg/kg (n = 41)	(n = 44)	0.15 mg/kg - Placebo	0.30 mg/kg - Placebo	0.50 mg/kg - Placebo	0.15 mg/kg - Placebo	0.30 mg/kg - Placebo	0.50 mg/kg - Placebo
0.25	-0.5	1.1	1.2	2.2	-2.7	-1.2	-1.0	2.7	4.3	4.4
0.5	4.9	-1.0	3.9	2.6	2.3	-3.6	1.3	7.6	1.8	6.6
0.75	7.8	2.5	2.1	3.8	4.0	-1.3	-1.6	8.6	3.3	2.9
1	4.5	2.1	4.3	3.2	1.3	-1.1	1.1	6.5	4.2	6.2
1.5	5.3	2.6	2.9	2.9	2.4	-0.3	0.1	7.2	4.5	4.8
2	6.4	2.8	4.7	4.5	1.9	-1.7	0.2	6.9	3.4	5.2
2.5	2.1	-0.5	3.4	2.1	0.1	-2.6	1.3	5.6	3.1	6.9
3	6.0	4.1	5.1	3.0	3.0	1.1	2.1	7.9	6.1	7.1
4	3.2	4.4	2.7	3.7	-0.5	0.7	-1.0	4.4	5.6	3.9
6	9.0	5.5	6.7	6.2	2.8	-0.8	0.5	9.1	5.5	6.7
8	8.5	3.2	3.4	3.1	**5.3**	0.1	0.3	**10.4**	5.2	5.3
10	5.7	4.3	5.1	5.0	0.6	-0.8	0.1	6.0	4.7	5.4
12	0.5	0.2	0.3	0.6	-0.1	-0.4	-0.3	5.0	4.7	4.7
23.5	-4.8	-1.4	-4.6	-4.1	-0.7	2.7	-0.5	4.8	8.3	4.9

The results of the assay sensitivity analysis are shown in Table 12. Assay sensitivity was not established since none of the lower bounds of the mean difference of moxifloxacin and placebo after baseline correction for QTcI exceeded 5 ms even before multiple endpoint adjustment was performed.

Table 12: Assay Sensitivity Analysis of Time-Matched and Baseline Adjusted QTcI (ms) by Time Point

Time Point (hr)	Least Square Means		Treatment Diff. Moxifloxacin - Placebo	90% Confidence Intervals Moxifloxacin - Placebo	
	Placebo (n = 42)	Moxifloxacin (n = 43)		Lower Bound	Upper Bound
0.25	-1.0	-1.5	-0.5	-4.5	3.6
0.5	-1.8	2.2	4.1	0.2	8.0
0.75	-2.5	1.9	4.4	0.6	8.2
1	-2.7	1.9	4.7	0.2	9.1
1.5	-2.5	5.8	8.3	3.9	12.6
2	-4.5	0.5	4.9	0.7	9.2
2.5	-1.8	4.3	6.1	1.9	10.3
3	-2.6	3.6	6.2	2.0	10.3
4	-2.8	5.8	8.7	4.4	13.0
6	-6.5	1.3	7.8	3.4	12.2
8	-2.6	3.0	5.7	1.8	9.6
10	-4.5	3.8	8.3	3.4	13.2
12	-1.8	4.4	6.2	1.1	11.4
23.5	5.9	10.4	4.5	-0.1	9.0

We also performed an analysis based on our own calculation of QTcI and found similar results.

For categorical analysis, we conducted the analysis based on the raw QT/QTc without averaging the triplicates at each time points. We confirmed that no subject had an absolute QTcI interval above 500 ms post treatment. However, there were several

subjects which had an absolute QTcI interval between 450 ms and 500 ms pre and post treatment. As shown in Tables 14 and 15, there were also an unusually large number of subjects who had an increase from baseline between 30 and 60 ms and several subjects with increasing more than 60 ms in all the treatment groups.

Table 13: Frequency for QTcI : 450 ~ 500 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - MNTX 0.15 mg/kg	40	5	13%	1800	11	1%
Baseline - MNTX 0.30 mg/kg	39	1	3%	1749	1	0%
Baseline - MNTX 0.50 mg/kg	41	3	7%	1841	7	0%
Baseline - Placebo	44	1	2%	1906	3	0%
Baseline - Moxifloxacin 400 mg	42	1	2%	1857	1	0%
Treatment - MNTX 0.15 mg/kg	40	3	8%	1673	5	0%
Treatment - MNTX 0.30 mg/kg	39	1	3%	1638	1	0%
Treatment - MNTX 0.50 mg/kg	41	2	5%	1707	2	0%
Treatment - Placebo	44	0	0%	1806	0	0%
Treatment - Moxifloxacin 400 mg	42	2	5%	1758	6	0%

Table 14: Frequency for Delta QTcI: 30 ~ 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Treatment - MNTX 0.15 mg/kg	40	22	55%	1623	48	3%
Treatment - MNTX 0.30 mg/kg	39	24	62%	1592	41	3%
Treatment - MNTX 0.50 mg/kg	41	27	66%	1640	61	4%
Treatment - Placebo	44	27	61%	1680	54	3%
Treatment - Moxifloxacin 400 mg	42	32	76%	1600	115	7%

Table 15: Frequency for Delta QTcI: > 60 ms

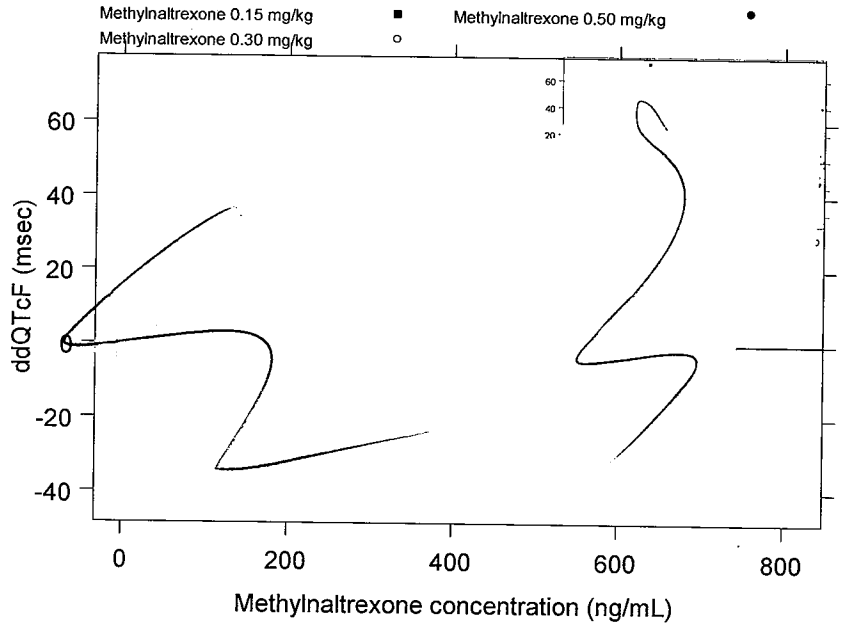
Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Treatment - MNTX 0.15 mg/kg	40	2	5.0%	1623	2	0.1%
Treatment - MNTX 0.30 mg/kg	39	2	5.1%	1592	2	0.1%
Treatment - MNTX 0.50 mg/kg	41	2	4.9%	1640	2	0.1%
Treatment - Placebo	44	2	4.5%	1680	3	0.2%
Treatment - Moxifloxacin 400 mg	42	8	19.0%	1600	10	0.6%

Reviewer's comments: The large number of subjects with large changes in QTc from baseline suggests something amiss with the conduct of the study.

4.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The reviewer is in agreement with the pharmacokinetic analyses provided by the sponsor. Exposure response analyses relating plasma MNTX concentraction and baseline corrected change in QTcF from placebo (ddQTcF) were conducted (Figure 5).

Figure 5: MNTX concentration and ddQTcF relationship (Inset: relationship at lower MNTX concentrations ≤ 50 ng/mL) .The horizontal line marks ddQTcF=0.



In the presence of poor assay sensitivity (see statistical analyses), these results should be interpreted with great caution. However, this analysis finds no concentration dependent increase in QTcF within the range (up to 800 ng/mL) of MNTX concentrations studied in this trial.

- No pharmacokinetic delay in concentration-QTcF relationship was noticeable.
- The unusual shift (Figure 3) in the QTc interval at ~23.5 hrs was seen in all dose groups including placebo. Therefore, the ddQTc interval was not affected by such shifts.

4.3 Clinical Assessments

No significant AEs were observed during the study.

5 APPENDIX

5.1 TABLE OF STUDY ASSESSMENTS

Assessment Study Day (hour)	Screening ≤ 16	Pre-Study -2 (-36 to -24 hr)	Baseline -1 (-24 to 0 hr)	Dosing 1 (0 hour)	Treatment 1-2 (0 to 24 hr)	Discharge 2 (24+ hr)	Follow-up 30-33	Early Termination
Informed Consent	X							
Inclusion/Exclusion	X	X						
Medical History	complete	update						
Concomitant medications/tobacco use	X[1]	X	X		X	X	X	X
Physical Exam	X	X				X		X
Vital signs[2]	X	X	X		X	X		X
Safety ECG[2]	X		Pre-treatment		Pre-dose, 1 hr	X		X
Hematology, clinical chemistry, urinalysis	X	X				X		X
Serology	X							
Drugs of abuse screen	X	X						
Serum pregnancy test	X	X						
Alert subjects to diet restrictions	X	query						
Adverse events		X	X		X	X	X	X
Clinic check-in		<7:00 pm						
Eligibility confirmation		X	X					
Confinement to clinic		X	X	X	X			
Onset and conclusion of study-related fasting		7:00 pm (≥12 hr)	4 hr post ECG & ≥7:00 pm		4 hr post dose			
24-hr, 12-lead digital ECG			X[3]		X[3]			
Randomization			X					
Administration of MNTX, moxifloxacin, or placebo				X				
Blood samples for PK			X[4]	X[4]	X[4]			
Early termination								X

(1) Prior medications used within the past 30 days were recorded

(2) Safety ECGs and vital signs were determined within 10 minutes of nominal times, and prior to the corresponding blood samples in order to avoid the confounding effects of possible vasovagal reactions to phlebotomy.

(3) To allow for replacement of Mortara H-12 Plus flash memory cards, actual elapsed time for recording Baseline ECG data could be 23.75 to 24 hr, starting at -24 hr (predose). Data from the second flash memory card encompassed "time zero" (time of study drug administration) and ended at 23.75 to 24 hr post dose.

(4) Blood samples were drawn at Baseline (Day -1 to Day 1) at time 0 (within 30 minutes of the initiation of Mortara H-12 Plus ECG recording), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 23.75 hours after initiation of 24-hr ECG. Samples on Day 1 were taken before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours following dosing. The predose sample corresponded to the 23.75-hr sample from the Baseline Period. Two samples were not taken for this time point. Deviations from nominal sampling times were documented.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stephen Grant
8/28/2007 12:12:43 PM
MEDICAL OFFICER

Christine Garnett
8/28/2007 01:41:35 PM
PHARMACOLOGIST
Pravin Jadhav was the clinical pharmacology reviewer.

Joanne Zhang
8/28/2007 01:59:08 PM
BIOMETRICS

Kate L Dwyer
8/28/2007 02:01:51 PM
BIOMETRICS

Norman Stockbridge
8/28/2007 05:21:39 PM
MEDICAL OFFICER